Original Research Article

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The interplay between tumor necrosis factor alpha, disease activity, and depressive symptoms among Egyptian female patients with systemic lupus erythematosus

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Abstract

One of the most remarkable presentations of systemic lupus erythematosus (SLE) is depression. Our aim was to elucidate the potential relationship between disease activity, depressive symptoms, and tumor necrosis factor alpha (TNF–α) in patients with SLE. Sixty female patients with SLE and thirty comparable healthy controls were recruited. According to systemic lupus erythematosus disease activity index, patients were subdivided into two similar groups; active and inactive. Complete clinical and laboratory assessments were done to authenticate the diagnosis of SLE and outline its activity. All participants were assessed using the Beck depression Inventory (BDI) to diagnose and determine the severity of depressive symptoms. TNF–α level was assessed using Enzyme linked immunosorbent assay technique. Using BDI, patients with SLE activity showed higher prevalence of depression 19 (63.3%) compared to those with inactive SLE and control groups (P < 0.001). TNF-α level was markedly elevated amongst patients with active SLE in comparison to inactive and control groups (P <0.001). TNF-α differentiated SLE patients into with and without depression at cut-off value (>360 ng/l) (AUC = 0.726; P=0.0008; 95% CI 1.3-2.7). Multivariable regression analysis for prediction of depression revealed that TNF-α was the only independent predictor of depression (P= 0.011). In conclusion, patients with increased SLE activity are more prone to depression especially, moderate to severe degree. TNF-α level could be of significance in predilection of depression and SLE activity in patients with SLE. Hence, future studies are essential to test the treatment modalities targeting TNF-α in those patients.

Keywords: Depression; Systemic lupus erythematosus; tumor necrosis factor alpha (TNF-α); disease activity

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Introduction

Systemic lupus erythematosus (SLE) is the prototypic autoimmune disease, characterized by several clinical manifestations affecting all systems of the body with a varying course and prognosis.[1] Central nervous system involvement develops in almost 93.1 % of patients. The vast majority of patients could have one neuropsychiatric event; however 17.4 % of the patients would have two or more events.[2] Around 24 % of nervous system involvement develops as an initial presentation.[3]

Depression is considered one of the most common psychological presentations among patients with SLE. Zhang et al. suggested that the prevalence of depression is almost 39% among patients with SLE.[4] Besides, some researchers stated that depression severity increases proportionally with the disease activity.[5] It should be noted that, the occurrence of SLE co-morbid with depression may raise the risk of suicide.[6] Researches investigating the correlation between depressive symptoms and lupus identified several factors being implicated including; more serious SLE presentations, higher disease activity, and longer disease duration.[1, 7, 8, 9] Different studies had focused on the degree of neurological insult, particular circulating pro-inflammatory cytokines concentration and specific auto-antibodies.[10, 11] The significance of psycho-neuro-immunological hypothesis is now widely accepted in the pathogenesis of depression. Patients with depression generally have an abnormal peripheral immune system[12], and substantial amounts of pro-inflammatory cytokines such as interferon (IFN)-γ, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-2, IL-6 and IL-8.[13]

TNF-α is a pleiotropic cytokine released from diverse kinds of cells such as lymphoid cells, activated macrophages, endothelial cells, mast cells, cardiac myocytes, fibroblasts, adipose tissue and neurons.[14] The greatest concentrations of TNF-α receptors are found in several areas of the brain such as the hypothalamus, amygdala, hippocampus, and prefrontal cortex, which perform an important role in the regulation of emotions and is supposed to be linked to depression.[15]

Immune complex formation is considered the main pathogenesis of SLE. It activates macrophages which in turn produce great amounts of TNF-α as a result of inflammation and tissue destruction. TNF-α is considered an orchestrating, pro-inflammatory cytokine.[16] It promotes maturation of dendritic cells and B cells and its class switching. Likewise, it helps expression of anti-apoptotic molecules, and inhibits T cells hyper-responsiveness. Altogether, it augments the inflammation resulting into more tissue necrosis subsequently; more auto-antigens are formed.[17] Many studies observed high TNF-α level amongst patients with SLE especially those in activity.[18] In the meantime patients with SLE encounter more depressive symptoms than healthy control, hence, we studied its relationship with SLE disease activity, and tested the hypothesis that TNF-α may be able to predict both depressive symptoms and SLE activity.

Patients and Methods

Participants

Sixty female patients diagnosed with SLE were enrolled in the current study. Diagnosis of SLE was based on classification criteria set by Systemic Lupus International Collaborating Clinics (SLICC).[19] Recruitment of patients was either from the Rheumatology and Immunology outpatient clinic, Ain Shams University hospitals (provided that they were regularly following up for at least six months), or from the inpatient wards, during the period from March 2017 to January 2019. Patients were allocated equally into active and inactive groups according to SLEDAI score. The control group consisted of 30 apparently healthy females of comparable age.

Participants having acute or chronic infection, history of alcohol or illicit drug abuse, or having any co-morbid psychiatric illness apart from depression were excluded from the study. We also precluded those on psychotropic medications.

Details of the study had been described to the participants. Authors affirmed that the gathered information would be kept confidential, and assured that the participants could withdraw from the research at any time. Those who objected on collaboration were excluded.

Methodology

Clinical evaluation

Patients with SLE were clinically assessed through; medical history taking in details, comprehensive physical examination, and application of SLE disease activity index (SLEDAI) to measure SLE activity based on clinical and biochemical parameters. SLEDAI score varies from 0 to 105; scoring (< 6) was considered clinically inactive, whereas scoring (≥ 6) labeled the active group [20]. All patients were regularly receiving their medications which most likely included; corticosteroids, hydroxychloroquine, or immunosuppressive agents.

Psychometric assessment

All participants were subjected to Beck Depression Inventory (BDI)[21], being the most widely used psychometric tool for diagnosing depression and assessing its severity. It is a self-reported inventory, consisting of twenty one questions covering the symptomatology of major depression. Labeling the diagnosis of major depression depends on scoring 14 points or more.[22] Meanwhile, determining the severity of depressive symptoms depends on the test scores whereas; no or minimal depression (0-13 points), mild depression (14-19 points), moderate depression (20 to 28 points), and severe depression (29 to 63 points).

Laboratory tests

Complete blood picture with differential white blood cell count by automated cell counter[23], Erythrocyte sedimentation rate (ESR): Estimation was done by the Westergren method (mm/hr),[24] C-reactive protein by latex agglutination test[25], Serum creatinine by calorimetric method (mg/dl)[26], Complete urine analysis with assessment of active urinary sediments (RBCs, WBCs, proteins or cast) by urine test strip and microscopic examination[27], and Protein/creatinine ratio (P/C) by Turbidimetry[28]. Antinuclear antibody (ANA)[29], anti-double stranded DNA antibody[30] by indirect immune-fluorescence test, Serum Complement C3 and C4 were measured by Nephelometry, where they were consumed if C3 was < 89 mg/dl and C4 was < 15.5 mg/dl.[31]

Assessment of TNF–α

Eight millimeters of blood were taken from all the study participants. Then, centrifuged and serum was obtained and kept at -50 °C. TNF–α was assessed by ELISA technique (pg /ml), Bioassay technology laboratory: Cat. No E0082Hu. First, Human TNF–α antibody pre-coated the plate. TNF–α existing in the sample attached to antibodies coated on the wells. Later, biotinylated human TNF–α antibody was added and bound to TNF–α in the sample. Streptavidin- HRP was inserted and bound to the Biotinylated TNF–α antibody. Color appeared on mixing substrate solution equivalent to the amount of human TNF–α. Finally, acidic stop solution was added to end the reaction and the absorbance was estimated at 450 nm.

Statistical methods

Data was analyzed using IBM© SPSS© Statistics version 25 (IBM© Corp., Armonk, NY, USA). Numerical variables of continuous variant of normally distributed data were expressed as mean and standard deviation (SD). Comparisons between different groups were done using either the independent-samples t-test (compares two groups), or one way analysis of variance (ANOVA) (for multiple-group comparison). Numerical variables which are not normally distributed were expressed as median and interquartile range. Comparisons between groups were done using Mann–Whitney U test to compare two groups & Kruskal–Wallis to compare three groups. Categorical data was demonstrated as number and percentage; differences were evaluated using the chi-squared test and Fisher's exact test. Correlations were tested using the spearman correlation. Receiver-operating characteristic (ROC) curve analysis was used to examine the diagnostic and predictive value of TNF-α in SLE patients. Binary logistic regression analysis was used to determine predictors of depression in SLE patients. P-value <0.05 were considered statistically significant.

Results

Characteristics of patients with SLE, their mean age was 31.8 ± 10.3 years, duration of disease was 3 (0.8-6.8) years, and SLEDAI score was 6.5 (2-16) (Table 1).

Upon applying Beck depression inventory, depression was diagnosed in 51.6% in the SLE group compared to 16.7% in control. Among the active SLE group 19 patients (63.3%) were identified versus 12 (40%) in the inactive group (*P*< 0.001). Moderate to severe grades of depression were reported predominantly among the active SLE group (68.4% and 21.1% respectively) with *P* value < 0.001 (Table 1).

Patients with lupus showed higher TNF-α values 540 (345-700) ng/l compared to controls 140 (120-157.5) ng/l. Furthermore, patients with increased disease activity had significantly higher TNF-α values 650 (412.5-727.5) ng/l compared to the inactive SLE 385 (240-577.5) ng/l and control groups (*P* <0.001) (Table 1). TNF-α could distinguish active and inactive SLE patients via Receiver-operating characteristic (ROC) curve with p value <0.0001, where TNF-α cut-off level was (>630 ng/l). Sensitivity and specificity were 53.33% and 86.67% respectively.

Table 1. Socio-demographic and clinical characteristics of the participants

Variable	Active SLE (n=30)	Inactive SLE (n=30)	Control (n=30)	*P*-value*
Age (years)	30.8 ± 10	36 ± 9	31 ± 11	NS [a]
Duration of illness	3 (0.6-6)	4 (2-7)		
	3 (0.8-6.8)			
SLEDAI score	16 (14-21.3)	2 (0-2)		
	6.5 (2-16)			
Hemoglobin (g/dl)	9.7 ± 1.8	11.1 ± 1.3	11.4 ± 1.1	<0.001 [a]
WBC (k/mm3)	5.7 (2.7-8.6)	7.3 (5.7-9.3)	5.3 (4.3-7.2)	0.028 [b]
Platelets (k/mm3)	206 (112.8-320.3)	286.5 (163.8-358.8)	268.5 (227.3-314.3)	NS [b]
Creatinine (mg/dl)	0.9 (0.7-1.3)	0.7 (0.7-0.9)	0.8- (0.6-0.9)	NS [b]
ESR (mm/h)	81.5 (52.5-113.5)	33 (17-48.5)	14 (7.5-18)	<0.001 [b]
TNF-α (ng/l)	650 (412.5-727.5)	385 (240-577.5)	140 (120-157.5)	<0.001 [b]
	540(345-700)			
Prevalence of depression	19 (63.3%)	12 (40.0%)	5 (16.7%)	0.001 [c]
BDI	24 (20-29)	15 (13-18.75)	8(6.5-14.5)	<0.001 [b]
Severity of depression				
Minimal	0 (0.0%)	0 (0.0%)	3 (60.0%)	<0.001 [d]
Mild	2 (10.5%)	8 (66.7%)	1 (20.0%)	
Moderate	13 (68.4%)	4 (33.3%)	1 (20.0%)	
Severe	4 (21.1%)	0 (0.0%)	0 (0.0%)	

Data are presented as mean ± standard deviation (SD), median (interquartile range (IQR)) and number percent (%). SLE: systemic lupus erythromatosis, SLEDAI: SLE activity index, WBCs: white blood cells, ESR: erythrocyte sedimentation rate, TNF: tumor necrosis factor, a: one-way ANOVA test, b: Kruskal–Wallis test, c: Chi-squared test, d: Fisher's exact test, *P* > 0.05 is not significant (NS).

TNF-α was significantly positively correlated with SELDAI score (r= 0.364, *P*=0.004), BECK score (r=0.385, *P*=0.002) and ESR (r=0.316, *P*=0.014). Nonetheless, it wasn't correlated neither with age of patients, nor disease duration of SLE (Table 2, Fig 1, 2). On comparing patients with lupus and depression with those without depression, TNF-α was found to be the only significant factor (p is 0.003). Surprisingly, age, SLEDAI score, disease duration, and ESR (mm/h) didn't exhibit any statistical significance (table 3).

Table 2. Correlation between TNF-α and other quantitative variables in SLE cases.

Variable	TNF-α	
	r_s	*P*-value
Age (years)	0.147	NS
Disease duration (years)	-0.135	NS
ESR (mm/h)	0.316	0.014*
SLEDAI score	0.364	0.004**
Beck score	0.385	0.002**

r_s: Spearman's Correlation coefficient, ESR: erythrocyte sedimentation rate, SLEDAI: systemic lupus erythromatosis activity index, *Correlation is significant at the 0.05 level (2-tailed), **. Correlation is highly significant at the 0.01 level (2-tailed). *P*>0.05 is not significant (NS).

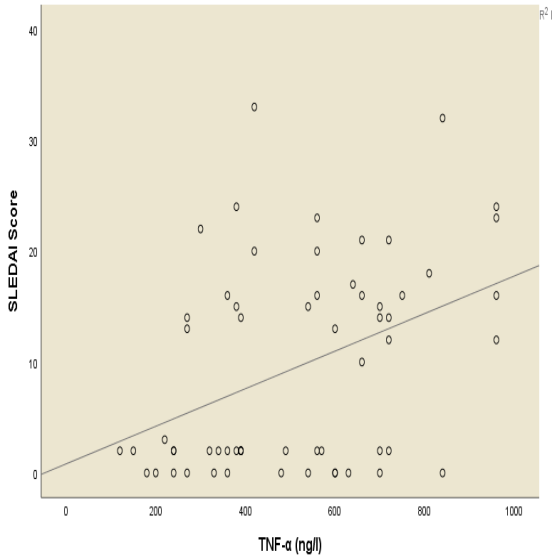

Figure 1. Scatter plot showing the correlation between TNF-α and SLEDAI score in patients with SLE.

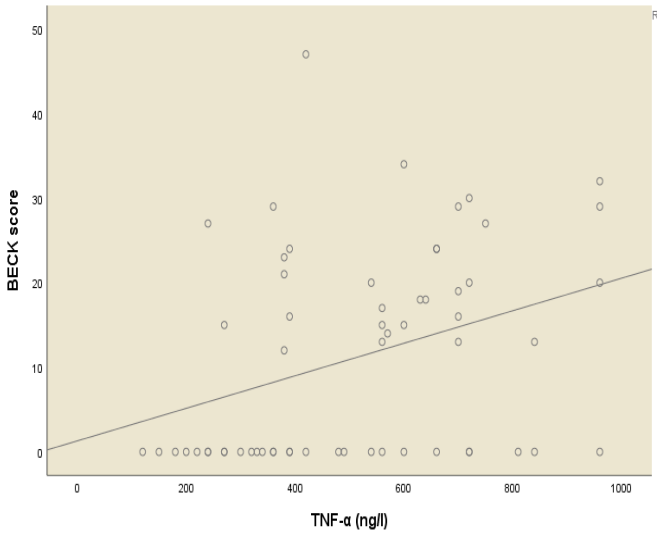

Figure 2. Scatter plot showing the correlation between TNF-α and BECK score in patients with SLE.

TNF-α levels were increased among both patients with active and inactive SLE with depression compared to those without depression. Yet, statistical significance was only attained among patients with inactive disease (*P* =0.002) (Table 3). TNF-α cut-off value (> 360ng/l) could differentiate patients with SLE with and without depression by means of ROC curve (*P*= 0.0008). Sensitivity was 90.32% while, specificity was 51.72%. On applying this level on SLE patients, TNF was positive among 90.3% of SLE patients with depression compared to 48.3% of patients with no depression which was highly significant (*P* is 0.001). (Table 4)

Table 3. Comparison between SLE patients with or without depression

	Cases of SLE (n=60)		*P-value
	Depression (n=31)	No depression (n=29)	
Age (years)	34.2 ± 10.6	32.6 ± 9.1	NS[a]
Disease duration (years)	3 (0.7-7)	3.5 (1.3-6)	NS[b]
TNF-α (ng/l)	600 (390-700)	360 (255-580)	0.003[b]
TNF-α (ng/l) in *Active SLE*	640 (420-720)	660 (300-810)	NS[b]
TNF-α (ng/l) in *Inactive SLE*	585 (382.5-700)	335 (215-412.5)	0.002[b]
ESR (mm/h)	54 (36-100)	40 (18.5-79)	NS[b]
SLEDAI score	14 (2-16)	2 (0-16)	NS[b]
SLE			
Active	19 (61.3%)	11 (37.9%)	NS[c]
Inactive	12 (38.7%)	18 (62.1%)	

Data are presented as mean ± standard deviation (SD), median (interquartile range (IQR)). SLE: systemic lupus erythromatosis, ESR: erythrocyte sedimentation rate, SLEDAI: SLE activity index, TNF tumor necrosis factor, a: Independent Samples t Test, b: Mann–Whitney U test, c: Chi-squared test, *P* > 0.05 is not significant (NS).

Table 4. TNF positivity in patients with or without depression in either SLE group

		Depression	No depression	p-value
TNF-α (ng/l)	Positive	28 (90.3%)	14 (48.3%)	<0.001[a]
	Negative	3 (9.7%)	15 (51.7%)	

TNF: tumor necrosis factor, a: Chi-squared test, *P*<0.05 is significant.

A binary logistic regression analysis for prediction of depression in patients with SLE analysis showed that TNF-*α was the only independent predictor of depression* in patients with SLE (odds ratio = 1.004, 95% CI = 1.001 to 1.008, *P* =0.022). Nevertheless, after adjustment of the effect of other variables, there was no statistically significant correlation between activity of SLE, or disease duration and depression (Table 5).

Table 5. binary logistic regression analysis for prediction of depression in patients with SLE

	Odds ratio	95% CI	*P*-value
Age	1.021	0.950 - 1.096	NS
SLEDAI Score	1.038	0.951 - 1.134	NS
Duration of illness	0.995	0.853 - 1.160	NS
WBC (k/mm3)	1.068	0.816 - 1.397	NS
Hemoglobin (g/dl)	0.986	0.638 - 1.524	NS
Platelets (k/mm3)	1.002	0.997 - 1.008	NS
Creatinine (mg/dl)	0.442	0.174 - 1.126	NS
ESR (mm/h)	1.011	0.990 - 1.034	NS
TNF-α (ng/l)	1.004	1.001 - 1.008	0.022

95% CI=95% confidence interval, WBCs: white blood cells, ESR: erythrocyte sedimentation rate, TNF tumor necrosis factor, *P* > 0.05 is not significant (NS).

Discussion

This study was conducted to explore the prospective role of TNF-α in predicting depressive symptoms among Egyptian female patients with SLE. We selected sixty female patients with SLE (30 active and 30 inactive according to SLEDAI score), and compared them to 30 apparently healthy females.

In the present study, 31 patients with SLE (51.6%) were diagnosed with depression. This was in agreement with the outcome of previous studies, which examined the association between SLE and depression, where frequency of depression was estimated to be 45.2%[32] and 50%.[33] Other studies reported higher prevalence of depression[34, 35] (64%, 67.6%, and 64.5% respectively). On the contrary, the systematic review done by Zhang et al. [4] concluded that the prevalence of depression was 39% among patients with SLE. This disparity could be clarified as half of our patients with SLE were selected in activity and hence, depression was more prevalent and more severe among the active group.

Another substantial finding was that, moderate to severe degrees of depression (according to BECK score), were principally found among the active SLE group (P <0.001). This was supported by the results of Raafat et al., who noted that patients with SLE, who developed depressive symptoms, experienced more severe degree, along with increased SLE activity.[34]

In the current study, patients with lupus and depression showed higher SLEDAI scores than those without. However, this was not of statistical significance. This was in agreement with some preceding studies.[1, 36] Contrarily, Bachen et al. concluded that disease activity was a significant predictor of depression (OR= 1.10; P = 0.001). The authors utilized the modified Systemic Lupus Activity Questionnaire (SLAQ) so as to abolish the influence of symptoms overlapping with depression (fatigue, depression, and amnesia). Discrepancy with our results might be due to different modalities used to evaluate the activity of SLE.[8]

Researches exploring the correlation between SLE activity and TNF-α value showed conflicting results. Our results concluded that TNF-α value was significantly elevated in the active SLE group compared to the inactive SLE and control groups. Furthermore, there was a significant positive correlation between TNF-α level and SLEDAI score (r= 0.364, P <0.004). Comparable outcomes were obtained by different studies.[37, 38, 39] On the other hand, Gómez et al. affirmed that patients with lupus showed higher levels of TNF-α yet, it was higher amongst the inactive SLE group than active ones, and this was contradictory with our aforementioned results.[40] This conflict could be speculated by the fact that TNF-α has both immune regulatory and pro-inflammatory roles.[41] TNF receptor 1 mediates both inflammatory and anti-inflammatory actions, while TNF receptor 2 mediates the inflammatory role only.[42]

Our findings indicated that, patients with SLE and depression had significantly higher serum TNF-α level with respect to those without depression (P= 0.003). This corroborates the results of previous studies,[39, 43] where the authors found that patients with SLE and major depression had significantly higher levels of serum TNF-α compared to controls. Likewise, we concluded that TNF-α was the only independent predictor of depression (P=0.022). This supports the preceding research by Postal et al., who stated that, serum TNF-α levels were independently associated with depressive symptoms (P=0.002) through a multivariate analysis.[39] Pathogenesis of major depression extends beyond the classic monoamine concept.[44] Pro-inflammatory cytokines especially TNF alpha were found to be high in patients with depression. They could alter the physiology of both neurotransmitter activity and endocrinal glands.[45]

To sum up, studies relating TNF-α to depression in patients with SLE found that TNF-α levels were significantly correlated with both SLE disease activity[18, 37] and severity of depressive symptoms,[38, 39] thus highlighting the potential role of TNF-α in anticipating SLE activity and depressive symptoms in SLE patients.

Our study was limited by relatively small sample size, short period of follow up and being limited to one tertiary hospital. Further studies are needed about treatment modalities targeting TNF-α in those patients.

In conclusion, frequency of depression is high among patients with SLE especially those with

increased activity. TNF-α is the independent predicting factor for depression in this population. Screening for depression is essential during follow up of patients with lupus and referral for treatment once detected.

Author Contributions

AO designed the idea and the tools of the study. MN revised step by step the recruitment of patients, and the tools used, DA collected, analyzed and interpreted the data. MH performed the interview and psychological assessment of patients, AM made the statistical analysis and interpreted the results. RSh proposed the methodology of the study, and ST wrote the manuscript. All authors agreed with the results and conclusions of this article. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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

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Ethical approval

Approval of the research protocol ethically was done by the Research Ethics Committee, Faculty of Medicine, Ain Shams University.

Informed consent

All participants signed a written informed consent before performing clinical, neuropsychological, and biochemical assessments.

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