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ORIGINAL ARTICLE

Serum Homocysteine Levels and Microalbuminuria in Patient with Systemic Lupus Erythematosus

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SUMMARY

Background: **At present, the relationship between serum homocysteine and microalbuminuria (MAU) in systemic lupus erythematosus (SLE) patients is still unclear. Therefore, the aim of our study was to analyze the association between serum homocysteine and MAU in SLE patients.**
Methods: **The study analyzed 150 patients with SLE at Affiliated Hospital of Youjiang Medical University for Nationalities retrospectively, and we collected for clinical and laboratory data.**
Results: **We found a positive correlation between serum homocysteine and MAU in SLE patients ($r = 0.430$, $p < 0.001$). We found that serum homocysteine levels were increased in SLE patients with MAU positive compared to those who were MAU negative ($p < 0.001$). After adjusting for multiple confounding factors, we found that serum homocysteine maintained a positive correlation with MAU in patients with SLE in multivariate correlation analysis ($p = 0.253$, $r = 0.002$). The receiver operating characteristic (ROC) curve with an area under the curve of 0.730, and serum homocysteine had 72.2% sensitivity and 61.9% specificity with cutoff values 9.0 to identify the SLE patients with MAU positive.**
Conclusions: **The current results found a correlation between serum homocysteine and MAU in SLE patients, suggesting that elevated serum homocysteine levels might be an adverse factor for SLE patients with kidney injury.**
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KEY WORDS

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by autoantibody production, abnormal immune response, and inflammation [1, 2]. Lupus nephritis is caused by immune complex deposition with renal dysfunction [3]. It has been well demonstrated that lupus nephritis is a main complication in patients with SLE, and lupus nephritis increases the risk of cardiovascular disease such as atherosclerosis and myocardial infarction myocarditis [1,4]. Previous evi-

dence suggests that microalbuminuria (MAU) has been considered to be a predictor for early kidney damage in patients with hypertension, diabetes, and rheumatic disease [5,6].

As a sulfur-containing amino acid, homocysteine is an important intermediate in methionine and cysteine metabolism. Serum homocysteine is a noninvasive and available marker in biochemical routine tests. Recent reports suggested that elevated serum homocysteine levels are related to hypertension, type 2 diabetes mellitus, and cardiovascular disease [7]. Increased serum homocysteine is associated with higher risk of artery atherosclerosis, small artery occlusion, and ischemic stroke [8,9]. Furthermore, there is evidence that serum homocysteine levels are independently related to increased risk of terminal kidney failure [10], and MAU is a marker of early kidney injury in patients with SLE. Therefore, the aim of our study was to analyze the association between serum homocysteine and MAU in SLE patients.

MATERIALS AND METHODS

Patients

The study analyzed 150 patients with SLE at the Affiliated Hospital of Youjiang Medical University for Nationalities retrospectively (131 females and 19 males; mean age: 33 years). The diagnosis of patients with SLE was based on the American College of Rheumatology classification criteria [11]. The exclusion criteria were determined: neoplastic disease, hypertension, diabetes mellitus, acute or chronic infection, and mental disease. The Ethical Committee of the Affiliated Hospital of Youjiang Medical University for Nationalities approved this study.

Laboratory tests

We collected clinical and laboratory data. MAU was determined with immunonephelometry. The serum homocysteine levels were measured by enzyme cycle. Glucose (GLU) was detected by the hexokinase method. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were checked using a substrate method. High density lipoprotein cholesterol (HDL-C) was measured by direct method-selection inhibition, low density lipoprotein cholesterol (LDL-C) was measured by using direct method-surfactant removal method. Cholesterol (CHL) was measured by using CHOD-PAP. Triglyceride (TG) was measured using GPO-PAP. Urea nitrogen (UN) and uric acid (UA) were checked by using an enzymatic method. Creatinine (Cr) was checked by using sarcosine oxidase method. These tests were carried out by using an automatic biochemical analyzer (Hitachi 7600, Japan).

Statistical analysis

The data were analyzed by IBM SPSS version 20 for Windows (IBM Corporation, Armonk, NY, USA). The categorical variables were expressed as percentages, and continuous variables were presented as median (range interquartile). Mann-Whitney *U* test was used to compare two independent groups. We tested the correlations with Spearman's approach. The multivariate regression analysis was conducted to assess the correlation between serum homocysteine and MAU in SLE patients. The receiver operating characteristic (ROC) curve was used to estimate the performance of serum homocysteine for SLE patients with MAU positive. All p-values were two-sided, and a value less than 0.05 was defined as statistically significant.

RESULTS

The correlation analysis between serum homocysteine and biochemical data in SLE patients

Clinical and biochemical characteristics of patients with SLE are shown in Table 1. The negative correlations between serum homocysteine and age, ALT, and AST were observed in patients with SLE ($r = -0.195$, $p = 0.017$; $r = -0.251$, $p = 0.002$; $r = -0.333$, $p < 0.001$), and serum homocysteine levels were found to be positively correlated with UN, Cr, and UA ($r = 0.440$, $p < 0.001$; $r = 0.536$, $p < 0.001$ and $r = 0.461$, $p < 0.001$). Importantly, we found a positive correlation between serum homocysteine and MAU in SLE patients ($r = 0.430$, $p < 0.001$).

Multivariate regression analysis determined by serum homocysteine levels in SLE patients

Multivariate regression analysis was used in the present analysis. Age, gender, ALT, AST, UN, UA, Cr, GLU, and homocysteine were included into independent variables in multivariate regression analysis. We found that serum homocysteine maintained a positive correlation with MAU in patients with SLE in multivariate regression analysis ($p = 0.253$, $r = 0.002$), as shown in Table 2.

The diagnostic efficacy of serum homocysteine for SLE patients with MAU

The patients with SLE were grouped into SLE patients with MAU positive and negative. We found that serum homocysteine levels were increased in SLE patients with MAU positive compared to those who were MAU negative ($p < 0.001$), as shown in Figure 1. Further, we used ROC curve to identify the diagnostic efficacy of serum homocysteine for SLE patients with MAU positive, the results found that the ROC curve with area under the curve was 0.730, and serum homocysteine had 72.2% sensitivity and 61.9% specificity with cutoff value of 9.0 (Figure 2).

Table 1. Clinical and biochemical characteristics of patients with SLE.

Parameters	n = 150
Age	33 (25 - 43)
Gender (female, n %)	131 (87.3%)
Glucose	4.7 (4.3 - 5.1)
Alanine aminotransferase	21 (12 - 31)
Aspartate aminotransferase	22 (16 - 36)
High density lipoprotein cholesterol	1.2 (0.9 - 1.5)
Low density lipoprotein cholesterol	2.3 (1.6 - 3.0)
Cholesterol	4.4 (3.5 - 5.4)
Triglyceride	1.6 (1.1 - 2.4)
Urea nitrogen	4.8 (3.5 - 7.0)
Uric acid	315 (238 - 429)
Creatinine	65 (53 - 92)
Homocysteine	10.6 (7.8 - 16.6)
Microalbuminuria	76 (16 - 10,396)

Table 2. The multivariate regression analysis correlated with microalbuminuria in SLE patients.

		Unstandardized coefficients	Standardized coefficients		
	B	Std Error	Beta	t	p-values
Homocysteine	7.421	2.330	0.253	3.185	0.002

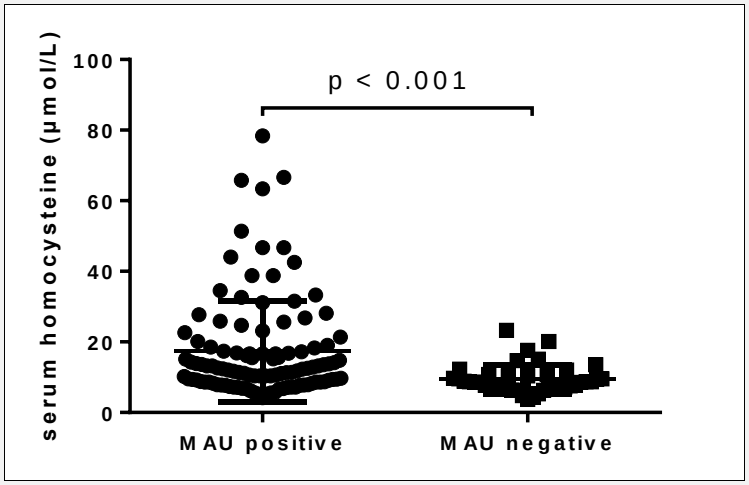

Figure 1. Increased serum homocysteine levels in SLE patients with MAU positive compared to those who were MAU negative ($p < 0.001$).

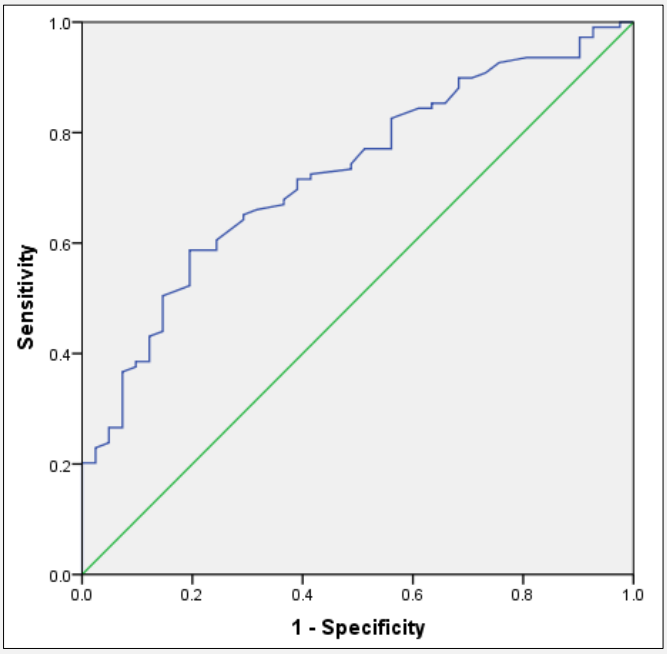

Figure 2. The diagnostic efficacy of serum homocysteine for SLE patients with MAU positive.

DISCUSSION

Evidence has suggested that serum homocysteine levels are closely associated with atherosclerosis, myocardial infarction, and stroke, and serum homocysteine is an independent predictor of cardiovascular disease [7,12-14]. In a previous study, increased serum MAU is not only associated with early kidney damage, diabetes, and hypertension, but it is also a useful indicator for cardiovascular disease [15,16]. Von Feldt JM et al. [17] found that serum homocysteine levels were independently correlated with coronary artery calcification in SLE patients. Hyperhomocysteinemia has been observed in patients with renal disease, particularly in patients with renal function declines [18]. In our study, we found serum homocysteine levels were positively correlated with MAU in patients with SLE.

Several mechanisms may be involved: First, inflammation is an important contributor to this phenomenon, solid evidence showed that elevated serum homocysteine levels are positively correlated with hs-CRP in patients with cardiovascular and lichen planus diseases [19]. Increased serum homocysteine causes atherosclerosis by elevated inflammation and oxidative stress, and serum homocysteine can increase activity of reactive oxygen species [20]. Second, oxidative stress-related signaling pathways may be involved in this current relationship, homocysteine can activate MAP kinase protein-1 to induce endoplasmic reticulum stress in mesangial cells of glomerular disease [21], and homocysteine stimulates ceramide-mediated redox signaling by nuclear factor-κB activation [22,23]. Third, immunological factors may play an important role since homocysteine is related to immune parameters, and homocysteine can activate T lymphocytes to secrete cytokines by the ROS-NF-κB pathway [24-26]. Finally, hyperhomocysteinemia also may lead to endothelial dysfunction and endothelial damage for systemic and renal blood vessels. The factor directly leads to aberrant microalbuminuria in patients with SLE [18-20]. In reverse, inflammation, oxidative stress, and immunologic factors were strongly associated with the appearance of MAU in SLE patients [27-29].

There were several main limitations: First, our study was a small sample size design with retrospective analysis. Second, because this study was a cross-sectional design, we had no way to assess the causal relationship between serum homocysteine and MAU in SLE patients. Third, the influence of treatments on this relationship were not evaluated. Finally, our study did not analyze the specific mechanism for the relationship between serum homocysteine and MAU in SLE patients. Finally, the serum levels of folic acid and vitamin B were associated with serum homocysteine; however, serum levels of folic acid and vitamin B were not tested in SLE patients.

CONCLUSION

The current results found a correlation between serum homocysteine and MAU in SLE patients, elevated serum homocysteine levels might be an adverse factor for SLE patients with kidney injury.

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Declaration of Interest:
The authors have no financial conflicts of interest.

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