Serum Levels of Soluble Fractalkine in Patients with Systemic Lupus Erythematosus

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ABSTRACT

Background*: Fractalkine (Fkn)/CX3CL1 which is a unique member of the CX3C chemokine subfamily, and expressed on inflamed endothelium appears to possess immunoregulatory properties that affect inflammatory/immune cell interactions and inflammatory responses at sites of inflammation.* ***Objective****: The purpose of the present study was to determine the Fractalkine/CX3CL1 level in SLE patients and correlates that level with indices of disease activity and damage, trying to disclose its role in the pathogenesis of SLE.* ***Methods****: The study was carried on forty SLE patients (classified into 15 active and 25 inactive by using clinical and the BILAG disease activity index assessment), thirty patients with rheumatoid arthritis (RA) as disease control group and twenty healthy as control group. Levels of soluble Fkn were measured by enzyme-linked immunosorbent assay. Expression of Fkn /CX3CL1 was quantified by real-time polymerase chain reaction.* ***Results****: Both serum sFkn levels and mRNA expression of Fkn /CX3CL1 were significantly higher in patients with SLE compared with RA patients and healthy controls ($P<0.05$) and were significantly higher in SLE patients with active disease than in those with inactive disease. Also, serum levels of sFkn were positively correlated with disease activity, organ damage, anti–double-stranded DNA (anti-dsDNA) antibody titers, anti-Sm antibody titers, immune complex C1q levels, anti-phospholipid, anti-RNP and ESR level and negatively correlated with total hemolytic complement activity (CH50).* ***Conclusion****: sFkn and CX3CL1 mRNA expression play crucial roles in the pathogenesis of SLE and that sFkn may serve as a serologic inflammatory marker of disease activity and organ damage.*

Key wards: *Soluble Fractalkine (sFkn); Fractalkine (Fkn)/CX3CL1; SLE; Disease activity.*

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multi-organ damage with infiltration and sequestration of various immune cells[(1)]. It is a connective tissue disease with evident formation of autoantibodies and immune complexes leads to activation of complement systems and subsequent inflammation[(2-4)]. SLE patients exhibit numerous aberrations in the immune system, comprising B cells, T cells, monocytes, and dendritic cells, resulting in B and T cell activation and consequent

autoantibodies production against a large variety of autoantigens [(5)]. Angiogenesis and microvascular endothelial injury play a role in the pathogenesis of SLE[(6)]. Moreover, SLE is characterized by an inflammatory immune response mediated, in part, by cytokines and chemokines produced by antigen presenting cells (APC) and other immune cells, contributing for disease development and progression[(7)]. The exact etiology still remains unclear; however defective clearance of apoptotic material and/or aberrant apoptosis, in combination with susceptible genetic background have been suggested to be involved in SLE development and progression[(8-10)].

Fractalkine (Fkn) (CX3CL1) is the unique member of the CX3C chemokine subfamily because it is synthesized as a transmembrane molecule consisting of an extracellular N-terminal domain (residues 1–76), a mucin-like stalk (residues 77–317), a transmembrane α helix (residues 318–336) and a short cytoplasmic tail (residues 337–373) [(11)]. In contrast to other chemokines, it exists in two forms, each mediating distinct biological actions [(11-13)]. The membrane-anchored protein, which is primarily expressed on the inflamed endothelium, serves as an adhesion protein promoting the retention of monocytes and T cells in inflamed tissue. The soluble form resembles more a conventional chemokine and strongly induces chemotaxis [(14)]. Fkn is expressed at very low levels by resting endothelial cells but undergoes marked upregulation following stimulation of the cells by cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1ß (IL-1ß) [(15)].

Fractalkine/CX3CL1 expressed on inflamed endothelium may play a role as a vascular gateway for cytotoxic effector cells (CX3CR1-expressing cells) by rapidly capturing them from the blood and promoting migration into tissue [(11)]. Indeed, investigations by several groups, have implicated CX3CL1 in a variety of inflammatory disorders, including glomerulonephritis, RA, systemic sclerosis and SLE [(16, 17)].

The purpose of the current study was to determine the Fractalkine / CX3CL1 level in SLE patients and correlates that level with indices of disease activity and damage, trying to disclose its role in the pathogenesis of SLE.

MATERIALS & METHODS

Forty SLE patients (36 females and 4 males with mean age of 28 ±11.6 years) who were fulfilling the American College of Rheumatology (ACR) Classification Criteria for SLE [(18)] were recruited for the study. Mean disease duration was 9 ±5.5 years. For disease activity in our patients mean BILAG global score was 12 ± 4.8. SLE patients were classified into two groups, active and inactive according to the BILAG

- Group 1 comprised 15 patients with active SLE (14 females and a male with mean age of 32 ±9.8 years).
- Group 2 comprised 25 patients with inactive SLE (22 females and 3 males with mean age of 27 ±10.6 years).

Disease control group comprised 30 patients with rheumatoid arthritis

(RA) (22 females and 8 males; with mean age of 38 ±15.7 years) who were fulfilling the American College of Rheumatology (ACR) Classification Criteria [19]. Healthy control group was established and comprised twenty healthy volunteers (18 female and 2 males with mean age of 30±12.5 years) who were comparable to patients in their age and gender and were clinically and laboratory free. Patients with a previous diagnosis of another connective tissue disorder which might associates SLE such as rheumatoid arthritis, primary Sjogren's syndrome, mixed connective tissue disease, systemic sclerosis, anti-phospholipid antibody syndrome or idiopathic inflammatory myositis were excluded from this study group. All human experiments were carried out in accordance with protocols approved by the Human Subjects Research Committee at our hospital. An informed consent was obtained for every subject participating in the study.

Clinical assessment:

Full clinical examination including thorough history taking was done for all patients. All the patients were subjected to disease activity measurement in the following manner:

- Overall clinical assessment and disease activity index of SLE patients: was done using the BILAG (British Isles Lupus Assessment Group) disease activity index [20].
- The Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index [21] was used to assess organ damage.

Laboratory tests:

Full blood count, ESR, CRP, and total hemolytic complement activity (CH50), immune complex (C1q). Auto-antibodies were screened at the base line visit and included each of the following: antinuclear antibody (ANA), anti-Ro, anti-La, anti-phospholipid (IgM, IgG) anti-Sm, anti-RNP, and anti-dsDNA. ANA was measured using immunofluorescence; antibodies to dsDNA were measured by ELISA or Farr assay. Testing for extractable nuclear antigens (anti-Ro, anti-La, anti-Sm and anti-RNP) was done by ELISA followed by a confirmatory immunoblot. Seropositivity was defined as one or more positive assays for that particular antibody measured at any point during a patient's disease course. Clinical laboratory tests were performed according to standard hospital laboratory procedures.

Soluble Fractalkine (sFkn) level was detected by ELISA Kits from R&D system, Minneapolis-MN, USA; Catalogue number DY365. Briefly, standards, samples and controls were pipetted into wells, pre-coated with monoclonal antibody specific for Fkn, any Fkn present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme linked polyclonal antibody specific for Fkn is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of Fkn bound in the first step. The reaction stopped with the addition of stop solution and the microtiter plate was then read at 450 nm wave length. The level of Fkn was

calculated from standard curve corresponding to the measured optical density. The results were expressed as pg/ml.

Expression of FKN/CX3CL1 mRNA by PCR:

RNA was extracted from PBMCs using RNA isolation kit (QI Aamp RNA Blood Mini Kit [Qiagen] Cat. no. 52304, according to manufacturer's instructions. The specificity of the *FKN/CX3CL1* amplification was confirmed by the observation of a uni-molecular dissociation curve and a single band on a 3% agarose gel electrophoresis.

Thereafter, RNA was reversed transcribed from 2.5 µg total RNA according to the manufacturer's instructions, using random hexamers (Invitrogen). cDNA was used for real-time PCR with the help of StepOne™ real-time PCR system (Applied Biosystems, Foster City, CA, USA).

The sequences of oligonucleotide primers used in the PCR for detection of *FKN* / CX3CL1 expression levels, were as follows: for human Fkn 5-GCT-GAG-GAA-CCC-ATCCAT (sense), 5-GAG-GCT-CTG-GTA-GGT-GAA-CA (antisense); for GAPDH sense: 5′-GAAGATGGTGATGGGATTTC-3′ and anti-sense: 5′-GAAGGTGAAGGTCGGAGT-3′.

Cycling conditions were as follows: *step 1*, 15 minutes at 95°C; *step 2*, 20 seconds at 94°C; *step 3*, 20 seconds at 60°C; and *step 4*, 20 seconds at 72°C, with repeat from *step 2* to *step 4* for 45 cycles. Data from the reaction were collected and analyzed. The relative copy numbers of gene expression were quantitated using the comparative threshold cycle (ct) method.

Statistical analysis:

Data was analyzed using Microsoft Excel 2007(Microsoft Corporation, NY, USA) and SPSS version 13 (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program. Parametric data was expressed as mean ± SD and nonparametric data was expressed as number and percentage. Student's unpaired "t" test was done to compare between groups. Pearson Correlation Coefficient "r" was done to correlate between different parameters among groups. The relationship between sFkn levels and the indicated parameters was evaluated using Spearman's rank correlation. P values less than 0.05 were considered significant.

RESULTS

(1) Serum sFkn (CX3CL1) levels by ELISA:

SLE patients (n = 40) had significantly raised plasma levels of CX3CL1 (mean ± SD 444.8 ±120.7 pg/ml) compared with RA patients (n = 30) (210.7 ± 59.7 pg/ml; P <0.05) and healthy controls (n= 20) (2.4 ± 1.2 pg/ml; P < 0.05). Furthermore, patients with active disease (n= 15) had significantly raised CX3CL1 levels (532.8 ±180.7 pg/ml) compared with the patients in inactivity (n= 25) (322.3 ±110.7 pg/ml) (P <0.05), while there is a significant increase in sFkn levels in inactive SLE patients when compared to RA patients and control group (P <0.05). Table (1) and figures (1) and (2) illustrate these results.

Table (1): Serum sFkn levels by ELISA in different studied groups

Group	Serum sFkn levels (pg/ml) Mean± SD	P
SLE (N = 40)	444.8 ±120.7	
RA (N=30)	210.7 ± 59.7	P <0.05
Healthy control (N =20)	2.4 ± 1.2	

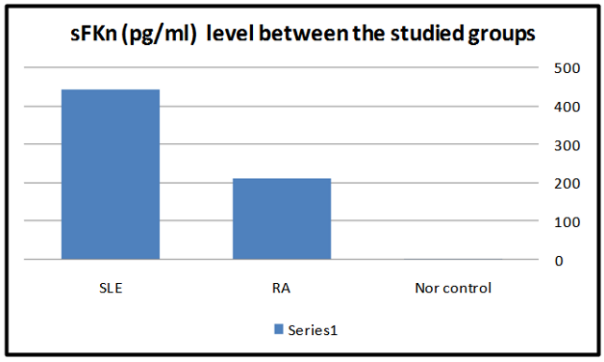

Figure (1): Comparison between studied groups for level of sFKN (pg/ml) by ELISA

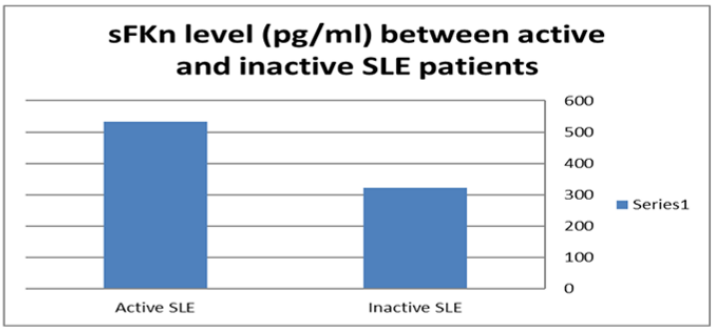

Figure (2): Comparison between active and inactive SLE patients for level of sFKN (pg/ml) by ELISA

(2) Expression of *FKN/CX3CL1* messenger RNA (mRNA):

Fkn (CX3CL1) mRNA expression is detected in statistically significant (P<0.05) level in SLE patients (0.44 ±0.17) compared to RA patients (0.27 ± 0.19) and healthy control group (0.19 ± 0.02). Moreover, patients with active SLE (n= 15) had significantly raised Fkn/ CX3CL1 levels (0.57 ±0.31) compared with the patients in inactivity (n= 25) (0.33 ±0.14) (P <0.05), while there is a significant increase in sFkn levels in inactive SLE patients when compared to RA patients and control group (P <0.05). Table 2 and figures 3, 4 and (5) illustrate these results.

Table (2): Fkn (CX3CL1) mRNA expression in different studied groups

Group	**Fkn levels** Mean± SD	**P**
SLE (N = 40)	0.44 ±0.17	
RA (N=30)	0.27 ± 0.19	P <0.05
Healthy control (N =20)	0.19 ± 0.02	

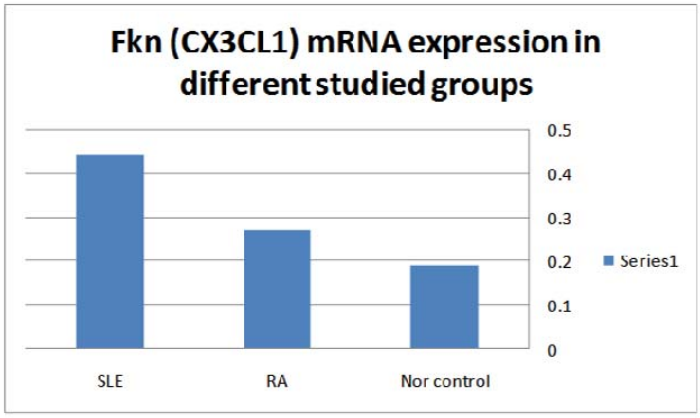

Figure (3): Comparison between studied groups for level of Fkn messenger RNA (mRNA)

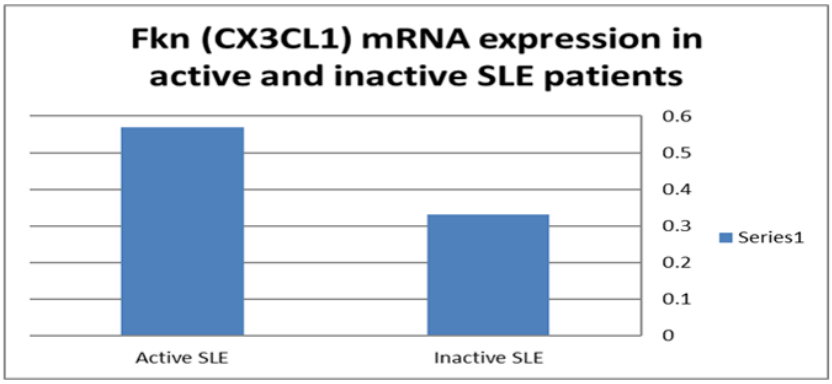

Figure (4): Comparison between active and inactive SLE patients for level of Fkn messenger RNA (mRNA).

Figure (5): represent amplification plot of FKN/CX3CL1 positive SLE cases and internal control

(3) Relationship between serum levels of sFkn (CX3CL1) and studied variables in SLE patients:

For the relationship between serum levels of sFkn (CX3CL1) and disease activity assessed by BILAG disease activity index and organ damage assessed by SLICC/ACR damage index and the related serologic parameters, the following results were obtained. Serum levels of sFkn were positively correlated with disease activity ($r = 0.331$, $P<0.05$), organ damage ($r=0.349$ $P<0.05$), anti-dsDNA antibody titers ($r = 0.345$, $P<0.05$), anti-Sm antibody titers ($r=0.311$, $P<0.05$), immune complex C1q levels ($r=0.301$, $P <0.05$), anti-phospholipid (IgM, IgG, $r = 0.321$, 0.319 respectively, $P<0.05$ for each) , anti-RNP ($r = 0.342$ $P <0.05$), ESR level ($r = 0.402$ $P <0.05$). However, sFkn serum levels were negatively correlated with CH50 ($r = 0.292$, $P < 0.05$). Table 3 illustrates these results.

Table (3): Correlation between sFkn level by ELISA and studied variables in SLE patients.

Variable	r	P value
BILAG activity index	0.331	P <0.05
SLICC/ACR damage index	0.349	P <0.05
ANA	0.190	P > 0.05
Anti-dsDNA	0.345	P <0.05
Anti-Sm	0.311	P <0.05
Anti RNP	0.342	P <0.05
Anti Ro	0.212	P > 0.05
Anti La	0.190	P > 0.05
Anti-phospholipid (IgM	0.321	P <0.05
Anti-phospholipid (IgG)	0.319	P <0.05
Total hemolytic complement activity (CH50)*	0.317	P <0.05
Immune complex (C1q)	0.301	P <0.05
ESR	0.402	P <0.05
CRP	0.180	P > 0.05

*Statistical significance: all are positive correlation with level of sFKN except total hemolytic complement activity (CH50) has a negative correlation.

DISCUSSION

In the current study, we show increased plasma levels of CX3CL1 either sFkn/CX3CL1 detected by ELISA or Fkn/CX3CL1 mRNA detected by PCR in SLE patients with particularly high levels of the ligand in those with active disease. This was shown after comparison of our SLE cohort with a group of disease RA controls, and normal healthy volunteers. Moreover, a positive correlation was detected between CX3CL1 and disease activity index by BILAG score and disease damage index by SLICC/ACR. Furthermore, a positive correlation was found also with laboratory immunological autoantibodies relating to disease activity like anti-dsDNA, anti-Sm, beside high ESR and immune complex (C1q). Of interest, other autoantibodies were found to have a positive correlation with CX3CL1 like anti-phospholipid (IgM, IgG), and anti RNP. Since these findings are unique, they need further work to declare the correlation between CX3CL1 like with other autoimmune rheumatological disorders linked to SLE, like mixed connective tissue disorder (for anti RNP) and antiphospholipid antibody syndrome (for anti-phospholipid antibodies).

A wide range of reports have published denoting levels of the chemokine fractalkine in patients with SLE. To our knowledge, all of these reports demonstrated elevated Fkn level either the soluble form detected in the serum by ELIZA, or Fkn mRNA expression by real-time PCR[16,17,22,23,]. Our results are in agreement with these findings. In 2010, **Li et al.,** suggested that a

Fkn/CX3CL1 antagonist may delay the progression of human SLE [24]. Also, **Abu-Zahab et al.,**[23] and **Yajima et al.,**[16] reported a positive correlation between levels of Fkn and SLE disease activity using SLE Disease Activity Index (SLEDAI) and organ damage assessed by SLICC/ACR damage index [16, 23]. Although we have used BILAG disease activity index for measurement of disease activity, it yields the same findings.

The pathological role of Fkn /CX3CL1 in rheumatic diseases has been discussed in many reports. **Jones et al.,** in their review stated that Fkn /CX3CL1 mediates the mechanism for leukocyte adhesion in a unique fashion [17]. The chemokine domain is presented at the top of the membrane-bound, mucin-like stalk, where it acts as an adhesion molecule making the association with proteoglycans and other adhesion molecules unnecessary. Interaction between Fkn /CX3CL1 and CX3CR1 can markedly enhance integrin affinity, which further facilitates extravasation of leukocytes during the initial tethering and trans- migration steps [17]. Fkn /CX3CL1 expression on inflamed endothelium along with the co-expression of intercellular adhesion molecule (ICAM)-1and vascular cell adhesion molecule (VCAM)-1, greatly enhances cell adhesion function by capturing CX3CR1-expressing cells from the blood and promoting migration into tissue [13]. Studies have suggested that Fkn /CX3CL1 expression at the site of inflammation can attract and activate natural killer (NK)cells, resulting in the consequent lysis of neighboring endothelial cells [26, 27]. Increased Fkn /CX3CL1, ICAM-1, andVCAM-1 expression on endothelial cell membranes can result from certain conditions such as viruses/bacteria, ischemia, or cytokine induction (IL-1, TNF-α, IL-6) [28]. The resulting expression of adhesion molecules and Fkn /CX3CL1 increases the adhesion and transmigration of NK cells between endothelial cells, causing inflammation.

In conclusion, we have reported increased plasma levels of Fkn / CX3CL1 in patients with SLE which was linked to disease activity and organ damage. Our results suggest that Fkn / CX3CL1 plays a role in the disease process and its pathogenesis in SLE, including inflammation and leukocyte adhesion. However, further studies are needed to determine the relative importance of Fkn/ CX3CL1compared with other chemokines in SLE, and to clarify its specific role in SLE and other linked disorders, which is distinct from its role in other inflammatory diseases.

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مستوى مادة الفراكتألكين في مصل الدم في مرضى الذئبة الحمراء

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كلية الطب- جامعة المنصورة

مادة الفراكتألكين هي مادة متفردة في نوعها من عائلة المحفزات الكيميائية و تعبر عن نفسها في الخلايا المبطنة للأوعية الدموية الملتهبة و التي يبدو أن لها خاصية التنظيم المناعي المؤثر على التفاعل الداخلي بين خلايا المناعة و الخلايا الملتهبة.

الهدف من هذه الدراسة هو تحديد مستوى مادة الفراكتألكين الذائبة في مصل الدم في مرضى الذئبة الحمراء و ربط ذلك بمؤشرات نشاط المرض محاولين الكشف عن دوره في نشوء المرض و ذلك باستخدام طريقة الاليزا في تحديد مستوى مادة الفراكتألكين الذائبة و التعبير الجيني مستخدما طريقة تفاعل التلمرة المتسلسل ، و أشارت النتائج إلى أن مستوى

مادة الفراكتألكين أعلى في مرضى الذئبة الحمراء عنها في مرضى الروماتويد المفصلي و مجموعة الضبط الصحية وكان الارتفاع ذو دلالة إحصائية. كذلك أعلى في مرضى الذئبة الحمراء النشط عنها في مرضى الذئبة الحمراء الغير نشط كذلك وجدت علاقة ارتباد ايجابية و ذات دلالة إحصائية لمستوي الفراكتألكين الذائب مع بعض دلالات نشاط المرض كمستوى الاجسام المضادة للحمض النووي مزدوح الفرعين في مصل الدم. و خلص إلى أن مادة الفراكتألكين تلعب دورا أساسيا في نشوء المرض و يمكن استخدامها كدلالة على نشاط المرض و درجة اتلافه لأجهزة الجسم.