



Association of systemic lupus erythematosus activity with serum levels of sTWEAK and CD160: A cross-sectional study

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is a relatively common disease among the patients referred to the rheumatology clinics. Tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK), as a cytokine, is a member of TNF family, and CD160 is an essential natural killer (NK) cell activator, both of which have been argued to be associated with SLE activity. Here, we aimed to evaluate the serum levels of sTWEAK and CD160 and their association with SLE activity.

Methods: In a descriptive cross-sectional study, 48 patients with SLE, as the case group, and 40 healthy subjects, as controls, were enrolled. SLE activity was assessed using SLE Disease Activity Index (SLEDAI) in the case group. Moreover, the serum levels of sTWEAK and CD160 were determined using enzyme linked immunosorbent assays (ELISA) method in both groups.

Results: Mean serum level of sTWEAK was 19.09% lower in the control group compared to the case group (730.15 ± 170.21 pg/ml vs. 895.39 ± 451.25 pg/ml, respectively). Further, mean serum level of CD160 was 47.31% lower in the healthy subjects than that of SLE patients (206.16 ± 88.97 pg/ml vs 391.30 ± 283.46 pg/ml, respectively). The differences in both occasions were found to be significant ($P = 0.013$ and $P = 0.001$, respectively). Mean SLEDAI in the patients was 8.68 ± 4.00 . There was no significant correlation between serum levels of sTWEAK and CD160 with SLE activity.

Conclusion: The serum levels of sTWEAK and CD160 markers in patients with SLE are significantly higher than those of healthy subjects. However, we found no correlation of these markers with the disease activity.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of antibodies against cellular nucleus components. The disease affects most commonly women in the childbearing age, and in the long run causes disability and mortality due to the damage to vital organs

such as kidneys, heart, and central nervous system (CNS).¹

The exact cause of the disease is unknown. However, many studies have been conducted to assess the factors which affect the onset of the disease and to propose a hypothesis in this regard. One of these postulations is the counterbalance and dysregulation of factors

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involved in the programmed cell death or apoptosis of the immune system cells.² Another hypothesis proposes that defected production of different cytokines occurs during SLE that can be a key factor determining various manifestations of the disease.³

Abnormal production of various cytokines in SLE is an intrinsic defect of mononuclear cell (MNC) and the immune system that may be the key element for a variety of clinical manifestations of this disease.

The incidence of illness is higher in the second, third, or fourth decades of life. SLE has a wide range of clinical manifestations varying from mild dermatologic complaints and joint pains to renal insufficiency or cytopenia. With the involvement of various organs in patients and physical disability, the need for more care becomes necessary. The definitive diagnosis of the disease is based on a set of clinical and laboratory signs and symptoms. To further evaluate the severity of the disease, various indexes have already been designed and presented. It has been shown that the clinical course, activity, and relapse of the disease is commonly associated with serum antibody levels.^{4,6} Moreover, quite recently, novel serum and urine biomarkers such as chemokine (C-C motif) ligand 3 (CCL3), chemokine (C-C motif) ligand 5 (CCL5), interleukin-17 (IL-17), B-lymphocyte stimulator (BLyS), A proliferation-inducing ligand (APRIL), growth factor beta (TGF β), and tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) have been found to predict disease activity and renal involvement.⁷

TWEAK is a small pleiotropic cytokine, whose gene is located on the chromosome 17p13 and is expressed in tissues such as heart, brain, kidneys, and also MNCs of the blood. This cytokine plays an important role in the cell proliferation, differentiation and apoptosis.⁸ Evidence suggests that TWEAK is also involved in the pathogenesis of SLE, and increases during the disease.⁹

Further, CD160 is an essential natural killer (NK) cell activator, whose performance

has not been well known until now. This receptor identifies structures that are not usually recognised by other immunoglobulin receptors. CD160 gene is located outside the NK complex and is expressed with the Cd56 and CD16 phenotype.¹⁰ It has been found that major histocompatibility complex (MHC) class I molecules bind to CD160 on circulating NK lymphocytes, and that their interaction stimulates the activity of these cells and increases cytokine production.¹¹

We conducted this study to assess the association of TWEAK and CD160 serum levels with the disease activity considering the burden of SLE on the patients and healthcare system and the lack of definitive studies in this field.

Methods

In a cross-sectional analytical study, 48 patients with SLE referred to the rheumatology clinic of Tabriz University of Medical Sciences, Tabriz, Iran, (case group), and 40 healthy subjects (control group) were randomly selected using convenient sampling and enrolled into the study. These subject were matched in age and sex with the case group. This study was conducted for one year between February 2016 and February 2017.

We included all patients who were diagnosed with SLE by a rheumatologist based on Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE. On the other hand, every patient who had 1) liver disease unrelated to SLE, 2) kidney disease unrelated to SLE, 3) severe infections, 4) any malignancies, 5) rheumatologic inflammatory diseases, 6) diabetes mellitus type one and two, and 7) thyroid disorders was excluded from the study. Every patient who declined to participate in the study was also excluded.

All subjects in both groups were first evaluated by a rheumatologist for indications for enrollment into this study. In the case group, disease activity was determined using SLE Disease Activity Index (SLEDAI) which has been explained as follows (the total score ranges from zero to 105):

1. Eight scores: Seizure, psychosis, cerebral organ syndrome, visual disturbances (retinal changes, retinal neuritis bleeding), cerebrovascular disorders, lupus headache, cerebrovascular accidents, and vasculitis
2. Four scores: Arthritis, myositis, urinary cramps, hematuria, proteinuria, and pyuria
3. Two scores: Rash, oral ulceration, pleurisy, pericarditis, low complex, and increased anti-double stranded DNA (anti-dsDNA)
4. One score: Fever, platelet below 100000, and lymphopenia (lymphocytes less than 1500)

The patients were referred to one of the laboratories under the supervision of Tabriz University of Medical Sciences, to measure sTWEAK, CD160, and other variables including complete blood count (CBC), antinuclear antibody (ANA), ds-DNA, and complements levels. 5 ml blood was obtained from each patient after 12 hours of fasting. Then the samples were centrifuged and the serum was isolated. Serum samples were stored at -70 °C until freezing.

Serum TWEAK (TNFSF12) level measurement: Enzyme linked immunosorbent assays (ELISA) method was used to evaluate the serum levels of sTWEAK in serum samples using human TWEAK ELISA kit (USA, Thermo scientific, 7335 Excutive Way, Frederick, MD 21704).

The kit's standard was combined with a diluting solution in a one-to-one ratio, and then serial dilution was performed. Following the preparation of standard concentrations (0, 46.88, 93.75, 187.50, 375, 750, 1500 pg/ml), 100 µl of these solutions were added to each well, and in the next step, the plate was placed at room temperature for 2.5 hours. After the completion of incubation time, the washing step was performed with the aid of an ELISA washer (Stat Fax 2600). In the next step, 100 µl of the biotinylated antibody was added to the solution and incubated for 45 minutes at room temperature. Then, 100 µl of horseradish peroxidase (HRP)-conjugated streptavidin was added, and the solution was incubated

for another 45 minutes. Accordingly, 100 µl of the chromogen solution was added and incubated for 30 minutes in the darkness. Finally, 50 µl of the stop solution was added to each of the wells, and the absorbance of the plate was read using ELISA reader (Stat Fax 2100). The readings were carried out at 450 nm wavelength and within 10 minutes after the addition of the stop solution. The sample concentration was calculated using standard curve drawn based on the serial standard concentrations.

Serum CD160 level measurement: To assess serum levels of CD160 in the serum samples, ELISA method was applied using the cloud-clone corp (CCC) (1304 Langham Creek Drive, Suite 226, Houston, TX 77084, USA) commercial kit. All procedures were performed according to the manufacturer's instructions.

The kit's standard was combined with a diluting solution in a one-to-one ratio, and then serial dilution was performed. After preparation of the standard concentrations (0, 78, 156, 312, 625, 1250, 2500 pg/ml), 100 µl of these solutions were added to each well and incubated for 1 hour at 37 °C. Then, 100 µl of reagent A was added to the solution and incubated for one hour at 37 °C. After washing, 100 µl of reagent B was added and incubated for another 30 minutes. Subsequently, the plate was washed, 90 µl of the substrate solution was added, and the plate was placed at 37 °C for 20 minutes. After incubation, 50 µl of the stop solution was added to each of the wells. In the next step, the plate absorbance was read using ELISA reader (Stat Fax 2100). The readings were carried out at 450 nm wavelength and within 10 minutes after the addition of the stop solution. The sample concentration was calculated using standard curve drawn based on the serial standard concentrations.

All statistical analyses were performed using SPSS software (version 20, IBM Corporation, Armonk, NY, USA).

Data were expressed as mean ± standard deviation (SD) and frequency and percentage. The normal distribution of the data was evaluated using Kolmogorov-Smirnov test (K-

S test). Chi-square test was used to compare qualitative variables, and independent t-test or Mann-Whitney U test was used to compare quantitative variables. Moreover, Pearson's correlation was used to evaluate the relationship between variables. The sample size was determined using the number of patients used in the previous studies, the power of 80%, and the acceptable error rate (α) of 5%; which yielded the number of 25 patients. In all comparisons, $P \leq 0.05$ was considered to be statistically significant.

In the present study, we thoroughly explained the purpose and manner of conduction of the study to the subjects studied, and stated that all their information would be kept confidential, and their personal information would not be mentioned anywhere. There was no additional diagnostic and therapeutic intervention in the entire study, except obtaining 5 ml peripheral blood samples and assessing the level of cytokines. Moreover, the cost of examining and conducting relevant tests was provided by the project manager and supported by the Vice Chancellor of Tabriz University of Medical Sciences, and no additional costs were received from the subjects and their families.

Results

In the case group, 4 (8.3%) patients were men, and 44 (91.7%) were women. In the control group, 4 (10.0%) patients were men, and 36 (90.0%) were women. There was no significant difference regarding gender between the two groups ($P = 0.452$).

The mean age of the patients in the case group was 29.14 ± 8.32 years (ranging between 8 and 49 years). On the other hand, the mean age of the subjects in the control group was 30.77 ± 11.86 (ranging between 14 and 59 years). The difference was not statistically significant ($P > 0.999$). Mean duration of the

disease in the case group was 43.83 ± 24.72 months (ranging between 2 months and five years). Tables 1 and 2 show the frequency of clinical and laboratory findings of the included SLE patients, respectively. Based on these findings, SLEDAI score of the patients was 8.68 ± 4.69 (ranging between 2 and 22).

Table 1. Frequency of the clinical findings in the included patients with systemic lupus erythematosus (SLE)

Clinical findings	n (%)
Skin involvement	15 (31.3)
Joint involvement	15 (31.3)
Kidney involvement	21 (43.8)
Central nervous system involvement	4 (8.3)
Serositis	3 (6.3)
Cardiac involvement	1 (2.1)
Pulmonary involvement	0 (0)

Results showed that serum levels of TWEAK and CD160 were significantly higher in SLE patients than those of the control group ($P = 0.013$ and $P = 0.001$, respectively) (Table 3).

Table 2. Frequency of the laboratory findings in the included patients with systemic lupus erythematosus (SLE)

Laboratory findings	n (%)
ANA+	48 (100)
Anti-dsDNA+	46 (98.8)
Low C3	20 (41.7)
Low C4	13 (27.1)
Low CH50	7 (14.6)
Anti-Ro	13 (27.1)
Anti-La	9 (18.8)

ANA: Antinuclear antibody; Anti-dsDNA: Anti-double stranded DNA

There were no significant correlations between the serum levels of TWEAK and SLEDAI ($P = 0.110$, $r = 0.169$) as well as anti-dsDNA levels ($P = 0.133$, $r = 0.309$) in patients with SLE. Further, we found no significant correlation between serum TWEAK levels and renal, neurological, and cardiac involvement ($P > 0.050$) (Table 4).

Table 3. Comparison of sTWEAK and CD160 serum levels in patients with systemic lupus erythematosus (SLE) and healthy subjects

Variable	SLE patients (mean \pm SD)	Control group (mean \pm SD)	P
sTWEAK (pg/ml)	895.39 ± 451.25	730.15 ± 170.21	0.013
CD160 (pg/ml)	391.30 ± 283.46	206.16 ± 88.97	0.001

SLE: Systemic lupus erythematosus; TWEAK: Tumor necrosis factor-like weak inducer of apoptosis; SD: Standard deviation

Table 4. The serum levels of TWEAK and CD160 in patients with systemic lupus erythematosus (SLE) based on the involvement of various organs

Organ	sTWEAK (pg/ml) (mean ± SD)			CD160 (pg/ml) (mean ± SD)		
	Not involved	Involved	P	Not involved	Involved	P
Kidney	881.5 ± 639.0	906.2 ± 231.8	0.100	380.1 ± 300.1	299.9 ± 275.3	0.730
Skin	776.2 ± 241.7	949.6 ± 13.6	0.240	516.8 ± 334.3	334.3 ± 241.7	0.010
Joints	794.2 ± 240.9	941.3 ± 596.4	0.210	419.2 ± 321.9	378.6 ± 268.6	0.730
CNS	710.8 ± 197.5	912.2 ± 465.2	0.270	360.7 ± 274.9	394.1 ± 287.2	0.550
Serositis	1003.5 ± 246.3	882.2 ± 462.5	0.320	443.9 ± 192.4	387.8 ± 289.7	0.280

CNS: Central nervous system; TWEAK: Tumor necrosis factor-like weak inducer of apoptosis; SD: Standard deviation

Besides, no correlation was shown between CD160 and SLEDAI ($P = 0.643$, $r = 0.069$) as well as anti-dsDNA levels ($P = 0.099$, $r = 0.241$) in SLE patients. There was no significant correlation between serum CD160 levels and renal, neurological, and cardiac involvement ($P > 0.050$) (Table 4).

Results revealed that 44 patients (91.7%) received prednisolone, 12 patients (25.0%) received mycophenolate mofetil (cellcept), 9 patients (18.8%) received cyclosporine, 3 patients (6.3%) received rituximab, and 2 patients (4.2%) received cyclophosphamide. Table 5 shows the serum levels of TWEAK and CD160 in SLE patients based on the drug they used.

Table 6 represents the serum levels of TWEAK and CD160 in SLE patients based on SLEDAI.

Discussion

Our results showed that sTWEAK levels were significantly higher in the SLE patients than those of the control group. Moreover, there was no significant correlation between SLEDAI and sTWEAK in the studied patients. Further, we found no significant correlation between the clinical symptoms associated with the disease and the serum levels of TWEAK.

In line with that, Frago-Loyo et al.

determined the level of TWEAK in serum and cerebrospinal fluid (CSF) as an indicator of neuropsychiatric disease in patients with lupus. The results of this study showed that TWEAK level was higher in lupus patients compared to the healthy subjects, but there was no correlation between the recurrence, severity, and activity of the disease with TWEAK level.¹²

On the other hand, Schwartz et al. conducted a study to investigate the association of urine TWEAK with lupus nephritis. The results of this study showed that urine TWEAK was significantly higher in patients with lupus nephritis compared to other SLE patients, and was more useful in the diagnosis of lupus nephritis compared to anti-dsDNA. This study also showed a direct correlation between the disease activity and the uTWEAK.¹³ Different results of this study might stem from the fact that Schwartz et al.¹³ measured the urinary levels of TWEAK and we determined its serum levels.

Further, in a study by Choe and Kim, the association between sTWEAK and SLE activity was investigated. Surprisingly, it was found that sTWEAK was a key determinant of SLEDAI score as well as renal involvement, and could be a serologic biomarker to predict disease activity.¹⁴

Table 5. The serum levels of TWEAK and CD160 in patients with systemic lupus erythematosus (SLE) based on the drug they used

Drug	sTWEAK (pg/ml) (mean ± SD)			CD160 (pg/ml) (mean ± SD)		
	+	-	P	+	-	P
Cyclosporine	677.1 ± 204.9	960.5 ± 476.1	0.010	512.9 ± 412.0	359.6 ± 45.8	0.190
Rituximab	1661.5 ± 1571.3	250.2 ± 544.3	0.570	246.6 ± 55.9	400.9 ± 290.1	0.300
Prednisolone	894.4 ± 465.0	906.5 ± 301.7	0.460	376.7 ± 281.8	551.9 ± 288.6	0.150
Cellcept	828.5 ± 207.3	917.7 ± 507.8	0.690	360.4 ± 313.4	401.6 ± 276.8	0.480
Cyclophosphamide	259.5 ± 169.8	901.3 ± 459.5	0.540	218.8 ± 12.6	398.8 ± 287.3	0.180

TWEAK: Tumor necrosis factor-like weak inducer of apoptosis; SD: Standard deviation

Table 6. The serum levels of TWEAK and CD160 in patients with systemic lupus erythematosus (SLE) based on the SLE disease activity Index (SLEDAI)

SLEDAI score (number) (mean \pm SD)	sTWEAK (pg/ml)	CD160 (pg/ml)
< 6 (8)	992.0 \pm 215.9	330.1 \pm 153.4
7-10 (25)	842.9 \pm 259.3	426.4 \pm 354.9
> 10 (15)	931.2 \pm 730.4	365.4 \pm 192.2
P	0.940	0.130

SLEDAI: Systemic lupus erythematosus disease activity index; TWEAK: Tumor necrosis factor-like weak inducer of apoptosis; SD: Standard deviation

ElGendi and El-Sherif also studied the correlation between TWEAK and lupus nephritis and disease activity. The results of this study showed that TWEAK was significantly higher in lupus patients than in the control group, and this marker could be used to evaluate the disease activity and presence of lupus nephritis.¹⁵ Similarly, in the present study, serum levels of TWEAK were significantly higher in the patients with SLE than in the control group. However, we found no significant correlation between sTWEAK levels and disease activity, as well as lupus nephritis in our study.

Liu et al. also conducted a study to assess the level of TWEAK in the peripheral blood mononuclear cells (PBMCs) and its association with disease activity and renal function in SLE patients. The results of this study showed that TWEAK was significantly higher in patients with lupus than that of patients with rheumatoid arthritis and healthy subjects. Also, they found that TWEAK in PBMCs was positively associated with the disease activity.¹⁶

In this study, we also showed that serum levels of CD160 in the SLE patients were significantly higher than those of the control group. Further, there was no significant correlation between SLEDAI and CD160 serum levels in the studied patients. In addition, we showed no significant correlation between the clinical symptoms associated with the disease and the serum levels of CD160. Unfortunately, we found no study evaluating the correlation between CD160 serum level and the disease activity

in SLE patients; therefore, the direct comparison of the results of this study with other studies is not possible. Here, we have summed some of the articles that have assessed CD163 levels correlation with SLE activity.

The results of Nakayama et al. study showed that patients with lupus had a higher serum level of CD163 than healthy subjects, higher levels of anti-dsDNA and leukopenia.¹⁷ Moreover, Endo et al. showed that increase in the number of CD163 positive macrophages was associated with increased severity of lupus nephritis. Also, the urinary content of this marker was higher in patients with active lupus nephritis.¹⁸ The results of Endo et al.¹⁸ study were consistent with the results of Nakayama et al.¹⁷ study. Accordingly, in our study serum CD160 levels were significantly higher in patients with lupus than in the control group, but there was no significant correlation between laboratory findings and symptoms of lupus disease with serum CD160 levels.

This study had some limitations. First, we included a limited number of patients in this study, and studies with more case numbers should be conducted in the future. Second, we did not assess the effects of disease duration on the serum levels of TWEAK and CD160; as patients with varying disease duration may have different serum values of these factors. This may affect the outcome of the study. Third, we could not be able to assess the association of other serum or urine biomarkers with disease activity which could be addressed in the future studies.

Conclusion

Based on the results of this study and most studies in this field, serum levels of sTWEAK and CD160 markers are significantly higher in patients with lupus than those of healthy subjects. Although we found no significant correlation between sTWEAK and CD160 serum levels with SLE activity, most studies have shown the contrary; and therefore, it seems that sTWEAK and CD160 markers could be used

to determine the severity of the disease. Some differences observed in this regard are due to the differences in the received treatment, sample selection as well as study method, and the duration of disease. Further studies in this field are necessary for better decision making.

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Authors' Contribution

Study concept and design: Mehrzad Hajjalilo, Amir Ghorbani-Haghjo

Acquisition of data: Haleh Darbandi

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important intellectual content: Mehrzad Hajjalilo, Amir Ghorbani-Haghjo
Statistical analysis: Farid Karkon-Shayan
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Study supervision Mehrzad Hajjalilo.

This paper is based on Haleh Darbandi's speciality dissertation submitted to the School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

Conflict of Interest

Authors have no conflict of interest.

Ethical Approval

This study was approved by the Regional Medical Ethics Committee of Tabriz University of Medical Sciences under the number 94/3-5/7.

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