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# Role of CXCL-10 as a Biomarker for Rheumatoid Arthritis

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## ABSTRACT

**Background:** CXCL-10 has been discovered as a pro-inflammatory chemokine that mediates leukocyte trafficking and modulates innate and adaptive immune responses after being demonstrated in the sera, synovial fluid (SF), and synovial tissue (ST) of cases with rheumatoid arthritis (RA). It contributes to several biologic processes and is essential to the inflammatory response.

**Objective:** This study aimed to evaluate the predicative significance of chemokine CXCL10 in RA and to identify its relation to disease activity.

**Patients and Methods:** 30 cases with RA and 30 healthy controls made up a case-control study. For each patient, a clinical examination was conducted. ELISA was utilized to measure the amount of CXCL10 in the blood, and the Disease Activity Score (DAS-28) that was utilized to assess the disease activity in the patients.

**Results:** In terms of the blood level of CXCL-10, it was watched a high significant difference between the patients and controls with a high sensitivity and specificity in regard to RA diagnosis. According to the DAS-28, there was a significant difference between the different activity groups when CXCL-10 levels in patients with various grades of disease activity were compared.

**Conclusion:** Our research confirmed the pivotal function of CXCL10 in the RA inflammatory cascade and shown its importance as a biomarker for RA disease prediction. Additionally, it is essential for RA inflammation and might be a marker of disease activity in RA.

**Keywords:** Rheumatoid arthritis, CXCL10, Chemokine receptor, Disease activity.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that is characterized by synovial inflammation with gradual deterioration of bone and cartilage in the joints [(1)]. Different leukocytes, comprising T cells, B cells, monocytes, neutrophils, eosinophils, dendritic cells (DC), and natural killer (NK) cells are proposed to be comprised in RA pathogenesis although its etiopathogenesis isn't totally identified [(2)].

According to many studies, RA represents a "window of opportunity" within which effective treatment may stop the irreparable destruction and stop the transition from acute, reversible inflammation to chronic persistent inflammation. Up till now, only a little is known about the pathological mechanisms underlying early and pre-clinical RA than is the case with established RA [(3)].

T helper (Th) 1 and Th17 cells are primarily defined as participating factors in the context of RA pathogenesis in the current paradigm of the T-cell subsets [(4)]. The synovial fluid (SF) cytokines in RA, however, has been demonstrated to differ from that in confirmed RA and to have a Th2 and Th17 bias (demonstrates increased level of interleukins; IL-2, IL-4, IL-13, IL-17, IL-15, BFGF, and EGF in comparison with confirmed RA) [(5)]. Additionally, it was demonstrated that, when compared to healthy controls, patients with RA who are not receiving treatment have higher serum levels of cytokines linked to Th17 polarisation, neutrophil recruitment, and stimulation [(6)].

The CXCL10 gene in humans produces the 8.7 kDa protein known as C-X-C motif chemokine ligand 10 (CXCL10), also known as small-inducible cytokine B10. Small cytokine C-X-C motif chemokine 10 is a member of the CXC chemokine family. The CXCL10 gene is part of a cluster with numerous additional CXC chemokine genes on human chromosome 4 [(7-9)]. The important function of CXCL10 in chronic inflammatory disorders has been thoroughly described. CXCL10 increases the production of CXCL10 in numerous cell types, leading to positive feedback that amplifies CXCL10 and Th1 responses in inflamed tissues where IFN-γ is released by Th1 cells via CXCR3 [(10)]. Human RA patients have been demonstrated to have higher blood and SF levels of CXCL10 [(11)].

Several cell types can secrete CXCL10 under the effects of IFN. Many immune and non-immune cells can produce it when stimulated by interferons. Monocytes, endothelial cells, and fibroblasts are some of these cell types. Numerous functions of CXCL10 have been identified, comprising chemoattraction of monocytes/macrophages, T cells, NK cells, and DC, promotions of T-cell adhesion to endothelial cells, antitumor activity, and suppression of angiogenesis and BM colony formation [(12)]. Myositis and rheumatoid arthritis are two autoimmune disorders in which CXCL10 has been identified as a biomarker [(13)].

In the context of animal models of RA, block of the CXCL10-CXCR3 axis is demonstrated to lessen the severity of arthritis and bone and cartilage damage while also preventing the influx of inflammatory cells, such as T cells and macrophages, into inflamed joints.



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CXCL10 is found to boost RANKL expression in CD4+ T cells in addition to its chemotactic impact [14].

Four chemokine receptors—CCR4, CCR6, CXCR3, and CXCR5—in the CD4+ or CD4+CD45RA$^{neg}$ compartment were combined to determine T-helper cell subsets in the **Pandya *et al.*** investigation in RA patients [15].

The blood of RA patients differs from that of controls in terms of the presence of any chemokines which bind to the aforementioned chemokine receptors, as well as how these chemokines relate to T-cell subsets and clinical disease activity. **Pandya *et al.*[15]** had analysed the next fifteen chemokines (cells expressing corresponding chemokine receptor demonstrated in brackets): CXCL9, CXCL10, and CXCL11 (Th1 and NK cells), CCL2, CCL3, CCL4, and CCL5 (Th2, macrophages,), CCL17 and CCL22 (Th2 and T-regs), CCL20 (Th17, B cells, and DC), CXCL13 (Th and B cells), CCL11 (eosinophil and basophil), and CXCL1, CXCL5, and CXCL8 (neutrophils). Additionally, they looked into the associations between chemokine concentrations, T-cell subset composition, and disease activity in RA. They discovered via the usage of multivariate analysis that the chemokine profiles of RA cases and HC were different from each other. Additionally, they discovered that RA patients had significantly higher blood levels of CXCL9, CXCL10, CXCL13, CCL4, and CCL22 compared to controls. Only CXCL10 displayed an association with clinical disease activity among the discriminator chemokines [15]. We aimed to assess CXCL-10's function in RA patients and how it relates to disease activity.

## PATIENTS AND METHODS

This was a prospective case-control study conducted on thirty patients with RA with matched age and sex healthy control (HC) subjects (n=30). They were collected between August 2021 and February 2022 from the Physical Medicine, Rheumatology, and Rehabilitation Department, Faculty of Medicine, Ain Shams University Hospital. A prospective case-control study in which comparison of CXCL-10 as a diagnostic biomarker for RA between RA cases and HC.

**Subjects and Sample size:** 30 rheumatoid arthritis patients diagnosed based on ACR/ EULAR 2010 classification criteria for RA [16] as a patient group and 30 healthy controls matching in age and sex as control group.

**Exclusion criteria:** Patients with secondary causes of bone diseases such as**:** Chronic Renal failure (CRF). Patients with chronic hepatic disorders. Patients had performed parathyroidectomy. Patients with other chronic inflammatory conditions and autoimmune diseases (AIDs, psoriasis, SLE and Systemic sclerosis). Patients on corticosteroids therapy (< 7.5 mg for less than 3 months). Patients with diabetes mellitus. Pregnancy.

**All participants underwent:**

**Full history taking:** Name, age, place of residence, and profession and personal details. Previous medical history: Previous medical history. Past medications history. Any previous complications.

**Full clinical examination:** Clinical assessment included disease activity and functional impairment. Disease activity was assessed by DAS 28 score [17]. Complete general examination including cardiac, abdominal, chest, and neurological examinations. Joint examination and complete skeletal examination. During the physical examination, we evaluated stiffness, tenderness, painful range of motion, swelling, deformity, motion restriction, extra-articular symptoms, and rheumatoid nodules.

The defining hallmark of RA is the involvement of the joints. Small joints in the hands and feet were typically affected in a fairly symmetrical pattern. The most often afflicted joints were the cervical spine, hip, elbow, shoulder, ankle, metacarpophalangeal (MCP), proximal interphalangeal (PIP), knee, metatarsophalangeal (MTP), and temporomandibular joints, in decreasing order of frequency. Joints that were affected displayed swelling, soreness, warmth, and a reduction in range of motion (ROM). Tenosynovitis, or inflammation of the tendon and the sheath that surrounds it, and joint inflammation were two additional often seen musculoskeletal symptoms [18].

**Radiological examination:** Plain X-ray was performed for the hands, foot and joints for any skeletal deformity.

**Laboratory investigations:** Complete Blood Count (CBC) was done by electronic counting machine e.g., Beckman-Coulter counter. When testing for Rheumatoid Factor (RF), a latex-enhanced nephelometric assay was used. Erythrocyte Sedimentation Rate (ESR) using standard Wintergreen method in mm/hour, taking the reading of the first hour. C-reactive protein (CRP) "nephelometer assay" was performed using immunoturbidimetric test. Liver function tests including serum alanine transaminases (ALT), and aspartate transaminase (AST) was performed by using the optimized UV-test according to International Federation of Clinical Chemistry. Kidney function tests such as BUN and serum creatinine were performed using Jaffe's method.

**Assay for CXCL-10:** By using a sandwich ELISA kit from Bio kit (Quantikine human CXCL-10, Shanghai Sunred Biological Technology Co., Ltd.) serum CXCL-10 concentrations were assessed. The outcomes, which were determined automatically using

the standard curve's straight-line regression equation using the values for the standard density and optical density, were represented in pg/mL. For the detection of CXCL-10, this assay offers very high sensitivity and excellent specificity. Between CXCL-10 and analogues, no appreciable interference or cross-reactivity was seen. The CXCL-10 level measuring range's sensitivity ranges from 75 pg/mL to 6000 pg/mL. The measurement range's lowest protein concentration value was 35.11pg/mL. The amount of CXCL-10 in the serum of the patients and the controls was quantitatively detected. Within four hours of blood collection, serum was extracted from the blood using density gradient centrifugation at 4°C and stored in 200L aliquots at 80°C till testing.

***Ethical considerations:***

**The study was authorized by Ain Shams University's Research Ethics Committee. Prior to taking part in the trial, all participants completed an informed consent form after receiving all necessary information. The study was conducted in line with the Helsinki Declaration.**

***Statistical analysis***

The statistical programme SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) was utilized to analyse the data. The Kolmogorov-Smirnov test was utilized to determine if the variables had a normal distribution. The study's groups were created based on the mean and standard deviation values. Group 1 consisted of RA patients, and group 2 of healthy individuals. Multiple analysis of variance (ANOVA) with the Bonferroni correction was utilized to analyse the changes between the two groups (post hoc comparisons). The correlation coefficient (r) between parameters in the two groups was examined using linear regression. To ascertain the link between the research variables, the Pearson correlation coefficient was also performed. P value $\leq 0.05$ was considered significant.

**RESULTS**

The age of RA group ranged from 23 to 65 years with a mean of 42.6 ± 10.1 years, 27 patients (90%) were females, whereas 3 patients were males (10%). Regarding demographic parameters, there was no significant difference between the RA and control groups (both groups were matched for age and sex).

The disease duration of the studied RA patients ranged from 1-30 years with a mean of 7.5 ± 6.4 years. Clinical manifestations were classified into articular and extra articular manifestations. Articular manifestations included assessment of tender joints which were ranging from 2-20 with a mean of 10.2 ± 5.5 and swollen joints were ranging from 0-11 with a mean of 3.6 ± 2.7. Regarding the extra-articular manifestations only 20% of the patients in the current study presented with them, six (10%) patients had subcutaneous nodules and the other six (10%) patients had 2ry Sjogren's syndrome.

Disease activity and functional impairment were both considered in the clinical assessment. DAS 28 score was utilized to evaluate disease activity. It had a range of 1.1 - 6.8 and a mean of 4.61 ± 0. 56.7% of RA patients had moderate disease activity, 35% had severe disease activity, and 8.3% had low disease activity.

Functional impairment was assessed by MHAQ score which was ranging from 0-1.8 with a mean of 1 ± 0.5. Ninety% of patients had mild-moderate functional impairment. Complete blood count, ALT and serum creatinine were done routinely for RA patients. Hemoglobin level ranged from 7.8–16.0 with a mean of 11.7 ± 1.3 gm/dl. Platelets count ranged from 164–582 $x10^3$/mL with a mean of 295.6 ± 75.1 $x10^3$/mL and WBC ranged from 3.3–74 $x10^3$/mL with a mean of 8.5 ± 8.9 $x10^3$/mL. ESR ranged from 8-105 mm/hr with a mean of 38.9 ± 23.4 mm/hr, while CRP ranged from 3.3–56.9 mg/dL with a mean of 13±12.3 mg/dl.

RF was positive in 41 (68.3%) patients with a range of 10–1094 (U/mL). Anti-CCP anti-body was positive in 33 (55%) patients with a range of 16.5–500 (U/mL) (table 1).

**Table (1):** Immunological profile of RA patients

| Immunological profile | RF (U/mL) | Anti-CCP (U/mL) |
|---|---|---|
| Number | 41 | 33 |
| Percent (%) | 68.3 | 55.0 |
| Range | 10 – 1094 | 16.5 – 500 |

Range: Non-parametric test. RF: Rheumatoid factor.

Table (2) showed that mean serum level of CXCL-10 was 784.6 ± 152.2 in RA patients, which was very high ($p<0.001$) compared to the control group (338.1 ± 83.5).

**Table (2):** Comparison between rheumatoid arthritis and control groups regarding CXCL-10 serum level

| CXCL-10 (pg/mL) | RA | Control | t | p-value |
|---|---|---|---|---|
| Mean ± SD | 784.6 ± 152.2 | 338.1 ± 83.5 | 16.35 | < **0.001*** |

t: pared t-test, P <0.001 = highly significant.

There was a significant difference between RA patients and control group regarding serum level of CXCL-10. Area under the Curve (AUC) for CXCL-10 was 0.951 and the 95% CI was ≤ 1. The cutoff point of CXCL-10 was 450 pg/mL with a sensitivity of 89.3%, specificity of 90.6%, accuracy of 90.2%, PPV of89.9% and NPV of83.6% that were able to differentiate between RA patients and control group (Table 3 & figure 1).

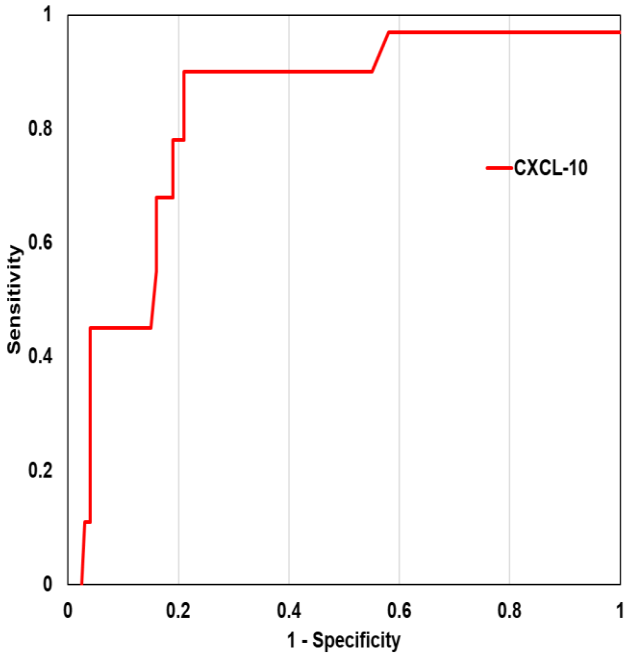


**Fig. (1):** ROC curve for CXCL-10 in differentiating RA patients from control group.

**Table (3):** CXCL-10 cut-off point in differentiating rheumatoid arthritis group from control group

| AUC | SE | P | 95% CI | Cut off |
|---|---|---|---|---|
| 0.951 | 0.026 | **<0.001** | 0.90 – 1.00 | 450 pg/mL |
| **PPV** | **NPV** | **Sensitivity** | **Specificity** | **Accuracy** |
| 89.9% | 83.6% | 89.3% | 90.6% | 90.2% |

Most of RA patients (70%) were on methotrexate with dose ranged from 12.5–25 mg per week, while sulfasalazine was the least drug used (5%) with a dose ranged from 1-2 gm per day. Thirty-five (58.3%) patients were on steroids with dose 5-20 mg per day.

**Table (4):** Comparison between the mean level of CXCL-10, DAS28 disease activity in RA patients

| DAS 28 score grading | Range | Mean ± SD | F-test | P |
|---|---|---|---|---|
| Low | 444 – 750 | 512.2 ± 112.3 | 1.324 | 0.001* |
| Moderate | 498 – 1023 | 764.8 ± 124.1 | | |
| High | 567 – 1350 | 914.4 ± 136.7 | | |

* P <0.001 = highly significant.

**Table (5):** Correlation coefficient (r) between CXCL10 and different variables for rheumatoid arthritis (RA)

| Variable | Correlation (r) | P value |
|---|---|---|
| Age > 50 years | 0.2617 | 0.028 |
| Females | 0.3094 | 0.011 |
| Duration of RA | 0.3122 | 0.009* |
| Tender joints | 0.2352 | 0.039 |
| Swollen joints | 0.2339 | 0.041 |
| DAS 28 score | 0.4341 | 0.0009* |
| MHAQ score | 0.3911 | 0.001* |
| Larsen score | 0.3624 | 0.002* |
| ESR | 0.4857 | 0.0006* |
| CRP | 0.1989 | 0.047* |

## DISCUSSION

Rheumatoid arthritis (RA) is a widespread, chronic inflammatory systemic disease characterized by a gradual infiltration of lymphocytes and macrophages into the synovial membrane, causing a synovial inflammatory reaction that lasts for a long time and results in the degeneration of bone and cartilage [(1)]. One of the most prevalent cell groups in the RA synovium, T lymphocytes, are abnormally activated, which promotes chronic inflammation and joint degeneration [(18)]. When T cells interact with different immune and resident cells, such as macrophages, they release cytokines and chemokines or come into direct contact with one another, which increases the formation of cytokines and chemokines that enhance the inflammatory process [(19)].

The age of RA group ranged from 23 to 65 years with a mean of 42.6 ± 10.1 years, 27 patients (90%) were females whereas 3 patients were male (10%). Females were more affected than males in our study which was confirmed by many studies [(15, 20, 21)]. All these studies mentioned that females were more affected with RA than males.

Our study found a significant positive correlation between the number of tender and swollen joints in RA cases and serum levels of CXCL10, where the number of tender and swollen joints was the most precise clinical indicator of disease activity in RA patients. The associations between CXCL 10 and the number of painful and swollen joints in RA patients was also observed by **Imam *et al.*** [(22)]**.** Also according to **Kuan *et al.*** [(11)] study in RA patients, there was a positive link between the blood level of CXCL10 and painful and swollen joints. As a result, CXCL10 may be crucial to the inflammation accompanied by RA and contribute to the evaluation of disease activity**.** Swollen joint counts (SJC) and tender joint counts (TJC) in individuals with established RA were assessed by **Pandya *et al.*** [(23)] who found a favourable connection between these clinical disease activity markers of painful and swollen joints. Interestingly, the study done by **Versini *et al.*** [(24)] who evaluated his RA patients by SJC & TJC

treated their RA patients with DMARDS, and they found no link between CXCL10 and clinical disease activity assessments of painful and swollen joints. Also, **Ichikawa *et al.*** [25] with his study on twenty-two patients with RA found that there are no correlations between number of tender joints and serum level CXCL10 as the sample of patients were on biological treatment as infliximab and Etanercept**.** In our study, RA patients had considerably higher measured blood levels of CXCL10 than healthy controls. Our findings corroborated those of **Imam *et al.*** [22] who studied the serum of 30 RA patients over a two-year period and found that CXCL10 levels were considerably elevated. This was also seen in earlier investigations by **Rabquer *et al.*** [26] who utilised an ELISA kit to assess the expression of chemokines and chemokine receptors in blood and who arrived to the same conclusions about the increased serum concentrations of CXCL10 in RA patients. In a similar vein, **Pandya *et al.*** [23] discovered that RA patients had higher blood levels of CXCL10. This was also in agreement with **Muhsin *et al.*** [21] who came to the same result that CXCL10 levels in blood from RA patients tended to be higher and suggested that CXCL10 was up-regulated in these individuals.

According to previous research, it was found that cases with established RA had higher serum levels of CXCL10 than healthy controls due to increased receptor activator of NF-κB ligand (RANKL) expression in synoviocytes, considerably elevated RANKL expression in CD4+ T cells, and RANKL's promotion of CXCL10 expression in osteoclast precursors [27, 28]. These findings are consistent with our own. Additionally, owing to interferon-γ (IFN-γ) and tumour necrosis factor, lymphocytes, monocytes, keratinocytes and fibroblasts secrete this biomarker. In addition to having angiostatic properties, CXCL10 principally acts by attracting leukocytes to areas of inflammation, including T cells, eosinophils, monocytes, and NK cells [29]. The serum of RA patients has been discovered to have a high expression of CXCL10. Furthermore, prior research has demonstrated that pharmacologic inhibition of CXCL10 signaling prevents the progression of arthritis in animal models, primarily by preventing T-cell migration into the joint [9, 19, 30]**.** Through the induction of a receptor activator in inflamed synovial tissue, CXCL10 is proposed to play pathogenic roles regarding bony destruction in RA patients [20]**.** On the other hand, despite the fact that disease-modifying antirheumatic drug (DMARD) therapy, which is thought to affect serum level of activity markers, was administered for 12 weeks to RA patients in 2010, **Kuan *et al.*** [11] have demonstrated that there were no differences in serum levels of CXCL10 in those individuals.

A positive correlation between serum levels of CXCL10, CRP, and ESR was found in the current investigation. **Pandya *et al.*** [23] used ESR and CRP to evaluate their RA patients' activity. They discovered a strong positive association between CXCL10 levels and both ESR and CRP. This comes in the same line with **Muhsin *et al.*** [21] who discovered a substantial correlation between CXCL10 levels and ESR and CRP. However, **Imam *et al.*** [22] discovered that no association was determined between CXCL10 and CRP serum levels. This was in line with the research conducted by **Han *et al.*** [8]**,** on 29 RA patients who found that CXCL10 was not correlated with the inflammatory markers CRP or ESR as all their patients were in high dose glucocorticosteroid therapy and were initiating adalimumab and etanercept in their treatment protocols.

Our results revealed a highly positive significant correlation between serum CXCL10 and DAS-28 ESR. This is in line with **Imam *et al.*** [22] results that showed positive correlation between serum CXCL10 and DAS-28 ESR. In agreement with our finding, **Pandya *et al.*** [23] who evaluated RA patients by assessing the following parameter: DAS-28 joints and ESR and they demonstrated a positive significant association between DAS-28 ESR and serum CXCL10 levels. **Kuan *et al.*** [11] in his study on 28 active RA patients come in line with our study showing that there is a positive correlation between CXCL10 & DAS28 and could be used as a RA disease activity marker.

Our study reported that the AUC in our results was 95.1 % and the cutoff point of CXCL-10 in our study was 450 pg/mL with sensitivity of 89.3% and specificity of 90.6%. These results indicated good validity of CXCL10 as a diagnostic marker for RA. **Han *et al.*** [8], reported that CXCL10 showed significant predictive ability based on AUC of 83.0 %. These results are consistent with our results with the validity of CXCL10 as a diagnostic marker for RA.

According to **Pandya *et al.*** [23]**,** CXCL10 levels are inversely correlated with disease activity and inflammation in patients. A genetic association research using single nucleotide polymorphisms (SNPs) supported this idea by demonstrating that the CXCL10 GG genotype was an independent factor linked with an increased likelihood of the development of extra-articular manifestations. When these cells were treated with TNF and IL-1β, CXCL10 secretion was identified. On the other hand, when such cells were activated by IFNγ and IFN, substantial discharge of all 3 chemokines was seen [31]. Owing to synovial hyperplasia, paracrine activity, and positive feedback loops among various cytokines and chemokines, associations between various chemokines can be seen even though CXCL10 and different chemokines are regulated differently in chronic inflammation.

As per our results, showing a link between CXCL10 and several clinical disease activity measures, our work is one of those studies that establishes CXCL10 as a disease activity marker in RA. The link between CXCL10 and several clinical disease activity measures and laboratory research in

RA leads one to believe that CXCL10 is crucial to the progression of the disease and can serve as a marker of disease activity in RA.

CXCL10 may have the ability to control inflammation on a number of levels, influencing the pathophysiology and progression of RA. Leukocyte homing to inflamed tissue, as well as the maintenance of inflammation and tissue injury, depend on CXCL10. In particular, CXCL10 causes integrin activation, enhances T-cell adherence to endothelial cells, and encourages directional migration of stimulated NK, monocyte, and T cells [(32)]. As a result, it can coordinate the dispatch of different immune cells to the area of inflammation. Additionally, RA synoviocytes and CD4+ T cells can express RANKL when exposed to CXCL10 [(28)], which could lead to bone resorption. Synovial hyperplasia may result from stimulation of fibroblast-like synoviocytes (FLS) with CXCL10, which has been demonstrated to increase the proliferation of these cells. The formation of inflammatory mediators which include cytokines, matrix metalloproteinases (MMPs), and other enzymes by FLS and chondrocytes in response to CXCL10 might result in the breakdown of cartilage and extracellular matrix (ECM) [(33)].

In fact, RA patients' SF and tissue have been found to contain higher concentrations of CXCL10 and other chemokines than individuals with osteoarthritis. CXCL10 has been found to have a chemokine gradient in individuals with established RA, with synovial fluid levels being greater than blood levels. CXCL10 had the most pronounced variations in concentration among them (>10 times greater concentration in RF SF in comparison with RA serum for both chemokines)[(23)].

## CONCLUSION

Our research confirms that CXCL10 plays a crucial part in the RA inflammatory cascade. The association between CXCL10 and clinical disease activity showed that CXCL10 is essential for RA inflammation and could be used as a marker for the condition. In conclusion, serum CXCL10 level is significantly increased in RA patients especially in RA and correlated with disease activity. It can act as a biomarker for diagnosis of RA disease at cut-off value of 450 pg/ml with sensitivity 89.3% and specificity 90.6%

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