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ORIGINAL ARTICLE

Clinical Association of Serum Interleukin-17 and Interleukin-6 in Systemic Lupus Erythematosus Patients

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ABSTRACT

Background: *Management of Systemic Lupus Erythematosus (SLE) would be greatly assisted by certain biomarkers that perfectly reflect changes in disease activity.* ***Objectives:*** *This study was conducted to evaluate the role of IL-17, IL-6 and their ratio in SLE as regard disease activity, central nervous system CNS and renal involvement.* ***Methodology:*** *A case control study including SLE patients were subjected to clinical examination, assessment of SLE disease activity index (SLEDAI) and laboratory investigations versus healthy controls, quantitative determination of serum IL-17A and IL-6 levels by ELISA.* ***Results:*** *Elevated serum IL-17A and IL-6 levels in SLE cases than control. Serum IL-6 level was higher in renal group, whereas, higher serum IL-17 was detected in neurologically affected patients.* ***Conclusion:*** *SLE patients had significantly upregulated IL-17 and IL-6 levels. SLEDAI was significantly positively correlated with IL-17/IL-6 ratio. Thus, IL-17/ IL-6 ratio may accurately characterize Th17-driven disease than serum IL-17 or IL-6 alone.*

INTRODUCTION

Systemic lupus erythematosus (SLE) is an incurable autoimmune disease with fluctuating activity that is clinically heterogeneous characterized by multisystem involvement [1].

It is characterized by production of inflammatory cytokines and autoreactive antibodies as a result of immune tolerance breakdown. This causes damage to various organs, such as joints, skin, kidneys and central nervous system [2].

In spite of the advances in understanding the pathogenesis of SLE, The exact mechanisms of this disease remain unclear. Multiple factors contribute to the expression of different clinical manifestations, including genetic, immunological, hormonal and environmental factors [3].

Fluctuating course with remissions and exacerbations is a character of SLE [4].

Interleukin-17 is a proinflammatory cytokine that contributes to tolerance breakdown in SLE patients and enhances the secretion of proinflammatory cytokines including IL-2, IFN-γ and granulocyte–monocyte colony-stimulating factor, with subsequent augmentation of SLE-induced tissue damage [5].

Interleukin-6 is a pro-inflammatory pleiotropic cytokine that contributes to SLE pathogenesis due to its close link with B-lymphocytes. IL-6 is mainly secreted by monocytes, fibroblasts and endothelial cells [6]. Among its multiple actions, IL-6 stimulates the maturation of B lymphocytes into plasma cells and amplifies immunoglobulin secretion [7].

Objectives of this study were to analyze the correlations between serum IL-17 and IL-6 concentration and SLE disease expression in terms of activity and organ involvement, and to assess if these cytokines can be used as biomarkers for CNS and renal activity. Lastly, the study analyzes the relationship between serum IL-17 levels and serum levels of IL-6.

METHODOLOLGY

This case-control study was conducted over 14 months from January 2016 to March 2017 at Microbiology and Medical Immunology Department & Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig University.

- **Case group:** Thirty nine SLE patients, (37 females and 2 males), their age ranged from (18-48) years with a mean value ± SD (32.72 ± 9.65) years and their disease duration ranged from (6 months to 15 years). They were collected from inpatients department and outpatient clinics of Rheumatology and Rehabilitation Department, Zagazig University Hospitals.

  They were diagnosed according to Systemic Lupus International Collaborating Clinics (SLICC) revision of the American College of Rheumatology (ACR) classification criteria for SLE [8].

- **Control group:** Thirty nine apparently healthy age and sex-matched subjects serving as controls who had no clinical findings suggesting immunological diseases.

Exclusion criteria

SLE patients undergoing renal dialysis, or having kidney disease due to causes rather than SLE, such as urinary tract infection, essential hypertension and diabetic nephropathy and patients with known comorbid neurologic conditions, such as traumatic brain injury or neoplasm were all excluded from the study.

Review and approval by the Institutional Review Board (IRB) (ID 2015/2526) committee was contracted at Faculty of Medicine, Zagazig University. A written consent was taken from all subjects for ethical consideration.

All patients incorporated in this study were subjected to assessment of disease activity according to Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

According to Esdaile et al. [9], they were subdivided into:

- ***Active group****:* Included twenty one patients whose SLEDAI score of > 6
- ***Inactive group****:* Included eighteen patients whose SLEDAI score of ≤ 6

Quantitative determination of serum IL-17A and IL-6:

Two milliliters of blood sample was taken under complete aseptic conditions from both SLE cases and healthy controls after informed consent. The blood was left for 30-60 minutes then centrifuged to separate sera. Serum was immediately aliquoted and stored at -20 ºC until time of examination.

All reagents were allowed to reach room temperature (18-25°C) before being used Sera were analyzed for cytokines by sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocols. Using Human IL-17A and IL-6 Platinum ELISA kit (BMS2017, affymetrix eBioscience, USA).

Optical density of each well was determined using ELISA reader (Stat Fax®303 Plus, USA) at 450 nm as the primary wave length and 630 nm as the reference wave length.

Standard curve was constructed by plotting the mean absorbance obtained from each reference standard against its concentration in pg/ml with absorbance values on the vertical or Y axis and concentrations on the horizontal or X axis.

The absorbance values for each sample were used to determine the corresponding concentration of both human IL-17A and IL-6 in pg/ml from the standard curve.

Statistical analysis

Data were statistically analyzed using SPSS version 12.0.1 (SPSS, Inc., Chicago, IL, USA). Shapiro–Wilk test was used to check normality. Categorical variables were expressed as percentages while continuous variables were expressed as mean ± standard deviation. For all tests, *p* value is considered significant when it is<0.05.

RESULTS

This case-control study was carried out on 78 individuals; they were divided into two groups:

Group I: Included 39 SLE patients. They were 37 females (94.9%) and two males (5.1%) and their age ranged from (18-48) years with a mean value ± SD of 32.72 ± 9.65 and their disease duration ranged from (6 months to 15 years).

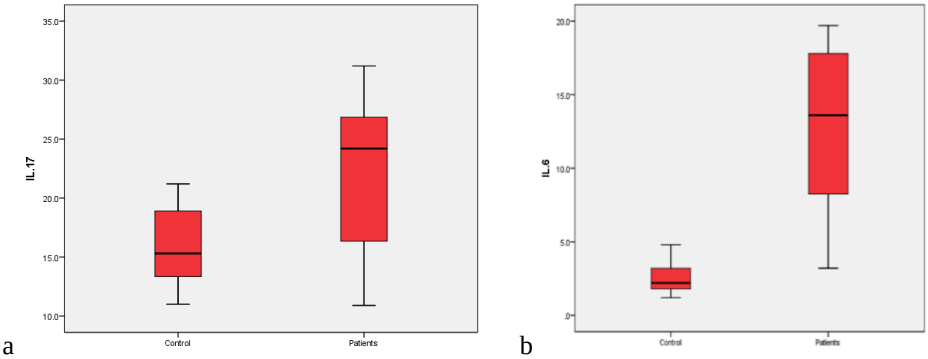
Group II: included 39 apparently healthy age and sex-matched subjects serving as controls who had no clinical findings suggesting immunological diseases. They were 37 females and 2 males with ages ranged from 20-46 years with a mean value ± SD of 32.95 ± 8.77

The most frequent clinical variables in SLE cases were malar rash, arthritis, fever then renal manifestations representing (76.9%), (51.3%), (46.2%) and (38.5%) respectively and the least frequent clinical variables were pericardial effusion and myositis representing (2.6%) for each one. CNS affection included headache, seizure and psychosis (7.7%), (7.7%) and (10.3%) respectively.

The most frequent laboratory findings in SLE cases were ANA positivity found in (79.5%), followed by anti-dsDNA positivity (56.4%) and hypo-complementemia C3 (56.4%) , while the least frequent laboratory finding was cellular casts representing (15.4%). Hypochromic and microcytic anemia were the most prominent hematologic findings, accounted for (53.8%) for both. However, proteinuria was the most frequent laboratory finding regarding renal impairment representing (35.9%).

In the present study IL -17 level was increased in all SLE cases (Mean ± SD = 22.1±6.2).

Interleukin-6 was high in all similarly cases (Mean ± SD = 12.9 ± 4.8) and the difference was found to be high statistically significant when compared to the control group (Mean ± SD = 2.6 ± 1.0) (P<0.001) (Fig. 1).



a b

Fig. 1 : Serum level of IL-17 (a) and IL-6 (b) in SLE patients

A strong positive correlation was detected between serum IL-6 and IL-17 (p value >0.001) (Fig. 2).

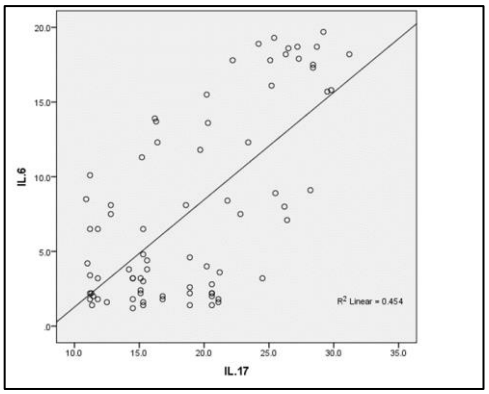


Fig. 2: Correlation between IL17 and IL-6 in SLE patients

In this study neurologically affected patients had higher serum IL-17 concentration than neurologically free patients and the difference was statistically significant (p value = 0.045).

There was no statistically significant difference in serum IL-17 concentration between renal and non-renal SLE patients in our study (p value = 0.93).

Higher IL-6 concentration was detected in patients with active SLE (Mean ± SD = 14.3±4.5) when compared with inactive group (Mean ± SD = 11.1±4.8) and the difference was statistically significant (P=0.043).

There was no statistically significant difference regarding serum IL-6 concentration among SLE patients with neurological affection (p value = 0.51) The results are shown in table (1).

Table 1: Association between serum cytokine levels, ratio and system affection in SLE patients.

		IL-17 (mean±SD)	IL-6 (mean±SD)	IL-17/IL-6 ratio (mean±SD)
CNS involvement	**(A) Negative (n=30)**	21±6.4	12.7±4.6	1.8±0.6
	(B) Positive (n=9)	25.9±3.6	13.6±5.9	1.9±2
	Test	-2.00•	-0.667•	-2.23•
	p-value	0.045 (S)	0.51 (NS)	0.039 (S)
Renal involvement	**(A) Negative (n=24)**	22.5±5.8	11.7±4.9	2.3±1.4
	(B) Positive (n=15)	21.5±6.9	14.9±4.1	1.4±0.2
	Test	-0.087•	-1.91•	-2.74•
	p-value	0.93 (NS)	0.043 (S)	0.006 (S)
Hematological abnormalities	**(A) Negative (n=13)**	18.5±5.7	10.2±4.8	2.3±1.8
	(B) Positive (n=26)	23.9±5.6	14.3±4.3	1.7±0.6
	Test	-2.74•	-2.61•	-0.45•
	p-value	0.006 (S)	0.008 (S)	0.66 (NS)
SLE activity	**(A)In-active (n=17)**	18.3±6.2	11.1±4.8	1.8±0.7
	(B)Active (n=22)	25.1±4.3	14.3±4.5	1.8±1.4
	Test	-3.31•	-2.02•	-1.98•
	p-value	0.001 (S)	0.043 (S)	0.047 (S)

A highly significant positive correlation was found between IL-17 concentration in all SLE patients and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (p value <0.001). The results are shown in **(Table 2)**.

A statistically significant difference was detected between IL-17/IL-6 ratios and both CNS involvement (p value =0.039) and with renal involvement (p value =0.006) **(Table 3).**

Table 2: Correlation between serum cytokines concentrations (Systemic Lupus Erythematosus Disease Activity Index) SLEDAI.

		SLEDAI	IL.17	IL.6	IL-17/IL-6 ratio
SLEDAI	Correlation Coefficient		.480*	.210*	.330*
	Sig. (2-tailed)		.002	.046	.040
IL.17	Correlation Coefficient	.480*		.594**	.261
	Sig. (2-tailed)	.002		.000	.109
IL.6	Correlation Coefficient	.210*	.594**		-.567**
	Sig. (2-tailed)	.046	.000		.000
IL-17/IL-6 ratio	Correlation Coefficient	.330*	.261	-.567**	
	Sig. (2-tailed)	.040	.109	.000	

** p <0.0001 highly significant

Table 3: IL-17/IL-6 ratio as a predictor for CNS and renal involvement.

Involvement	*Best cut off value of IL-17/IL-6 ratio*	*Area Under the Curve (AUC)*	*Sensitivity*	*Specificity*	*Positive Predictive value*	*Negative Predictive value*	*Accuracy*
CNS	1.49	0.63	77.8%	43.3%	29.2%	86.7%	51.9%
Renal	1.43	0.24	60%	25%	33.3%	50%	38.5%

DISCUSSION

Systemic lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by aberrant production of inflammatory cytokines and auto reactive antibodies as a result of immune tolerance breakdown. This leads to different clinical manifestations and damage to various organs, including skin, joints, kidneys and the central nervous system (CNS) [2]. This disease has a variable course characterized by remission and relapse periods. However, the SLE may end fatally when markedly affects the kidneys or CNS [4].

Disturbance of cytokines produced by different immune cell subsets, such as Th1, Th2, Th17 and Treg has been involved in the pathogenesis of SLE. Understanding these cytokine changes is of great value to develop effective targeting therapeutics [10, 11].

This study focused on two proinflammatory cytokines; IL-17 and IL-6 aiming to analyze the correlations between serum IL-17 and IL-6 concentration and the disease expression in SLE in terms of disease activity and organ involvement and whether these cytokines can be used as biomarkers for CNS and renal activity

The current study reported that IL -17 level was increased in all SLE cases and the difference was highly statistically significant when compared to that of control group. This result goes in line with the results of other studies [12-17].

A highly significant positive correlation was found between IL-17 concentration in all SLE patients and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (p value <0.001) (Table 1). Similar results in studies carried out by [16,17].

In contrary to other studies arguing that there was no significant correlation between IL-17 and SLEDAI [18-20].

Neurologically affected patients in this study have higher serum IL-17 concentration than neurologically free patients and the difference was statistically significant (p value = 0.045) (Table 2). These results were in agreement with the results of different authors [16,18]. On the other hand, others didn't meet with ours [15].

The present work disclosed that there was no statistically significant difference in serum IL-17 concentration between renal group and non-renal SLE patients in our study. Our result was in agreement with the other researchers [15,20].

In contrast to several studies who found that serum IL-17 level was significantly elevated in lupus nephritis patients [21-24].

The current study investigated IL-6 being a pleiotropic cytokine with a significant functions in the regulation of immune system. As a potent pro-inflammatory cytokine, it plays a pivotal role in host defense against pathogens and acute stress. However, increased or deregulated expression of IL-6 dramatically contributes to the pathogenesis of numerous human diseases. Numerous preclinical and clinical studies have exposed the pathological roles of the IL-6 pathway in inflammation, autoimmunity and cancer [20].

This research highlighted that Interleukin-6 was high in all SLE cases in present study (Mean ± SD = 12.9 ± 4.8) and the difference was found to be statistically highly significant when compared to that of control group. This highly significant difference in serum IL-6 between SLE cases and controls was consistent with that of other researches [25-28]. Meanwhile another study detected only a significant difference [29].

The current study showed higher IL-6 concentration in patients with active SLE (Mean ± SD = 14.3±4.5) when compared with inactive group (Mean ± SD = 11.1±4.8) and the difference was statistically significant (P=0.043) (Table 2). This was in agreement as stated in other researches [25,26]. Meanwhile, another work confirmed that patients with active lupus nephritis have markedly elevated urinary levels of IL-6 as compared to those with inactive disease or during remission [30].

Serum IL-6 concentration was higher in renal group than non-renal patients with statistically significant difference. These results were consistent with previous results [23, 30]. In contrast, some evidence denied any significant difference in IL-6 serum concentration between renal and non-renal SLE patients [20, 26].

No statistically significant difference in serum IL-6 concentration was observed among SLE patients with neurological affection. A line of thoughts[28,32]. supported this result. Nevertheless, A higher IL-6 level in SLE patients with nervous system involvement than controls was elicited by others [19].

A strong positive correlation was detected between serum IL-6 and IL-17. This finding was in line with expectations, as IL-6 is a proinflammatory cytokine that plays a role in combination with TGF-β, in differentiation of naïve T cells into Th17 cells [33]. This result was consistent with another study that confirmed a strong positive correlation between serum IL-6 and IL-17 levels[20].

High level of serum Interleukin 17 correlates with SLE disease activity [34]. It is proposed that IL-17 driven inflammation enhances SLE-induced tissue damage and contributes to tolerance breakdown in SLE patients [5].

This study verified that IL-17/IL-6 ratios were significantly associated with CNS involvement and with renal involvement.

Consequently, this ratio acts as a powerful predictor of SLE disease activity and specific organ involvement, with a sensitivity of 77.8% and specificity of 43.3% for CNS involvement and a sensitivity of 60% and specificity of 25% for renal involvement.

Ratio of serum cytokine levels within the same axis may be helpful markers of particular immune pathways activation, as previously reported for IL-17/TGF-β ratio in schizophrenia and IL-17F/IL-22 ratio in chronic hepatitis C virus infection[35].

This study underscores the ratio of IL-17/IL-6, as two major cytokines involved in Th17 pathway, could provide a beneficial marker for SLE disease activity and could be used as a forecaster for neurological and renal involvement in SLE patients, rather than either serum IL-17 or IL-6 level alone.

Serum cytokines level may not properly reflect their total production because they may be limited to the inflamed tissue, such as the brain. It is worth mentioning that, SLEDAI was significantly correlated with IL-17/IL-6 ratio in all patients included in the study [20].

Inconsistencies in these findings to other researches could be explained by different demographics coupled with variations in ELISA tests principle and sensitivity in various studies. In addition to the heterogeneity of clinical and laboratory manifestations in SLE patients, different disease expression between SLE patient groups, especially regarding major organ involvement, as well as uncontrolled underlying factors, as types of therapy and immunosuppressive medications. Any or a combination of these factors may affect serum cytokine levels.

Aftermaths of current study supports the suggestion that IL-17 and IL-6 are intensely involved in the pathogenesis of SLE and could play a vital role in both inflammation and tissue injury manifested with exacerbation of SLE.

CONCLUSION

To wrap up, SLE patients had significantly upregulated IL-17 and IL-6 levels. IL-17 was significantly elevated in patients with CNS involvement whereas; IL-6 was significantly elevated in patients with

renal involvement. These results might provide a great help in selecting treatment strategies in these patients.

It was perceived that, SLEDAI was significantly positively correlated with IL-17/IL-6 ratio. Thus, IL-17/IL-6 ratio may characterize Th17-driven disease more precisely than serum IL-17 or IL-6 alone.

Limitations of this study:

- Firstly, serum cytokines levels may not reflect actual inflammation as their functional state. The proportions of cytokine levels in serum and brain are likely to be more important than absolute levels of a single cytokine.
- Secondly, concurrent medications possibly affect cytokine levels.
- Thirdly, the cytokine panel we studied represents a significant portion of the inflammatory process in SLE, but other Th17 related cytokines like IL-12, IL-21 and IL-23, are also associated with autoimmune diseases. Those cytokine levels were not investigated in this study, which may weaken the specificity of IL-17 for SLE.

Recommendations:

Future studies should focus on determining whether IL-17 is a key cytokine in SLE or is simply upregulated with other pro-inflammatory cytokines such as IFN-gamma, IL-6, IL-12, IL-23, IL-21 and others.

No conflict of interest.

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