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Correlation of systemic lupus erythematosus disease activity (SLEDAI) with serum level of albumin in lupus patients

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is a common type of rheumatologic disease. Currently there is no universally accepted "gold standard" to measure disease activity. An inexpensive and clinically reliable serological marker for disease activity would therefore be useful to guide treatment and gauge responses to treatment; however, such a marker remains elusive.
Objectives: The aim of this study is to investigate the correlation of systemic lupus erythematosus disease activity index (SLEDAI) with serum level of albumin in lupus patients.
Patients and Methods: The SLEDAI criteria were obtained by reviewing clinical records and Serum albumin, dsDNA, C3 and C4 were measured in lupus patients, and also demographic data including the patients' age, and duration of disease were also collected.
Results: In this study, 60 patients (54 females and 6 males) age 31.10 ±6.63 years were enrolled. A significant negative correlation was observed between serum albumin and SLEDAI ($P = 0.001$, r=-0.42), however, no significant correlation was found between serum albumin with anti-dsDNA ($P = 0.73$, r=0.04), C3 ($P = 0.33$, r=0.14) and C4 (P=0.74, r=-0.05). There was also a direct significant relationship between SLEDAI with anti-dsDNA ($P = 0.02$, r= 0.31) and inverse correlations with C3 ($P = 0.007$, r=-0.40) and C4 level ($P = 0.02$, r=-0.31). Multiple linear regression analysis revealed that serum albumin is the most important factor in predicting SLEDAI among other factors including anti-dsDNA, C3 and C4 (β=0.64, $P = 0.001$). SLEDAI was higher in systemic lupus erythematosus (SLE) patients with hypoalbuminemia compared to SLE patients without hypoalbuminemia ($P = 0.003$).
Conclusion: We found a significant negative relationship between serum albumin and SLEDAI, and also the fact that SLEDAI was significantly higher in SLE patients with hypoalbuminemia than in those without hypoalbuminemia.

Introduction

Since systemic lupus erythematosus (SLE) is an autoimmune disease, which usually involves many organs, no specific marker was introduced as the gold standard to measure the activity of SLE (1). However, among approximately 60 different methods which are used globally to assess the disease activity, Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), seems to be associated with fewer limitations and higher sensitivity (2). On the other hand, studies suggest that serum albumin level may be a useful test to predict the disease activity in SLE patients. Previously, Yip et al conducted a study to evaluate the association of SLEDAI with serum albumin. They found, alongside with lower serum albumin level, there is a

Key point

In a study on 60 SLE patients, we found a significant relationship between serum albumin and SLEDAI.

higher SLEDAI score (3).

Serum albumin level may change in SLE patients through different conditions. The first mechanism is the increased albumin catabolism because of the chronic inflammation. The second is the inadequate intake of protein and calories, happening in some patients especially those who develop SLE. The other mechanism is the suppression of albumin synthesis in the hepatocytes in the case of systemic inflammation (4). Finally, lupus nephritis is an important complication of SLE, which leads to nephrotic range

proteinuria, causing decreased serum albumin level.

In addition to the changes of serum albumin level due to the different phases of SLE, which makes it a possible reliable predictor of the disease activity, it must be considered that serum albumin is an inexpensive available test, which is measured routinely in the patients in different visits. Moreover, studies have reported that serum albumin has been used to predict the outcomes of patients suffering a wide spectrum of diseases such as rheumatoid arthritis, pneumonia, glomerulonephritis and acute ischemic stroke.

The evidence suggests that serum albumin level is affected by a variety of mechanisms in patients suffering from SLE. Since it is an accessible non-aggressive test, which has been used previously to predict the outcomes of varied inflammatory diseases. It may also be useful as an independent predictor of SLE activity. In this study, we aimed to investigate the correlation of serum albumin level with SLEDAI-2K in the case of predicting the disease activity in SLE patients.

Objectives
The aim of this study was to investigate the correlation of serum albumin level with SLEDAI in the case of predicting the disease activity in SLE patients.

Patients and Methods
Study population
This study was conducted on 60 patients with SLE, who were followed up at the rheumatology department, Imam Reza hospital, Mashhad University of Medical Sciences in 2012. The patients who were diagnosed with lupus were included in the study. The exclusion criteria were as follows; patients with severe malnutrition according to MUST method (malnutrition universal screening tools), malignancy, ischemic heart disease, concurrent infections. Cerebrovascular disease, major trauma or surgery in the previous six months, pregnancy and/or other chronic and/or autoimmune systemic conditions (i.e., rheumatoid arthritis, cancer, multiple sclerosis and type 1 diabetes) not related to the main disease. Serum albumin (normal range 3.5–4.5 g/dL), dsDNA (Farr assay >7 U/mL regarded as abnormal), and complements C3 (normal range (90–180 mg/dL) and C4 (20–80 mg/dL) and also SLEDAI criteria, attached as a checklist, were examined; demographic data including the patients' age, and duration of disease were also collected. The criteria of SLE activity are based on SLEDAI-2K questionnaire, which was approved by the University of Toronto in Canada. According to this questionnaire, seizure, psychosis, brain organic syndrome, visual disorders, cranial nerve disorders, lupus headache, CVA (cerebral vascular accident) and vasculitis have 8 scores; score 4 is allocated to arthritis, myositis, urinary cast, hematuria, proteinuria, and pyuria; rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low levels of complement and increased DNA binding have two scores; finally, fever,

thrombocytopenia and leukopenia have one score.

Statistical analysis
Statistical analysis was conducted using SPSS version 15. The normality of data was asses through Shapiro–Wilk test. Additionally, the data were analyzed by chi-square, Fisher's exact, *t* test, Mann Whitney U and correlation coefficient tests. To evaluate the correlation between SLEDAI and serum albumin level, the Pearson's test was used in case of normal distribution; otherwise, Spearman's test was employed. The significance level (*P*) was considered less than 0.05.

Results
Our study group population consisted of 60 patients (54 females, 6 males, mean age; 31.10 ± 6.63 years). The data of demographics and other clinical parameters of SLE patients were presented in Table 1. The frequency of SLEDAI components in these patients was as follows: renal involvement; 26%, seizure; 13.6%, psychosis; 4.5%, pleurisy;13.6%, myositis; 4.5%, arthritis; 86.3%%, malar rash; 81.8%, alopecia; 43.1%, low complement; 38.8%, organic brain syndrome; 31.8%, visual disturbance; 18.18%, pericarditis; 1%, CVA; 4.5%, leukopenia; 27.27% and thrombocytopenia; 27.27%.

A significant inverse correlation was observed between serum albumin and SLEDAI ($P = 0.001$, r = -0.42); since, no significant correlation was found between serum albumin and anti-dsDNA, C3 and C4 levels. We also evaluated the relationship between SLEDAI with levels of anti-dsDNA and complements while, we found a direct significant

Table 1. Data of demographics and clinical parameters of SLE patients

Characteristics	n = 60
Women, n (%)	54 (90)
Age (years), (Mean ± SD)	31.10 ±6.63
SLE duration (months), median (IQR)	52 (27-60)
Serum albumin (g/L), (Mean ± SD)	34.18 ± 0.70
SLEDAI-2K, median (IQR)	23 (16-34)
Anti-ds-DNA (U/mL), median (IQR)	317 (150-785.25)
C3, (mg/dL) median (IQR)	58 (20-80)
C4, (mg/dL) median (IQR)	7.5 (6-22.25)

Table 2. Correlation between SLEDAI score and serum albumin with different demographic and laboratory investigations of the enrolled systemic lupus patients (n=60)

Characteristics	SLEDAI-2K		Serum albumin	
	r	*P* value	r	*P* value
Age (years)	-0.310	0.02	0.18	0.18
SLE duration (months)	0.19	0.15	0.66	0.06
Serum albumin (g/L)	-0.416	0.001	1	
Anti-ds-DNA (U/mL)	0.312	0.02	-0.04	0.73
C3 (mg/dL)	-0.391	0.007	0.15	0.33
C4 (mg/dL)	-0.310	0.02	0.05	0.74

relationship between SLEDAI with anti-dsDNA and C3 and C4 levels (Table 2).

Multiple linear regression analysis revealed that serum albumin is the most important factor in predicting SLEDAI among other factors including anti-ds DNA, C3 and C4 (β = 0.64, P = 0.001) (Table 3), as for the levels of the serum albumin, around 44% (26) of SLE patients have hypoalbuminemia. SLEDAI was higher in SLE patients with hypoalbuminemia compared to SLE patients without hypoalbuminemia (Table 4). However, anti-dsDNA, C3 and C4 did not show any significant difference between patients with hypoalbuminemia and those without hypoalbuminemia.

Discussion

In the present study, we found a significant inverse correlation between serum albumin with SLEDAI and we also observed that SLEDAI was significantly higher in SLE patients with hypoalbuminemia compared to SLE patients without hypoalbuminemia.

Yip et al found that higher SLEDAI is associated with lower levels of albumin in 1078 patients with and without lupus nephritis. This correlation is more important in patients over 50 years old and patients with lupus nephritis (3).

Idborg et al, recently suggested plasma albumin as a possible biomarker of disease activity in SLE (1), while Yip et al, found that higher SLEDAI scores were associated with lower serum albumin levels in a large patient population. This may be due to the fact that, low albumin levels in active patients are a result of kidney injury. Furthermore, the acute-phase response may influence albumin levels.

Serum albumin is a negative acute phase reactant that decreases in response to systemic inflammation in general. Hypoalbuminemia is caused by inflammation and is linked

to inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-a, which cause the metabolism to shift to a catabolic state. Overproduction may result from catabolic changes (5).

Pro-inflammatory cytokines such as IL-1, IL-6, and TNF-a are thought to play a role in the pathophysiology of SLE and are elevated in patients with active disease. Therefore, it is likely that serum albumin is inversely proportional to the magnitude of SLE disease (6). Previous research has shown a negative association between serum albumin levels and SLE activity in patients with renal or gastrointestinal involvement, which supports this hypothesis (7). Proteinuria is a typical symptom of SLE nephritis; therefore, hypoalbuminemia is likely to be more prevalent in these patients (8).

According to the study by Correa-Rodrguez et al, the prognostic nutritional index, which is calculated using both serum albumin and lymphocyte count, could be useful in clinical practice as simple and low-cost biomarkers for monitoring the disease activity in SLE patients (9).

Even after accounting for other laboratory variables commonly used to determine disease activity or inflammation, prognostic nutritional index, anti-dsDNA, and C3 were found to be significantly correlated with SLEDAI-2K, and with anti-dsDNA and C3 levels. TNF- and p-albumin are superior discriminators between patients with SLE and controls, according to Idburg et al (1). As for the levels of serum albumin, in the current study, around 45% (27 patients) of the enrolled patients were hypoalbuminemia. This was also in concordance with previous research (10).

Mild to moderate serum albumin suppression is common in patients with SLE and can be caused by a variety of factors such as kidney loss, disease activity, or protein-losing enteropathy (11).

Table 3. Summary of multiple linear regression analysis for variables predicting SLEDAI

Model	B	Coefficients Std Error	Standardized Coefficients Beta	t	P Value
Constant	60.19	6.988		8.615	0.000
Age (years)	-0.183	0.206	-0.104	-0.892	0.378
Albumin (g/L)	-8.013	1.555	-0.558	-5.152	0.000
dsDNA (U/mL)	0.009	0.004	0.236	2.119	0.040
C3 (mg/dL)	-0.50	0.033	-0.190	-1.547	0.130
C4 (mg/dL)	-0.490	0.123	-0.055	-0.399	0.692

Table 4. Demographic and laboratory investigations information of SLE patients with and without hypoalbuminemia

Variables	Groups		P value
	With hypoalbuminemia (n=27)	Without hypoalbuminemia (n=33)	
Age, years (Mean ± SD)	30.59 ±7.14	31.52 ±6.26	0.37
SLE duration, months, median (IQR)	55 (27.5-82.5)	50 (25-75)	0.65
Anti-ds-DNA, U/mL, median (IQR)	345 (172.5-517.5)	300 (150-450)	0.34
C3 mg/dL, median (IQR)	56 (28-84)	60 (30-90)	0.55
C4, mg/dL, median (IQR)	8(4-12)	7 (3.5-10.5)	0.80
SLEDAI-2K, median (IQR)	33 (16.5-49.5)	21 (10.5-31.5)	0.003

However, determining whether the hypoalbuminemia is caused by the disease or malnutrition is difficult (assessment of nutritional status and disease activity level in systemic lupus erythematosus patients at a tertiary care hospital), though unspecific, albumin is a good biomarker for SLE activity and is an inexpensive routine laboratory analysis done by simple instrumentation with a quick readout(12).

Several lupus activity indices, such as anti-dsDNA antibodies, C3 and C4, however, necessitate specialized laboratories, where analysis is expensive and time-consuming. In a world, where resources are often scarce, our findings are critical in ensuring that patients with SLE have equal access to health and treatment.

Conclusion
In our study, we observed a significant inverse relationship between serum albumin and SLEDAI. We found that lower levels of albumin are associated with the higher activity of lupus disease. Thus, the present study considered together with previous work suggests that serum albumin might be useful in clinical practice as straightforward, inexpensive biomarkers for the evaluation of disease activity in lupus patients. For monitoring disease activity in SLE patients. However, determining whether albumin levels can be considered as a lupus activity marker requires further studies.

Limitations of the study
This was a cross-sectional analysis, and all of the tests were conducted in one session, therefore further researches are necessary to validate the current findings. To better assess, albumin as a disease activity predictor, we recommend, that levels be monitored over time in longitudinal studies, with each person acting as their own monitor.

Authors' contribution
AAZ, ZS, MM and AA were the principal investigators of the study. KS, EM and TZ were included in preparing the concept and design. DZ revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest
The authors declare no conflict of financial interest.

Ethical issues
The thesis preceded the Declaration of Helsinki's tents. All study protocols were accepted by Mashhad University of Medical Sciences' institutional ethical committee (Research Code# 89937). Accordingly, informed consent was taken from all patients before any intervention. This study was supported by a research project, as an internal medicine residency dissertation by Maryam Masinaee in Mashhad University of Medical Sciences (Thesis# 2618). Additionally, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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