IJKD KIDNEY DISEASES

Serum Levels of CXCL10 and Vitamin D in Patients with Lupus Nephritis

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Keyword. systemic lupus erythematosus, inflammatory biomarkers, vitamin D deficiency

Original Paper

Introduction. Kidney involvement is a hallmark of systemic lupus erythematosus (SLE) and evaluation of its inflammatory response is demanding. It was the aim of the present study to evaluate the levels of CXCL10 and vitamin D in serum samples of cases with active lupus nephritis (LN).
Methods. Fifty lupus patients were enrolled in our study, 25 patients had lupus nephritis and 25 patients were without evidence of LN. Thirty-nine healthy subjects were also participated as a control group. Complete biochemical and serological parameters were measured and their correlation with serum levels of vitamin D and CXCL10 were assessed in the studied groups.
Results. Serum levels of CXCL10 were significantly elevated ($P \leq 0.020$), while vitamin D were diminished in SLE group and active LN as compared with healthy controls and SLE patients without nephritis, respectively. CXCL10 correlated with SLE disease activity index (SLEDAI) and renal activity ($P < .05$), while vitamin D correlated with C3 and anti-dsDNA antibody ($P < .05$). Based on the receiver operator characteristic (ROC) curve analysis, CXCL10 and vitamin D levels were not better than conventional biomarkers for discriminating LN patients from non-nephritis SLE patients; however, they could differentiate most of SLE cases from healthy individuals with area under the curve (AUC) ≥ 0.703 ($P < .05$).
Conclusion. Results indicated the importance of elevated levels of CXCL10 and deficiency of vitamin D on the pathogenesis of active LN disease.

IJKD 2019;13:380-8
www.ijkd.org

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that its etiology is not precisely known as other autoimmune disorders.[1] The autoimmune characteristics of SLE induce local inflammation and tissue degradation; therefore, the disease may have a variety of manifestations depending on the involved organs. Kidney involvement in lupus is known as lupus nephritis (LN). About 35% of adults with SLE show the clinical manifestation of nephritis at the time of diagnosis and 50% to 60% of patients develop the nephritis over the first 10 years of onset of the disease.[2] Despite recent advances in LN treatment, 10% to 30% of patients have advanced kidney disease and require dialysis or organ transplantation.[3]

The pathogenesis of LN is multifactorial and the most important factor is the immune complexes accumulation in the kidney.[4] In normal conditions, the production of inflammatory cytokines and chemokines in the kidney is in a low level, but the amount of these factors increases sharply following

pathophysiologic conditions such as ischemia, exposure to toxins, or acute inflammation in the body.[5] Recent studies have shown an imbalance in the secretion of inflammatory factors from subtypes of T helper (Th) cells in SLE. IFN-γ is the main cytokine secreted by Th1 that is associated with the CXCL10. CXCL10 is a known chemokine that is secreted by endothelial cells, fibroblasts, and monocytes that stimulated by IFN-γ. Local production of CXCL10 at inflammatory sites is responsible for triggering IFN-γ secretion from Th1 cells. After binding to its receptor, CXCR3, CXCL10 stimulates the migration of T cells to the inflammatory sites and plays a pivotal role in decreasing angiogenesis.[6,7] It has been shown that expression and production of CXCL10 are elevated in most autoimmune diseases like lupus, multiple sclerosis, and rheumatoid arthritis.[8]

Urine level of CXCL10 is reported to be a reliable biomarker for identification[7,9,10] and monitoring LN improvement following the treatment[9] in a way that diminished level of CXCL10 has been reported in treated *versus* untreated SLE patients.[11]

A recent study indicated that vitamin D has a potential role in the treatment and/or prevention of SLE and its vasculoprotective role is due to the effect of this vitamin in reducing the CXCL10 secretion by macrophages, and modifying endothelial function and repair mechanism in SLE patients, independent of SLE activity.[12]

It seems CXCL10 marker, especially in the LN, exhibits considerable changes due to renal involvement and the immune system activation. It was the aim of this study to evaluate the levels of CXCL10 and vitamin D in the LN cases for assessing the activity of lupus nephritis, which would certainly affect subsequent therapies.

MATERIALS AND METHODS

Study Population

The present study was conducted on 25 lupus patients without nephritis and 25 lupus patients with LN (with proteinuria and confirmed by biopsy) who were diagnosed by nephrologists. Additionally, 39 subjects, matched for gender and age with the patient group, were studied as control group. It is worth noting that during the sampling period, all patients who were qualified for contribution in the study were selected based on the defined criteria. The patients with a recent active infection, history of concurrent systemic diseases such as diabetes, history of malignancy, and history of previous use of vitamin D were excluded. LN patients underwent kidney biopsy and classified according to chronicity index and activity index. The disease activity index was assessed based on the systemic lupus erythematosus disease activity index (SLEDAI) score. The study was approved by the Ethics Committee of the Tabriz University of Medical Sciences under ethical code IR.TBZMED.REC.1396.58. All participants have signed informed consent.

Clinical and Biochemical Measurements

After recording the clinical data, serum samples (4 mL) were collected from participants and conventional biochemistry parameters, serum creatinine, urine analysis, and 24h urinary proteins, anti-double-stranded DNA (dsDNA) antibody, antinuclear antibodies (ANA), and serum complements (C3, C4) were analyzed. Serum levels of vitamin D and CXCL10 were measured using sandwich enzyme-linked immunosorbent assay (ELISA).

Statistical Analysis

Data distribution was tested with the Kolmogorov–Smirnov test. Categorical variables were shown as frequency and percentage. Data were presented as means (± SD) / median-interquartile range (IRQ) for continuous variables. Independent Student's t-test or ANOVA and Mann–Whitney U or Kruskal-Wallis tests were employed for comparing the differences between groups. Spearman correlation coefficient was used to check associations between the variables. Statistical software SPSS version 17 (SPSS, Inc., USA) was used for data analysis. The significance level was considered to be $P < .05$.

RESULTS

Clinical, demographic, and some relevant laboratory data of the studied cases presented in Table 1. Three groups including non-nephritis SLE patients (n = 25), SLE cases with biopsy-proven LN (n = 25), and healthy subjects (n = 39) were enrolled in the present study. In terms of mean age and sex, there were no significant differences between groups ($P > .05$). Generally, SLE cases (10 males and 40 females) with a mean age of

Table 1. Demographic and Baseline Clinical Data

Characteristics/Groups	Non-nephritis SLE Patients	SLE Patients with Nephritis	*P*[a]
Number of cases	25	25	
Male/Female (N, %)	5 (20) / 20 (80)	5 (20) / 20 (80)	> .05
Age, mean ± SD (years)	38 ± 10.9	35.4 ± 11.7	> .05
C3 (mg/dL)	72.28 ± 24.0	22.32 ± 10.98	< .001
C4 (mg/dL) [b]	9 (8 to 10)	8 (6 to 10)	> .05
Anti-dsDNA [b]	9 (8 to 11)	16 (12 to 43)	< .05
Creatinine	0.87 ± 0.10	1.14 ± 0.22	< .001
Proteinuria (mg/24 h) [b]	125 (92 to 170)	1368 (926 to 2000)	< .001
SLEDAI [b]	6 (5.5 to 9)	10 (8 to 14)	< .05
Activity index ± SD	-	10.8 ± 3.0	-
Chronicity index [b]	-	2 (2 to 4)	-

anti-dsDNA, anti-double strand DNA; C3/4, complements 3/4; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index
The quantity data are expressed as mean ± SD.
[a]Lupus Nephritis Versus Non-lupus Nephritis
[b]Median, Interquartile Range (IRQ)

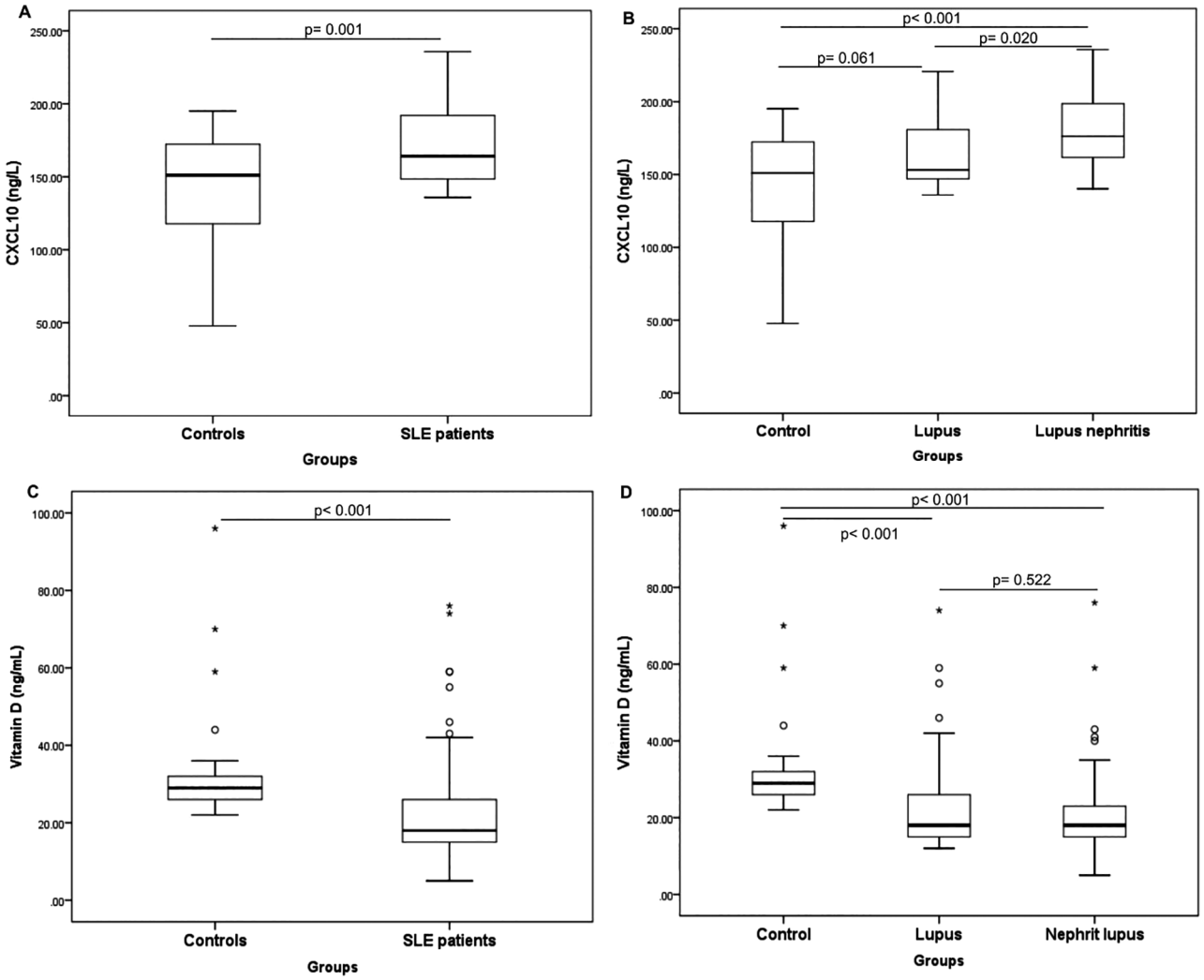

Figure 1. It determines serum level of CXCL10 and vitamin D in the studied groups [(serum levels of CXCL10 between (A) healthy controls and SLE patients, and (B) between SLE patients with and without nephritis), (serum levels of vitamin D between (C) healthy controls, and SLE patients and (D) between SLE patients with and without nephritis)].

36.7 ± 11.3 years included in this work. SLEDAI score was calculated in all SLE patients; 88% of them (n = 44) had an active disease (SLEDAI scores ≥ 6). There was statistically significant elevated SLEDAI score in LN group *versus* non-nephritis SLE group; median (IGR) of 10 (8 to 14) and 6 (5.5 to 9), respectively ($P < .05$). Furthermore, lower amount of the C3 ($P < .001$), and C4 ($P > .05$) were detected in LN group compared to SLE group. Moreover, elevated levels of serum creatinine (mean of 1.14 ± 0.22) and proteinuria (median of 1368) was seen in LN group. Additionally, 92% of cases with LN had active disease and 40% of them had hematuria (Table 1).

The results displayed that the SLE group had a significant higher level of serum CXCL10 (Median of 164.0 (148.5 to 192.0) than controls (Median of 151.0 (117.8 to 172.35), $P < .001$; Figure 1A). Additionally, level of CXCL10 significantly increased in LN [median 176.2 (161.7 to 198.6)] as compared to non-nephritis SLE patients [median 153.2 (147.0 to 180.8), $P < .001$; Figure 1B]. While, a decrease in serum levels of vitamin D was observed in SLE group [Median of 18.4 (15.8 to 26.7)] when compared to controls [Median of 29.6 (26.6 to 32.6), $P < .001$]; Figure 1C. Moreover, diminished levels of vitamin D was observed in LN group in comparison to controls ($P < .001$) and non-nephritis SLE patients ($P > 0.05$) (Figure 1D).

The organ involvement manifestations in LN patients were as follows: arthritis (60% of patients), leucopenia (24% of patients), rash (24% of patients), serositis (20% of patients), CNS (16% of patients), and thrombocytopenia (8% of patients). The results exhibited that the incidence of hematuria and rash was significantly different in the SLE groups ($P < .05$). Table 2 indicates levels of CXCL10 and vitamin D in SLE patients that are grouped based on clinical manifestations. Results showed that kidney, skin, and arthritis involvement were most common in

Table 2. Comparison of Serum Levels of CXCL10 and Vitamin D Based on Organ Involvement in SLE Patients (n = 50)

Manifestations	Normal Organ	Organ Involvement	*P*[a]
CNS			
n (%)	45 (90)	5 (10)	
CXCL10 (ng/L)	163.30 (148.50 to 183)	210.70 (192 to 243)	> .05
VitD (ng/mL)	19.40 (15.90 to 33.20)	13.90 (10.7 to 16.6)	< .05
Arthritis			
n (%)	24 (48)	26 (52)	
CXCL10 (ng/L)	165.8 (157 to 192)	163.35 (147 to 192)	> .05
VitD (ng/mL)	21.8 (15.75 to 40.85)	18.15 (16 to 23)	> .05
Serositis			
n (%)	42 (84)	8 (16)	
CXCL10 (ng/L)	164.05 (148.5 to 186.3)	182.30 (149.6 to 208.5)	> .05
VitD (ng/mL)	19.95 (15.8 to 33.2)	16.90 (14.85 to 20.25)	> .05
Thrombocytopenia			
n (%)	44 (88)	6 (12)	
CXCL10 (ng/L)	165.80 (151.30 to 194.9)	152.7 (140.6 to 183.5)	> .05
VitD (ng/mL)	18.4 (15.8 to 34.4)	18.75 (10.7 to 23.4)	> .05
Kidney			
n (%)	25 (50)	25 (50)	
CXCL10 (ng/L)	153.2 (147.0 to 180.8)	176.2 (161.7 to 198.6)	< .05
VitD (ng/mL)	18.5 (15.8 to 26.7)	18.3 (15.8 to 23.8)	> .05
Leucopenia			
n (%)	38 (76)	12 (24)	
CXCL10 (ng/L)	167.4 (153.2 to 191)	156.85 (145.5 to 194.9)	> .05
VitD (ng/mL)	18.4 (15.8 to 26.7)	20.4 (15.2 to 32.1)	> .05
Skin			
n (%)	24	26	
CXCL10 (ng/L)	166.9 (157.0 to 194.9)	158.8 (147.7 to 183.5)	> .05
VitD (ng/mL)	18.8 (15.6 to 25.2)	18.4 (15.8 to 33.2)	> .05

Variables were reported as Median (IRQ).
VitD, vitamin D; CNS, central nervous system
[a]*P* values indicate comparison between groups (Mann-Whitney t-test).

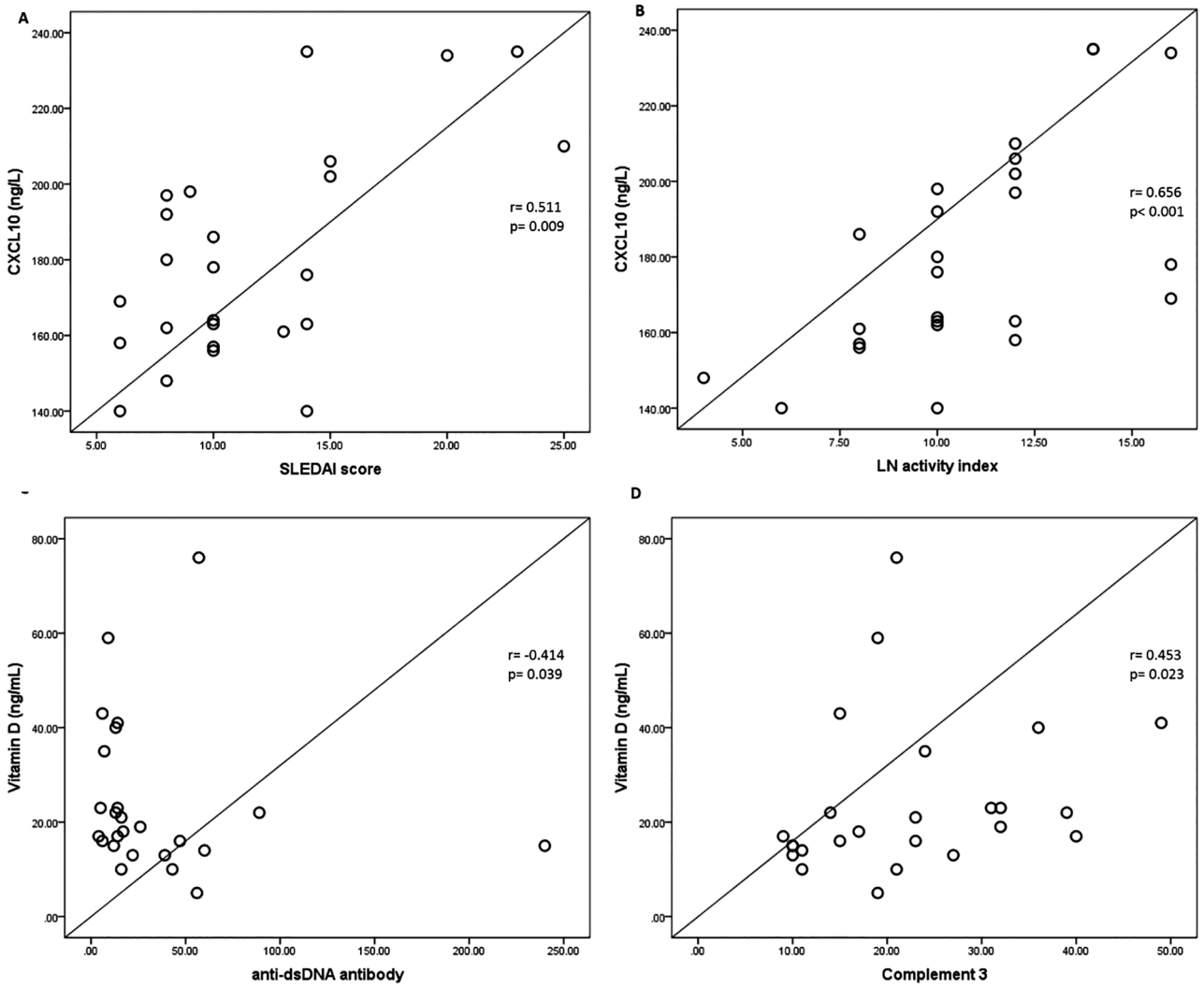

Figure 2. It shows Correlation of serum CXCL10 and vitamin D with clinical parameters [(correlation between serum CXCL10 and (A) SLEDAI and (B) LN activity index) (association of vitamin D and (C) anti-double strand DNA antibodies and (D) complement in SLE patients with nephritis)].

our patients; an increase in CXCL10 levels and a decrease in vitamin D levels detected in cases with different organ involvements. However, no significant differences were detected in levels of the serum factors in patients with and without different organ involvement, except for CNS and kidney.

Figure 2 and Table 3 demonstrate association between the studied variables among lupus groups with and without nephritis, respectively. In LN group, there was a positive association between serum CXCL10 and SLEDAI (r = 0.511, $P < .05$), and renal activity score (r = 0.656, $P < .001$). Vitamin D associated with C3 (r = 0.453, $P < .05$) and anti-dsDNA antibody (r = -0.414, $P < .05$). In non-LN group, a positive association was observed between CXCL10 and vitamin D and SLEDAI, anti-dsDNA antibody, and proteinuria ($P < .05$), significantly. Although there were correlations between CXCL10 and vitamin D and other variables, there were not statistically significant. Moreover, between vitamin D and CXCL10 (r = -0.090, $P > .05$) no association was detected.

ROC analysis indicated that serum levels of CXCL10 (AUC = 0.703) and vitamin D (AUC = 0.769) could distinguish SLE cases from healthy controls with respectively, 99 and 74% sensitivity; and 41 and 89% specificity. However, each parameter alone or their combination failed to differentiate most of LN patients from SLE patients (Table 4).

DISCUSSION

Recently, a considerable increase has brought

Table 3. Association Between Serum CXCL10 (ng/mL) and Vitamin D with Various Parameters in the SLE Patients With or Without Nephritis

Groups	SEL Without Nephritis		SLE With Nephritis	
Variable	CXCL10	Vitamin D	CXCL10	Vitamin D
Age	r = -0.091 *P* > .05	r = 0.124 *P* > .05	r = 0.145 *P* > .05	r = -0.372 *P* > .05
Gender	r = 0.042 *P* > .05	r = 0.042 *P* > .05	r = -0.361 *P* > .05	r = -0.333 *P* > .05
SLEDAI	r = 0.399* *P* < .05	r = 0.552* *P* < .05	r = 0.511* *P* < .05	r = -0.353 *P* > .05
Proteinuria	r = 0.526* *P* < .05	r = 0.425* *P* < .05	r = 0.230 *P* > .05	r = -0.392 *P* > .05
Hematuria	- -	- -	r = 0.192 *P* > .05	r = 0.017 *P* > .05
C3	r = 0.172 *P* > .05	r = -0.078 *P* > .05	r = -0.007 *P* > .05	r = 0.453* *P* < .05
C4	r = 0.083 *P* > .05	r = -0.177 *P* > .05	r = -0.007 *P* > .05	r = -0.069 *P* > .05
anti-dsDNA	r = 0.413* *P* < .05	r = 0.604* *P* < .05	r = 0.089 *P* > .05	r = -0.414* *P* < .05
Serum Creatinine	r = 0.218 *P* > .05	r = -0.031 *P* > .05	r = 0.199 *P* > .05	r = -0.227 *P* > .05
Activity Index	- -	- -	r = 0.656* *P* < .001	r = -0.141 *P* > .05
Chronicity Index	-	-	r = -0.071 *P* > .05	r = -0.063 *P* > .05
CNS	r = 0.255 *P* > .05	r = 0.113 *P* > .05	r = 0.287 *P* > .05	r = -0.499* *P* < .05
Rush	r = 0.028 *P* > .05	r = -0.173 *P* > .05	r = 0.065 *P* > .05	r = 0.091 *P* > .05
Arteritis	r = -0.029 *P* > .05	r = -0.029 *P* > .05	r = 0.079 *P* > .05	r = -0.283 *P* > .05
Leucopenia	r = -0.247 *P* > .05	r = -0.097 *P* > .05	r = 0.00 *P* > .05	r = 0.110 *P* > .05
Serositis	r = -0.324 *P* > .05	r = 0.017 *P* > .05	r = 0.388 *P* > .05	r = -0.250 *P* > .05
Thrombocytopenia	r = -0.008 *P* > .05	r = 0.030 *P* > .05	r = -0.388 *P* > .05	r = -0.460* *P* < .05

r, Spearman's rho correlation coefficient; anti-dsDNA, anti–double-stranded DNA; C3/4, complements 3/4; SLEDAI, systemic lupus erythematosus disease activity index

Table 4. ROC Analysis of CXCL10 and Vitamin D in Prediction of SLE Patients and Nephritis

Groups/Parameters	AUC (95% CI)	Youden Index	Associated Criterion	Sensitivity	Specificity	*P*
SLE patients from controls						
CXCL10	0.70 (0.59 - 0.81)	0.41	> 134.8	99 (92.9 - 100.0)	41 (25.6 - 57.9)	< .05
Vitamin D	0.77 (0.66 - 0.88)	0.64	≤ 24	74 (59.7 - 85.4)	89.7 (75.8 - 97.1)	< .001
CXCL10 + Vitamin D	0.73 (0.62 - 0.83)	0.40	0.39			< .05
LN patients from non-nephritis SLE patients						
CXCL10	0.69 (0.54 - 0.84)	0.40	> 153.2	88.0 (68.8 - 97.5)	52.0 (31.3 - 72.2)	< .05
Vitamin D	0.55 (0.39 - 0.71)	0.16	≤ 14.5	24.0 (9.4 - 45.1)	92.0 (74.0 - 99.0)	> .05
CXCL10 + Vitamin D	0.69 (0.54 - 0.84)					< .05

AUC, area under the curve; LN, lupus nephritis

in the detection of markers to assess kidney involvement in lupus. Many researchers studied the levels of various factors in urine and serum samples of cases with SLE, such as different types of cytokines and chemokines.[7,9,10,13] CXCL10 is secreted by endothelial cells that is stimulated with IFN-γ and participates in inflammatory, infectious, and autoimmune diseases.[14]

The results of our study indicated a significant rise in CXCL10 levels and a reduction in vitamin D levels in SLE group when compared to healthy group. Likewise, a significant difference in the levels of CXCL10 and vitamin D were seen in the SLE with nephritis group compared to the SLE and healthy subjects, a higher level of CXCL10 but lower vitamin D level were observed in LN group ($P < .001$). However, no significant difference was observed between vitamin D level in LN and non-LN groups.

Growing evidence suggests that CXCL10 levels are increased in the serum, urine, and the tissue samples of SLE cases[7] and this factor can be contributed to the pathogenic manifestations of SLE. El-Gohary *et al.* concluded that increased urine and serum levels of CXCL10 could be reliable biomarkers for assessing SLE activity (AUC = 0.753) compared to conventional markers. However, it could not differentiate LN from SLE without nephritis.[7] In contrast, recent studies examined urinary chemokine profiles in LN cases and demonstrated a good diagnostic value of CXCL10 in recognition of active disease.[10,15] However, the studied biomarkers in these reports were not better than proteinuria in distinguishing active LN.[10]

Similar to previous studies mainly performed on urine samples,[10,13] we found a noticeable increase in the CXCL10 level in cases with active LN. Marie *et al.* reported significantly higher urinary CXCL10 level as a marker in LN patients than those without LN. This study also displayed a significant relationship between CXCL10 levels and lupus activity, 24-hour urine protein levels, and renal involvement severity. This study counted the CXCL10 as a sensitive non-invasive marker specific in assessing LN.[13] As can be seen, these results are consistent with our research, except for no significant association detected between CXCL10 and proteinuria. It has also been revealed that serum and urinary CXCL10 level are useful marker of LN; but, only its urine level is indicative of renal activity. However, based on the ROC analysis, CXCL10 levels in both samples were not better than conventional biomarkers.[9] Likewise, in our study, serum levels of CXCL10 were significantly elevated in LN group, 92% of which had active nephritis and its level was not a reliable biomarker for differentiating LN patients from SLE patients (AUC = 0.691). The results of most studies are consistent with the findings of our study. Perhaps this indicates the importance and impact of CXCL10 in autoimmune and inflammatory SLE disease processes.

Recent studies suggest that in addition to the classic effects of vitamin D such as the role in calcium, phosphate, and metabolic homeostasis, it applies its significant effect on the immune system, the nervous system, and cardiovascular diseases (CVDs).[16] Vitamin D modulates the immune responses by preventing B cell proliferation, autoantibody production, T cell activation; therefore, it inhibits the innate and adaptive immune cells function. Moreover, vitamin D declines the production of IL-2, INF-γ, IL-12, and CXCL10 and increases production of IL-10.[17] Evidence supported that vitamin D deficiency acts both as a potential risk factor for SLE development[18] and a booster of disease severity and activity.[19,20] Therefore, vitamin D presents a potential function in the treatment and/or prevention of SLE and SLE-related manifestations such as CVD, fatigue, and skin rashes or photosensitivity.[12,20]

In some diseases, such as tuberculosis (TB), it has been displayed that supplementation with active vitamin D can reduce the inflammation, and inflammatory cytokines especially CXCL10, in the disease. This effect is associated with inhibiting IFN-γ secretion due to the impact of vitamin D on the CXCL10 in macrophages. It has even been concluded that the analysis of the CXCL10 levels provides a useful marker in the follow up of treatment response in these patients.[21] It is suggested that stimulation of vitamin D receptors reduces the inflammatory response of T helpers and the secretion of inflammatory factors such as IFN-γ and CXCL10.[22]

Kamen *et al.* examined the role of vitamin D in SLE cases. The results displayed that the serum levels of vitamin D were lower in the SLE patients than in the healthy subjects. Furthermore, SLE patients who had low levels of vitamin D had kidney problems.[18] Likewise, in our study, the serum levels of vitamin D in SLE patients were lower than those in healthy subjects and its level even more reduced in LN patients compared with other cases. Therefore, vitamin D deficiency should be considered intensely in SLE patients with nephritis. Serum levels of vitamin D could

differentiate SLE patients from controls; however, it failed to differentiate LN patients from other SLE patients (AUC = 0.553). The combination of CXCL10 and vitamin D presented a weak value in distinguishing patients with LN (AUC = 0.691).

We are aware of the limitations of our study; our study is a cross-sectional rather than a longitudinal one and it has a limited number of patients. Further longitudinal studies may be required to judge the roles of CXCL10 and vitamin D as a biomarker for prediction and following up patients with LN.

Based on the results, it can be concluded that the increased CXCL10 levels and decreased vitamin D levels can be symptoms of the lupus nephritis, they are linked with SLE disease activity in general and renal involvement in particular. Hereby the necessary measurements can be taken in the diagnosis and treatments.

ACKNOWLEDGEMENTS

The authors like to acknowledge the Research Center for Connective Tissue Diseases at Tabriz University of Medical Sciences (Tabriz, Iran) for the financial supports. They also thank all the patients for their participation in this research.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHORS CONTRIBUTIONS

Nakhjavani took responsibility for the integrity of the data and the accuracy of the data analysis. Study design and selection and treatment of patients were done by Nakhjavani and Abediazar. Interpretation of data was done by Ghorbanihaghjo. Statistical analysis was performed by Zununi Vahed. Abediazar and Zununi Vahed were contributed in preparing the manuscript.

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Received March 2019
Revised July 2019
Accepted September 2019