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Serum tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) and IL-17 levels are associated with disease activity in systemic lupus erythematosus patients with and without nephritis

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ABSTRACT

Introduction: Lupus nephritis (LN) is one of the most severe signs of systemic lupus erythematosus (SLE) and rapid diagnosis of kidney damage remains an important concern for LN.
Objectives: The aim of this study was to investigate the association of the serum levels of tumor necrosis factor-like weak inducer of apoptosis (TWEAK) and interleukin 17 (IL-17) with SLE severity, renal involvement, and other clinical manifestations in lupus patients.
Patients and Methods: In order to determine a better biomarker for the detection of renal damage, this study evaluated the ability of serum TWEAK (sTWEAK) and IL-17 in lupus patients with (n = 25) and without (n = 25) nephritis and healthy controls (n = 39). Moreover, it compared the levels of these cytokines with disease activity and chronicity as well as traditional serum markers including complement C3 and C4, creatinine, and proteinuria in lupus patients.
Results: Increased levels of sTWEAK and IL-17 were observed in SLE and LN groups compared to healthy controls and non-LN groups, respectively. Significant positive associations were observed between serum TWEAK and IL-17 levels and systemic lupus erythematosus disease activity index (SLEDAI), proteinuria, nephritis activity index, and some clinical manifestations ($P < 0.05$). Discriminating the ability of the studied cytokines were not better than the utility of any markers individually.
Conclusion: The serum levels of TWEAK and IL-17 in the SLE and LN groups were significantly higher than the control group and both markers were indicative of the renal disease severity; therefore, they could possibly indicate renal involvement in the lupus patients.

Implication for health policy/practice/research/medical education:
A reliable marker that can reveal the renal disease activity in lupus patients is desirable. In the present study, we evaluated the diagnostic values of serum tumor necrosis factor-like weak inducer of apoptosis (TWEAK) and IL-17 in serum samples of lupus patients with and without nephritis and healthy controls.
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Introduction

Lupus nephritis (LN) is one of the most severe signs of systemic lupus erythematosus (SLE), a complex inflammatory autoimmune disease, which leads to morbidity and mortality of patients. In spite of improvement in the treatment and survival rates of LN patients, its prognosis remains inacceptable. The prognosis of LN demands developing novel approaches with high sensitivity and specificity for the onset or relapse of kidney disease activity; consequently, permitting initiation of management plans at an earlier and proper time (1). Late LN diagnosis associates with a higher incidence of kidney deficiency and development of end-stage renal disease (ESRD), emphasizing the significance of early diagnosis. For these reasons, the identification of novel biomarkers is clearly needed.

Tumor necrosis factor-like weak inducer of apoptosis (TWEAK), is a member of TNF-ligand superfamily (2,

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3) and a multifunctional cytokine in kidney injury which is produced by monocytes and macrophages. TWEAK is involved in tissue repair and regeneration (4). TNF-like weak inducer of apoptosis by persistent activation of the NF-κB pathway, can contribute to autoimmune diseases (5). Moreover, TWEAK up-regulates other chemokines, cytokines, and pro-inflammatory mediators that are involved in LN (6). Furthermore, it increases the initiation of apoptosis (2) and activates TGF-β in renal proximal tubule cells (7). The biological activity of TWEAK is mediated through its receptor, fibroblast growth factor-inducible 14 (Fn14) (8). The TWEAK-Fn14 pathway activates the NF-κB signaling pathway to result in inflammation, cell proliferation, angiogenesis, and apoptosis (9). Moreover, TWEAK-Fn14 signaling is associated with the pathogenesis of renal damage and LN (8,10) since it is involved in numerous processes that trigger LN such as inflammation, mesangial cell proliferation, vascular activation, kidney cell death, and fibrosis (8, 11). Based on animal models, TWEAK has also a regulatory role in type I IFN pathway in LN (10). It is essential to note that TWEAK regulates different urinary cytokines and chemokines (MCP-1, IL-6, and IP-10) that are associated with the disease activity. Being involved in the inflammatory cascade, TWEAK is an attractive mediator that can be considered as a potential biomarker and a promising predictor of flare in LN.

Interleukin-17 (IL-17), a pro-inflammatory cytokine, is produced by T cells (T helper, γδT, and Th17 cells) (12, 13). The number of $CD4^+$ effector T cells that secret IL-17 are higher in SLE patients and its plasma level is associated with disease activity in SLE patients without nephritis (14, 15). In LN, the IL-17 level, is higher in active diseases in comparison to remission and it is associated with level of anti-dsDNA and proteinuria (16). Additionally, in glomeruli, the expression of IL-17 is increased in diffuse proliferative diseases and correlated with the histological activity index in comparison to healthy kidneys (17).

Objectives

The results of recent studies indicate the important role of IL-17 and TWEAK in the pathogenesis of inflammatory and autoimmune diseases, such as rheumatoid arthritis and lupus. Nevertheless, no study has so far been conducted to examine these two factors simultaneously as well as their correlation with each other and with the illness severity in the LN patient. Therefore, the aim of this study was to investigate the association of the serum levels of TWEAK and IL-17 with SLE severity, renal involvement, and other clinical manifestations in lupus patients.

Patients and Methods

Study population

The cross-sectional study included 50 SLE patients from the Imam-Reza hospital, Tabriz, Iran, consisting of 25 LN patients with active renal disease at the time of the visit and 25 non-LN SLE patients. LN cases were defined as SLE patients with renal involvement based on clinical manifestation and renal biopsies. Non-LN SLE cases were defined as SLE patients without any signs of recent and previous renal involvement. Moreover, 39 healthy individuals with no known history of kidney or autoimmune disease were recruited. An informed consent was obtained from all patients enrolled in the present study. Cases were collected within one year and met the SLE diagnostic criteria according to the American College of Rheumatology. Cases with active infection at the time of sampling, overlap syndrome, any other glomerulopathy, diabetes mellitus, history of malignancies, urinary tract infection, and those with ESRD under dialysis or renal replacement therapy were excluded.

Clinical and laboratory measurements

On the day of the sampling, the information about patient's demographic characteristics, medications, and disease activity was recorded. For each patient, fresh blood sample (4 mL) was collected. Sera were frozen after collection (within 2 hours) and stored at −80°C until further analysis. Serum creatinine and BUN levels, some biochemical parameters, complement (C3 and C4), antinuclear antibodies (ANA), anti-dsDNA antibody (anti-dsDNA), and the amount of proteinuria in 24-hour urine samples were assessed. Serum levels of TWEAK and IL-17 were determined by the enzyme-linked immunosorbent assay (ELISA) based on the manufacturer's instructions (ZellBio GmbH, Cat No: ZB-138223c-H9648, Germany). Plates were read at 450 nm. All measurements were made in triplicate.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of the Tabriz University of Medical Sciences, Tabriz, Iran (Ethical code: IR.TBZMED.REC.1396.599) and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The protocol of the study was clarified to all participants and written informed consent was achieved from the patients. The study was extracted from a residency thesis of Dr. Niloofar Esmaeili at Tabriz University of Medical Sciences, Tabriz, Iran (Research code; 58856).

Statistical analysis

Data were given as mean ± SD or median with interquartile range (IQR) for normally and non-normally distributed variables, respectively. Since the data were not normally distributed, the data therefore were expressed as the median and IQR and the differences between the groups were analyzed by the Mann–Whitney U and Kruskal-Wallis tests. Comparisons of categorical variables

were conducted using Chi-square testing. Correlations were performed using the Spearman's rank correlation coefficient to test correlations between the variables. Statistical analysis was performed using SPSS statistical software, version 16.0 (SPSS, Chicago, IL). $P < 0.05$ was considered significant.

Results

Patient characteristics

The demographic characteristics of the studied groups are presented in Table 1. All 50 SLE patients with a mean of 36.7 ± 11 years (male/female = 10/40) were included in the present study. Moreover, the control group included 39 age/gender matched healthy subjects with a mean age of 38.4 ± 9.7 years old. In all groups, more than 80% of the individuals were women. The LN group had a mean age of 35.4 ± 11.7 years old. Most of the studied SLE cases (88%) had an active disease (SLEDAI scores ≥ 6). Urine proteinuria (24 hours) >500 mg/d was defined as positive for proteinuria. Significantly, higher proteinuria [Median (IGR) of 1368 mg/d (926 to 2000 mg/d) versus 125 mg/d (92-170 mg/d)], and SLEDAI scores [Median (IGR) of 10 (8-14) versus 6 (5.5-9)] and lower levels of the complement C3 [Median (IGR) of 22.32 ±10.98 mg/dL versus 72.28±24.0 mg/dL] were observed in LN group compared to non-LN patients, $P \leq 0.001$ (Table 1).

Systemic organ involvements

Skin disease (52%), articular involvement (52%), and renal disease (50%) were the most common manifestations of the SLE patients. Twenty-four percent of SLE patients had leucopenia, 16% had a prevalence of serositis, 12% had thrombocytopenia, and 10% had Central nervous system (CNS) involvement. The renal involvement of SLE patients was diagnosed at the time of sampling and confirmed histologically. Patients with LN had a higher prevalence of serositis (20% versus 12%, $P = 0.700$), hematuria (40% versus 0%, $P = 0.001$), and CNS involvement (16% versus 4%, $P = 0.350$) than non-LN patients (Table 1).

Serum levels of TWEAK and IL-17 in different groups

As shown in Figure 1A, a higher serum level of TWEAK was observed in the SLE group (with or without LN) as compared to controls [Median (IQR) = 69.0 (64.8-78.3) versus 65.2 (53.3-70.5), $P<0001$]. Its level was even significantly higher in LN group in comparison to non-LN group [Median (IQR) = 76.40 (67.9-83.50) versus 66.7 (63.3-69.9), $P = 0.002$] (Figure 1B). Moreover, the levels of serum IL-17 were increased in all SLE cases [Median (IQR) = 23.8 (21.0-27.3) versus 21.4 (20.5-24.5), $P = 0.004$] (Figure 1C) and patients with LN [Median (IQR) = 25.2 (21.22-30.6), $P =0.077$] (Figure 1D) as compared to controls and those without LN, respectively.

Based on organ involvement, levels of sTWEAK and IL-17 in the SLE patients are presented in Table 2. Medians of sTWAEK increased significantly in SLE patients with neurological ($P = 0.001$) and skin ($P = 0.008$) involvement. Likewise, levels of IL-17 were significantly higher in patients with CNS involvement ($P = 0.001$) and serositis ($P = 0.004$) when compared to those with normal organs. Increased levels of the mentioned cytokines were observed in patients with other clinical manifestations including arteritis, thrombocytopenia, serositis, and leucopenia, however, they were not statistically significant when compared to normal organs ($P > 0.05$).

Correlations of TWEAK and IL-17 and traditional parameters

There was a significant internal correlation between serum levels of TWEAK with IL-17 in all SLE patients ($r = 471$, $P = 0.018$) and in LN patients ($r = 0.471$, $P = 0.018$). In LN group, there was a significant positive association between serum TWEAK and IL-17 levels with SLEDAI ($r = 0.513$, $P = 0.009$ and $r = 0.883$, $P <0.001$ respectively) and with level of proteinuria ($r = 0.668$, $P <0.001$ and $r = 0.461$, $P = 0.020$ respectively) (Table 3). More importantly, both sTWEAK ($r = 0.491$, $P = 0.013$) and IL-17 ($r = 0.463$, $P = 0.020$) markers associated with nephritis activity index, while only sTWEAK correlated with chronicity index ($r = 0.482$,

Table 1. Demographic and baseline clinical data

Characteristics/Groups	Non-LN group (n=25)	LN group (n=25)	*P* value[a]
Female (No., %)	20 (80)	20 (80)	1
Age, mean ± SD (y)	38 ± 10.9	35.4 ± 11.7	0.429
C3 (mg/dL)	72.28±24.0	22.32 ±10.98	< 0.001
C4 (mg/dL)[b]	9 (8 to 10)	6 to 10)8(	0.136
Anti-dsDNA[b]	9 (8 to 11)	16 (12 to 43)	0.002
Creatinine(mg/dL)	0.87 ±0.10	1.14 ±0.22	< 0.001
Proteinuria (mg/24 h)[b]	125 (92 to 170)	1368 (926 to 2000)	< 0.001
SLEDAI[b]	6 (5.5 to 9)	10 (8 to 14)	0.001
Activity index ±SD	-	10.8±3.0	-
Chronicity index[b]	-	2 (2 to 4)	-

Abbreviations: Anti-dsDNA, anti-double strand DNA; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index; C3/C4, complement components.
The quantity data are expressed as mean ± SD.
[a] Lupus nephritis versus non-lupus nephritis; [b] Median, Interquartile Range (IRQ).

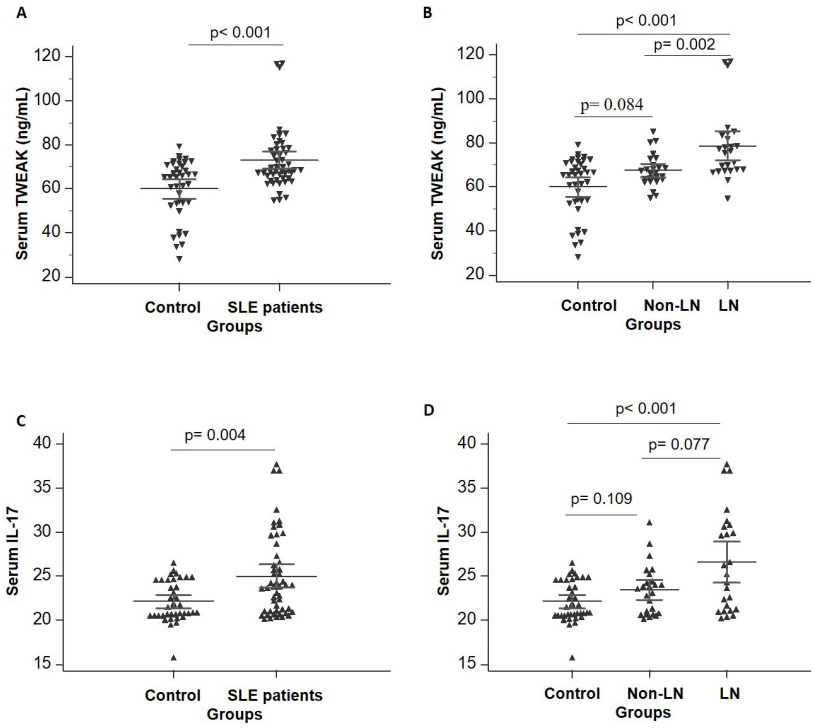

Figure 1. Serum level of TWEAK and IL-17 in the studied groups. (A,B) Serum levels of TWEAK between healthy and SLE groups with and without nephritis and (C,D) Serum levels of IL-17 between healthy and SLE groups with and without nephritis. Values are the mean± standard deviation. SLE; systemic lupus erythematosus.

0.015) and serum creatinine levels (r = 0.483, P = 0.014) in LN group. Additionally, statistically significant positive correlations exited between IL-17 and SLEDAI (r= 0.675, P < 0.001), C4 (r = 0.404, P = 0.045), and ANA (r= 0.461, P = 0.02) in non-LN patients. Similarly, serum TWEAK was correlated with SLEDI (r = 0.666, P < 0.001) and serum ANA levels (r = 0.444, P = 0.026) in non-LN SLE patients. Correlations between serum levels of TWEAK and IL-17 and clinical manifestations of the SLE cases are listed in Table 3.

Receiver operating characteristic curves analysis

Receiver operating characteristic (ROC) curves for serum TWEAK and IL-17 were calculated for distinguishing SLE patients from healthy controls and also SLE patients with LN from those with non-renal involvement. The diagnostic performance of IL-17 and sTWEAK presented lower sensitivity and specificity (Table 4). Receiver operating characteristic analysis indicated that serum levels of TWEAK (area under the curve (AUC) = 0.728) with 90% sensitivity and 46.15% specificity and IL-17 (AUC = 0.681) with 34% sensitivity and 97.44% specificity could discriminate SLE patients from healthy controls. However, each parameter alone or their combination failed to differentiate most of LN patients from SLE patients with both high sensitivity and specificity (Table 4).

Discussion

Assessing renal involvement has become an important part of LN patients' evaluation. In the present study, we revealed that high levels of serum TWEAK and IL-17 were correlated with SLEDAI, serum creatinine, abnormal

Table 2. Levels of serum TWEAK and IL-17 based on organ involvement in the SLE patients

Serum factors	TWEAK			IL-17		
Organ (N)	Not-involved	Involved	P value[a]	Not-involved	Involved	P value[a]
CNS (45/5)	68.0 (64.5-76.4)	115.9 (89.9-116.8)	0.001	23.6 (20.9-25.6)	32.6 (31.1-90.6)	0.001
Rash (24/26)	75.8 (67.2-84.0)	67.7 (62.9-69.9)	0.008	24.9 (21.2-30.2)	23.7 (20.7-25.2)	0.151
Arthritis (24/26)	68.2 (66.7-75.8)	71.3 (64.1-80.7)	0.503	23.2 (20.9-25.4)	23.9 (21.2-29.7)	0.327
Leucopenia (38/12)	68.2 (64.5-80.1)	69.7 (65.7-75.6)	0.982	23.8 (21.0-27.3)	22.3 (20.8-28.0)	0.725
Serositis (42/8)	69.0 (64.5-77.2)	73.1 (66.6-99.2)	0.278	23.3 (20.9-25.2)	29.2 (26.0-35.1)	0.004
Thrombocytopenia (44/6)	69.0 (64.3-78.5)	69.0 (66.7-73.0)	0.834	23.7 (20.9-26.9)	24.9 (22.1-30.6)	0.438

CNS: Central nervous system, SLE: systemic lupus erythematosus.
[a] Median, Interquartile Range (IRQ), Mann-Whitney test. P < 0.05 was considered significant.

Table 3. Correlations of serum TWEAK and IL-17 with demographic, clinical, and laboratory data of SLE patients with nephritis

Variable	Serum TWEAK		Serum IL-17	
	Spearman's rho	*P* value	Spearman's rho	*P* value
Age	0.447	**0.025**	0.176	0.399
Gender	0.0	1	0.055	0.792
SLEDAI	0.513	**0.009**	0.883	**<0.001**
Creatinine	0.483	**0.014**	0.204	0.327
Proteinuria	0.668	**<0.001**	0.461	**0.020**
C3	-0.202	0.333	-0.157	0.454
C4	0.026	0.901	0.064	0.762
ANA	0.113	0.590	0.0	1
anti-dsDNA	0.289	0.161	0.370	0.065
Activity index	**0.491**	**0.013**	**0.463**	**0.020**
Chronicity index	0.482	**0.015**	0.040	0.848
Hematuria	0.260	0.209	0.215	0.302
CNS	0.635	**0.001**	0.575	**0.003**
Rash	-0.286	0.166	-0.013	0.951
Arteritis	-0.294	0.153	0.260	0.209
Leucopenia	-0.026	0.902	0.091	0.666
Serositis	0.333	0.104	0.541	**0.005**
Thrombocytopenia	0.123	0.559	0.102	0.627

Anti-dsDNA: Anti–double-stranded DNA; SLEDAI: systemic lupus erythematosus disease activity index, C3/C4: complement components. $P < 0.05$ was considered significant.

24-hour urine proteinuria, and LN activity index. Our results suggested that serum TWEAK and IL-17 increased parallel to the severity of kidney damage, confirming the earlier discovery of the association of these markers with renal damage.

TWEAK can stimulate macrophage migration through the down-regulation of IL-10 expression and its level is elevated in the renal tissue of SLE patients with nephritis, and in the urine of cases with active LN (18). Elevated levels of urinary TWEAK are also evident in LN patients (2,19). Similar study reported that the urinary TWEAK (uTWEAK) was significantly higher in the LN patients than in the lupus and control groups and found a significant correlation with disease severity (20). In addition, high uTWEAK levels could predict nephritis in SLE patients with a high odds ratio of 7.36 (CI: 2.25-24.07) (2). Thus, its diagnostic value was more than anti-dsDNA antibodies and it can be considered as a disease-monitoring biomarker (19). Furthermore, uTWEAK was correlated with the renal SLEDAI score as well as other traditional biomarkers of LN activity such as anti-dsDNA antibodies and complement (2,5). Hence, the urinary TWEAK level may be a novel biomarker of LN activity status (9,18). These findings all suggest that the TWEAK can be an important marker for the diagnosis of the severity of lupus and LN. However, the LN cases could be better detected using uTWEAK (21). The result of the present study was in line with these reports, however, it was in contrast with the result of the study by Schwartz et al. They showed that sTWEAK level did not correlate with the presence of LN or the degree of nephritis activity (19). Nevertheless, we found a positive significant correlation between sTWEAK and nephritis activity and chronicity indices.

In this study, the IL-17 level in the lupus patients was higher than that in the control group, but no significant difference was observed between LN patients, non-LN, and healthy groups. Similar studies have reported significant correlations between the IL-17 level and disease severity in patients with lupus (22) and LN (16). In patients with LN, IL-17 was significantly higher in active disease compared with remission state and was correlated with dsDNA and proteinuria (16). Additionally, two other studies reported that the IL-17 levels were associated with the SLE disease activity (22,23). Another study underlined that the IL-17 is a potent cytokine with severe pre-inflammatory activity that is abnormally produced in lupus patients (24). It was stated that the IL-17 level in the active LN patients was higher in the controls and treated lupus patients, and was elevated with an exacerbation in the lupus disease severity. It was also observed that, the high level of IL-17 is a predictor of inappropriate histopathologic response of LN (20). Our results are consistent with these studies. However, Raymond et al showed that the level of IL-17 in lupus patients did not differ significantly from those in the control group and did not show a significant correlation

Table 4. Performance in evaluating renal involvement

	AUC	*P* value	Sensitivity	Specificity	Youden	Associatedcriterion	LR+	LR-
SLE from controls								
TWEAK	0.728	<0.001	90 [78.2-96.7]	46.15 [30.1-62.8]	0.36	>62.1	1.67	0.22
IL-17	0.681 [0.57 to 0.79]	0.0013	34 [21.2-48.8]	97.44 [86.5-99.9]	0.314	>25.63	13.26	0.68
Combined	0.763 [0.66 to 0.86]	<0.001						
LN from non-LN								
TWEAK	0.752 [0.610 to 0.863]	0.0003	56 [34.9-75.6]	88 [68.8-97.5]	0.44	>75	4.67	0.50
IL-17	0.646 [0.498 to 0.776]	0.0725	48 [27.8-68.7]	88 [68.8-97.5]	0.36	>25.8	4	0.59
Combined	0.763 [0.629 to 0.897]	0.001						

AUC: Area under the Curve. $P < 0.05$ was considered significant.

with the illness severity (22). In the analysis of the above studies, it can be seen that IL-17 plays an important role in the pathophysiology of lupus and LN. While it was observed in this research and some other studies, that increased IL-17 levels may even be associated with exacerbation of the disease. Hence, drugs likely to inhibit this cytokine may be effective in controlling the disease.

Elevated levels of sTWEAK and IL-17 in our LN group was associated with clinical manifestations including arteritis, thrombocytopenia, serositis, and leucopenia. However, differences in serum levels of these factors according to the various organ involvement were not statistically significant. It has been stated that the TWEAK levels in serum and CSF were greater in patients with lupus than in people without autoimmune disease, while its increase in CSF can cause lupus neurological manifestations (25). Likewise, in the present study, the elevated levels of sTWEAK and IL-17 were correlated with CNS involvement in the LN group. All of these data confirm that levels of TWEAK and IL-17 having biologically reasonable functions in the pathology of LN, hence, it can be intriguing biomarkers for LN. However, ROC analysis in the present study indicated that serum TWEAK and IL-17 did not have high accuracy, sensitivity and specify to discriminate all/most of LN patients from non-LN patients.

Conclusion

In conclusion, the results of our study exhibited that the TWEAK and IL-17 levels were significantly higher in the lupus patients, while, these two cytokines showed a significant and direct correlation with the severity of lupus and renal involvement. Although our study revealed higher serum levels of TWEAK and IL-17 in SLE patients with organ involvement, some of them were not significant.

Limitations of the study

We believe that relatively small sample size is a limitation of our study. The strength of the present study was that we had a control group and compared the serum marker levels between SLE patients with and without LN and normal subjects. Moreover, the combined effect of the studied cytokines was evaluated in the diagnosis of nephritis in SLE patients.

Authors' contribution

All authors contributed to the study. MRN and SA designed the study and selected the cases. NS did sampling. AGH and TP performed experimental analysis and interpretation of the data. SZV prepared the draft. All authors read and approved the final manuscript.

Conflicts interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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