Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2023.238595.2916 Volume 30, Issue 3, May 2024
Manuscript ID ZUMJ-2309-2916 (R1)
DOI /10.21608ZUMJ.2023.238595.2916
ORIGINAL ARTICLE.

Serum Level of CXCL12 in Rheumatoid Arthritis Patients and its Correlation with Disease Activity

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Submit Date 24-09-2023
Revise Date 07-10-2023
Accept Date 2023-10-11

ABSTRACT

Background*:* Synovial angiogenesis and inflammation with articular damage are the main pathologic changes in rheumatoid arthritis (RA). The implication of the chemokine CXCL12 in disorders of the immune system had been identified. CXCL12 is involved in the inflammatory process by triggering leukocyte recruitment and neovascularization. Therefore, this research aims to investigate the serum CXCL12 level in RA patients and define how it correlates with disease activity.

Methods*:* This study comprised 44 RA patients as well as 44 matched controls. Health assessment questionnaire disability index (HAQ- DI) as well as disease activity score (DAS-28) were determined. CXCL12 level was assessed in the sera of participants.

Results: Serum CXCL12 concentration was significantly elevated in RA patients (1475.16 ± 480.78 pg/ml) compared to controls (484.6 ± 177.85 pg/ml; p<0.001). Significant relations were detected between CXCL12 with tender joint count (p<0.001), swollen joint count (p<0.001), morning stiffness duration (p<0.001), DAS-28 (p<0.001), HAQ-DI (p<0.001), rheumatoid factor (RF) titer (p<0.001), anti-cyclic citrullinated peptide (anti-CCP) level (p=0.001), C-reactive protein (p<0.001), and erythrocyte sedimentation rate (p<0.001). Serum CXCL12 significantly discriminated RA patients from healthy subjects (AUC = 0.99; p<0.001), as well as active RA cases from those in remission (AUC = 0.96; p<0.001).

Conclusion*:* This study indicated the fundamental utility of serum CXCL12 in RA activity monitoring.

Keywords: Rheumatoid arthritis; CXCL12; Disease activity

INTRODUCTION

Rheumatoid arthritis (RA) is a highly prevalent inflammatory arthritis that affects around 1-3% of people globally, with a female predominance, and is one of the primary causes of disability if not treated effectively [1]. Although the precise cause of RA is not fully elucidated, both hereditary and non-genetic variables can influence its progression. Synovial angiogenesis, infiltration of the synovium with immune cells, pannus development, and bone degradation are among the pathological alterations that characterize RA. These events are orchestrated by a complicated interplay of chemokines, autoantibodies, and cytokines [2].

The intense study of biomarkers in rheumatology stems from a demand for clarity about the underlying pathogenesis of rheumatic illnesses. RA activity evaluation is a critical concern for monitoring therapeutic response and making the best clinical decisions essential for achieving disease remission. There is no one ideal test to determine RA activity. CRP and ESR lack specificity because of their rise in a variety of diseases. As a result, research on markers for use in RA activity evaluation is extremely important [3].

Chemokines are low molecular weight peptides of 8-10 kilo Dalton. Structurally, there are four subclasses (CXC, CX3C, C, and CC) depending on cysteine positioning [4]. CXCL12, formerly

identified as stromal cell-derived factor 1 (SDF-1), belongs to the CXC chemokine family and possesses two receptors (CXCR7 and CXCR4) [5]. CXCL12 is released by endothelial cells, dendritic cells, fibroblasts, osteoblasts, monocytes, and stromal cells [6]. It contributes to numerous biological effects including organogenesis, chemotaxis, angiogenesis, cellular proliferation, and autoimmunity [7].

Previous studies described the association of CXCL12 with multiple autoimmune diseases including adult-onset Still's disease [8], vasculitis [9], systemic lupus erythematosus (SLE) [10], systemic sclerosis [11], RA [7], and ankylosing spondylitis [12]. RA patients were reported to have overexpressed synovial fluid levels of CXCL12 as compared to controls [13, 14]. In addition, sparse studies revealed higher level of this chemokine in the serum of patients with RA and there was a dispute on its relationship with activity of the disease [13, 15]. As a result, this work was planned to evaluate the serum level of CXCL12 in RA patients and its relation with disease activity.

METHODS

Subjects

Sample size was calculated using the G*Power software (Version 3.1.9.2) and was based on earlier study [15] with respect to serum CXCL12 level in RA cases compared with healthy controls. A priori computed required sample size was 44 subjects per group (a total of 88 subjects) using an α error 5% and a power of 95%.

Forty-four consecutive RA patients from the rheumatology and rehabilitation outpatient clinic at Mansoura University Hospitals participated, in addition to 44 healthy volunteers with matched ages and sexes who served as controls. The standard of ethics outlined in the Helsinki Declaration was implemented in this case-control study. The consent form was given by every participant. Mansoura Faculty of Medicine's Institutional Research Board granted approval to this research (code: MS.21.02.1388).

Inclusion criteria: According to 2010 RA criteria of American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) [16], RA was diagnosed.

Exclusion criteria: Cases with cognitive or communication disorders, Alzheimer's disease, multiple sclerosis, hepatic or renal impairment, malignancy, diabetes mellitus, joint infection, or any other autoimmune illness were ruled out.

Methods

A comprehensive clinical evaluation was conducted for every patient. Disease Activity Score in 28 Joints (DAS-28) based on Erythrocyte sedimentation rate (ESR) was calculated [17]. The health assessment questionnaire disability index (HAQ-DI) was used for evaluating the patients' physical function [18].

laboratory tests:

Complete blood picture, fasting blood glucose, kidney and liver function tests, C-reactive protein (CRP), anti-cyclic citrullinated peptide (anti-CCP), ESR, rheumatoid factor (RF), and serum CXCL12.

Assay of serum CXCL12

Three milliliters of venous blood were withdrawn from subjects and centrifuged for 15 min at 3000 rpm to obtain serum. Serum samples were stored in (-80 °C) till the analysis was done. CXCL12 levels were estimated in the participants' sera by an enzyme-linked immunosorbent assay (ELISA) kit, adhering strictly to the manufacturer's directions of INNOVA Biotechnology Co., Ltd. (cat. no. In-Hu2703). The concentrations of CXCL12 were obtained via Infinite F50 ELISA reader (TECAN, Mannedorf, Switzerland).

STATISCAL ANALYSIS

Analysis of data was done by using Statistical Package for Social Sciences for Windows version 22 (IBM Corp., Armonk, N.Y., USA). Mean and standard deviation (SD) were used to describe continuous variables with normal distributions, whereas the median and interquartile ranges (IQR) were considered for representing non parametric variables. For presenting qualitative data, percentages and numerical values were adopted. When appropriate, the following statistical tests were applied: Student's t-test, Chi-square test, one-way analysis of variance (ANOVA) test, and post hoc Tukey test. Moreover, Pearson’s and Spearman’s rank correlations were done. In order to define the capability of serum CXCL12 to differentiate RA patients from control as well as active patients from those in remission, the receiver operator characteristic (ROC) analysis was applied. A statistically significant difference was defined as $P<0.05$.

RESULTS

The mean ages of patients and controls were: (46.4±8.5 and 43.7±8.8 years, respectively) (p=0.142). The distribution of gender within the groups was comparable, as each group included 36 females and 8 males. The characteristics of patients are depicted in Table 1.

The serum level of CXCL12 was highly significant in the RA group (1475.16 ± 480.78 pg/ml) compared to controls (484.6 ± 177.85 pg/ml; p<0.001) as represented in Figure 1.

Correlation of clinical and laboratory findings, HAQ-DI and DAS-28 with CXCL12 serum level are described in Table 2. As shown in Table 3, serum CXCL12 levels varied significantly with regard to disease activity grading (p<0.001). Moreover, highly active patients had greater serum CXCL12 in comparison to those in remission (p<0.001), mild activity (p<0.001), and moderate activity (p<0.001).

ROC analysis displayed that at 784.6 pg/ml cut-off level, serum CXCL12 had a substantial capacity in distinguishing between controls and RA patients with 94.3% accuracy, 93.2% sensitivity, and 95.5% specificity (AUC = 0.99, p<0.001) (Figure 2). Furthermore, serum CXCL12 at a cutoff level of 1076 pg/ml was shown to be a significant discriminator between active RA cases and those in remission (p<0.001), with 90% accuracy, 0.96 AUC, 88.6% sensitivity, and 88.9% specificity (Figure 3).

Table (1): The characteristics of rheumatoid arthritis patients

Variables	RA patients (n= 44)	
Demographic data:		
Age (years)	Mean ± SD (range)	46.4±8.5 (30-61)
Females	N(%)	36 (81.8%)
Clinical features:		
disease duration (years)	Median (IQR)	6 (4-8.5)
Duration of morning stiffness (minutes)	Median (IQR)	75 (30-120)
Number of tender joints	Median (IQR)	6 (2-12)
Number of swollen joints	Median (IQR)	2 (0-6)
Laboratory investigations:		
Hemoglobin (g/dl)	Mean ± SD	11.49±1.35
RBCs (million/mm^3)	Mean ± SD	4.38±0.46
Platelets (x10^3/mm^3)	Median (IQR)	263(212.5-337)
WBCs (x10^3/mm^3)	Mean ± SD	6.41±1.663
ALT (U/L)	Median (IQR)	19.3 (14.8-30)
AST (U/L)	Median (IQR)	26.5 (21.5-34.5)
Serum creatinine (mg/dl)	Mean ± SD	0.9±0.27
Fasting blood glucose (mg/dl)	Mean ± SD	92.4±13.1
ESR (mm/1sthr)	Median (IQR)	29 (20.5-57.5)
CRP (mg/dl)	Median (IQR)	26.3 (10.4-42.5)
RF (IU/ml)	Median (IQR)	35 (18-63)
positive RF	N (%)	33(75%)
Anti-CCP (IU/ml)	Median (IQR)	83 (8.8-320.7)
positive Anti-CCP	N (%)	32(72.7%)
HAQ-DI	Mean ± SD	1.21±0.61
Disease activity score:		
DAS-28	Mean ± SD	4.14±1.38
DAS-28 grades	Low: n (%)	5 (11.4%)
	Moderate: n (%)	14 (31.8%)
	High: n (%)	16 (36.4%)
	Remission: n (%)	9 (20.5%)

RA: rheumatoid arthritis, RBCs: red blood cells, WBCs: white blood cells, ALT: alanine transaminase, AST: aspartate transaminase, ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; Anti-CCP: anti-cyclic citrullinated peptide; HAQ-DI: health assessment questionnaire disability index; DAS, diseases activity score.

Table (2): Correlations between CXCL12 serum levels and clinical and laboratory findings, DAS-28and HAQ-DIin rheumatoid arthritis patients.

	Serum CXCL12 levels	
	Correlation coefficient	**p-value**
Age (years)	r=0.264	0.083
Clinical features:		
Disease duration (years)	r_s= 0.231	0.131
morning stiffness duration (minutes)	r_s= 0.897	**<0.001***
Number of tender joints	r_s= 0.858	**<0.001***
Number of swollen joints	r_s= 0.850	**<0.001***
Laboratory data:		
RF titer	r_s=0.626	**<0.001***
Anti-CCP	r_s=0.476	**0.001***
ESR	r_s=0.773	**<0.001***
CRP	r_s=0.783	**<0.001***
Hemoglobin	r= - 0.006	0.968
RBCs	r= - 0.230	0.133
Platelets	r_s= 0.034	0.825
WBCs	r=0.033	0.832
DAS28 score	r= 0.949	**<0.001***
HAQ-DI score	r= 0.955	**<0.001***

*RF: Rheumatoid factor, Anti-CCP: anti-cyclic citrullinated peptide, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RBCs: red blood cells, WBCs: white blood cells, DAS: diseases activity score, HAQ-DI: health assessment questionnaire disability index, *****Significant at p<0.05, r: Pearson's correlation coefficient, rs: Spearman's rank correlation coefficient.*

Table (3): Comparison of serum CXCL12 levels according tothe gradesof disease activity in rheumatoid arthritis patients

Disease activity grades	**Serum CXCL12 levels(pg/ml)**	**One-Way ANOVA**
	Mean ± SD	**p-value**
High (n=16)	1969.33±198.53	**<0.001***
Moderate (n=14)	1434.61±297.14	
Low (n=5)	1080.83±165.37	
Remission (n=9)	878.81±151.09	
Post hoc pairwise comparison (Tukey test) Low versus high (p**<0.001***) Low versus moderate (p=**0.022***) Low versus remission (p=0.386) Moderate versus high (p**<0.001***) Moderate versus remission (p**<0.001***) High versus remission (p**<0.001***)		

*Significant

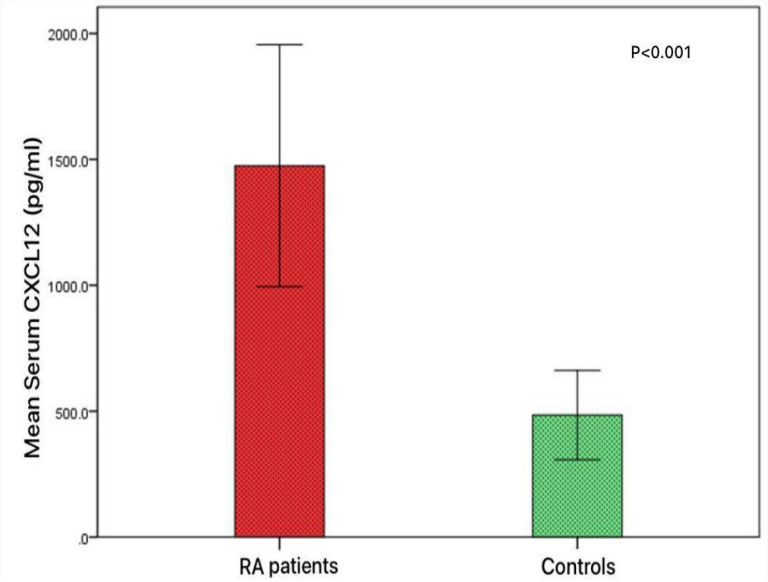

Fig (1): The mean serum CXCL12 levels in RA patients and the controls

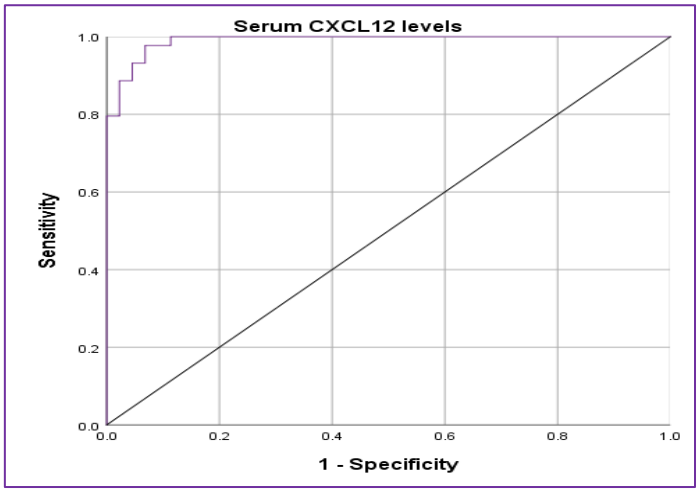

Fig (2): ROC curve for serum CXCL12 levels in distinguishing between RA patients and controls.

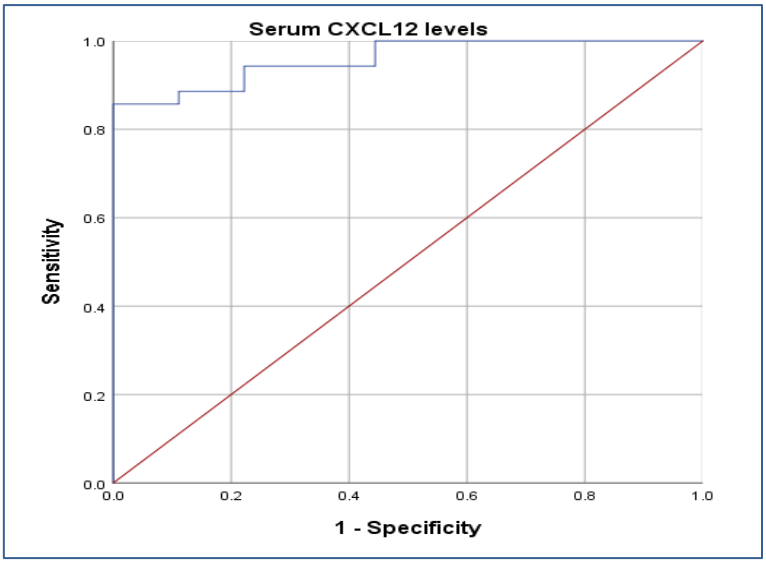

Fig (3): ROC curve for serum CXCL12 levels in distinguishing between the activity and remission of the disease.

DISCUSSION

RA is an immune-mediated disorder characterized by joint inflammation and damage, functional loss, and systemic features [19]. Despite innovations in RA biologic therapy, about half of patients get no benefit from these medications. Accordingly, discovering novel RA biomarkers as well as therapies is imperative [20]. The key role of chemokines in a variety of conditions, particularly autoimmune diseases, was demonstrated [21]. In Egyptian systemic lupus patients, CXCL12 was investigated [22], though this chemokine was not previously evaluated in Egyptians with RA.

The present study demonstrated considerably greater levels of serum CXCL12 in patients with RA than the control, which agreed with the study of Hansen et al. [15]. Peng et al. also reported that RA patients had over-expressed CXCL12 levels in synovial fluid and plasma than in osteoarthritis (OA) patients [13]. In addition, numerous studies detected increased levels of synovial CXCL12 in RA patients compared to controls [14, 23-25]. CXCL12 is primarily localized in the synovium's lining and endothelial layer [26]. Also, reduced CXCL12 gene promoter methylation explained the rise of CXCL12 in RA patients than OA group [27].

The assessment of RA activity is critical issue for monitoring therapeutic response and making the right clinical decisions in order to attain disease remission [28]. The current research detected significant relations between CXCL12 and DAS28- ESR, tender and swollen joints count, duration of morning stiffness, CRP, ESR, RF titer, anti-CCP level, and HAQ-DI. Moreover, there was a significant difference in serum CXCL12 among patients with different grades of disease activity being higher in those with highly active disease in comparison to those in remission. Our findings underline the importance of serum CXCL12 as an indicator of RA activity that was supported by the study of Peng et al. who reported significant relationship between serum CXCL12 and RF, CRP, ESR and DAS28 with greater levels of CXCL12 in highly active patients than those in remission and controls [13]. Furthermore, in a prior study involving RA patients treated with golimumab, a significant association was observed between DAS28-CRP and CXCL12 levels in synovial tissues [29]. In harmony, another study found that CXCL12 expression and CRP were significantly correlated [27]. However, the current results contrast those of Hansen et al., who found no association between all measures of ACR disease activity index and plasma CXCL12 [15].

Indeed, CXCL12 is a crucial player in perpetuation of inflammatory and destructive changes that characterize RA [30]. This chemokine has been described as an inducer of synovial neovascularization and the recruitment of macrophages and B and T lymphocytes into the synovium, thus leading to pannus formation [5, 31, 32]. CXCL12 triggers secretion of several cytokines, including TNF-α, IL-1, and IL-6 that have been recognized as essential mediators in the pathophysiology of RA [33]. Also, CXCL12 promotes Th17 cell migration, which in turn secretes IL-17. IL-17 has been shown to have a role in the augmentation of inflammation by inducing excess production of CXCL12 from synovial fibroblasts, which leads to positive feedback [7, 34]. IL-18, another inflammatory cytokine concerned with RA development, promotes CXCL12 upregulation in synovial fibroblasts via protein kinase C (PKC), phosphatidylinositol 3-kinase (PI3K), Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK) [35]. Down-regulation of CXCL12 in synovial fibroblasts was found to suppress development of RA [27]. Binding of CXCL12 to its receptors also stimulates the activity of Janus-activated kinase-signal transduction and activator of transcription (JAK-STAT) signaling, which was evidenced to participate in RA development [36]. CXCL12 is involved in erosive changes through promotion of osteoclastic activity, increasing expression of receptor activator of nuclear factor-kB ligand (RANKL) in T cells and synovial fibroblasts, and stimulating secretion of matrix metalloproteinases (MMPs) [7]. Interestingly, Joven et al. proposed the relation of the SDF-1 gene variant to the evolution of inflammatory and destructive processes associated with RA [37]. Additionally, CXCR4 blockers improved arthritis in an experimental arthritis model by blocking CXCL12-mediated angiogenesis [38, 39]. So, the importance of CXCL12 in RA activity measurement is supported.

In the current study, serum CXCL12 was considered a significant discriminator between RA cases and healthy subjects as well as active cases from those in remission. No prior investigations have determined the best cut off point of serum CXCL12 in identifying the RA cases from healthy control or to determine the disease activity. This is a main strength point in the current study; however it has to be confirmed in more research.

The current study's limitations were the limited number of participants and the absence of follow-up. Also, the synovial fluid level of CXCL12 was not investigated. Therefore, more prospective studies should be implemented to demonstrate the efficacy of CXCL12 in observing disease progression and therapeutic response.

In conclusion, serum CXCL12 could be an effective indicator for determination of RA activity.

Conclusions:

Cancer of the head and neck has become an urgent public health issue in Zagazig. Due to the high rates of tobacco use and HPV infection, screening programs and patient monitoring of various treatment modalities are crucial for the early diagnosis of HNC..

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To Cite :

Nasr, A., El-kady, B., Borg, A., Elmarghany, E. Serum level of CXCL12 in rheumatoid arthritis patients and its correlation with disease activity. Zagazig University Medical Journal, 2024; (739-747): -. doi: 10.21608/zumj.2023.238595.2916