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Serum level of matrix metalloproteinase 3 (stromelysin 1) in patients with systemic lupus erythematosus: relation to clinical nephritis and neuropsychiatric manifestations

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Abstract

Aim

The aim of this study was to assess serum matrix metalloproteinase 3 (MMP-3) level in patients of systemic lupus erythematosus (SLE) and its relation to various clinical and laboratory findings.

Patients and methods

The study involved 40 female patients with SLE as a study group and 20 sex-matched and age-matched healthy individuals as a control group. All patients were subjected to thorough clinical examinations and laboratory investigations. Disease activity was assessed using SLE Disease Activity Index, as well as Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. Serum level of MMP-3 was assessed using enzyme-linked immunosorbent assay technique. Patients who showed clinical manifestations of neuropsychiatric lupus were subjected to brain MRI.

Results

The mean serum MMP-3 was significantly higher in patients with SLE than controls (24.93 ± 21.67 vs. 6.98 ± 1.85 , $P < 0.001$) and in patients with nephritis or cerebritis than patients presented with other clinical features ($P = 0.009$ and 0.018 , respectively). Serum MMP-3 was significantly positively correlated with SLE Disease Activity Index ($P = 0.001$) and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index ($P = 0.02$) as well as laboratory markers of disease activity such as anti-double-stranded DNA antibodies and erythrocyte sedimentation rate ($P < 0.001$). Patients with neuropsychiatric lupus showed normal MRI brain findings, except one 21-year-old female patient who presented with psychosis showed atrophic changes. MMP-3 at cutoff of at least $26.7 \mu\text{g/ml}$ can significantly predict patients with nephritis with sensitivity of 77.8% and specificity of 95.5%; area under the curve was 0.842.

Conclusion

MMP-3 was reported to be higher in patients with SLE than controls and patients who presented with either nephritis or neuropsychiatric symptoms showed elevated level of MMP-3 than patients presented with other clinical manifestations. In addition to its proven role in development of lupus nephritis, this study highlighted the possible role of MMP-3 in neuropsychiatric disease.

Keywords: Matrix metalloproteinase 3, nephritis, neuropsychiatric lupus, systemic lupus erythematosus

INTRODUCTION

Matrix metalloproteinases (MMPs) comprise multiple zinc-dependent proteases with a wide range of interactions with extracellular matrix (ECM) components, cytokines, receptors, and cell motility factors [1].

Many human MMPs have been identified. On the basis of their function and structure, they can be subdivided into five

groups: (a) stromelysins-1 and stromelysins-2 (MMP-3 and MMP-10); (b) gelatinases A and B (MMP-2 and MMP-9); (c) collagenases (MMP-1, MMP-8, and MMP-13); (d) ‘classical’

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MMPs that comprise heterogeneous subgroup containing matrilysin (MMP-7), enamelysin (MMP-20), the MMP-20 gene product, macrophage metalloelastase (MMP-12), and MMP-19; and (e) membrane-type MMPs (1–4) and stromelysin-3, MMP-11 [2].

MMP-3 degrades several ECM proteins including fibronectin; elastin; laminin; types III, IV, IX, and X collagens; and cartilage proteoglycans [3].

MMP-3 is also involved in activation of other numerous MMPs including MMP-1, MMP-7, and MMP-9. So, MMP-3 is considered as an upstream MMP activator [4].

MMPs play a significant role in the pathogenesis of several autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE) [5], and Sjögren's syndrome [6].

The objective of this study was to assess serum MMP-3 level in patients with SLE and its relation to various clinical and laboratory findings.

PATIENTS AND METHODS

A total of 40 patients with SLE (diagnosed according to Systemic Lupus International Collaborating Clinics Classification Criteria [7]) were included in this study, along with 20 age-matched and sex-matched apparently healthy individuals as a control group. Patients with age above 18 years old were included, whereas pregnant and lactating women, as well as patients having other comorbidities including autoimmune, infectious, malignant diseases, diabetes, hypertension, or other chronic disorders were excluded.

This study was conducted according to the guidelines of Helsinki Declaration (2000) and was approved by the Ethics Committee of General Organization of Teaching Hospitals and Institutes.

The details of the study were explained to all patients and controls and written consent was signed by each participants before the beginning of the study.

The patients were subjected to full history taking, thorough clinical examination and routine laboratory investigations including immunological profile, in addition to serum MMP-3 assessment.

Disease activity was assessed using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) [8].

Patients were considered to have active renal disease if they fulfilled the following SLEDAI-2k criteria at any time during the study period: proteinuria (>0.5 g/24 h), hematuria (≥ 5 red cells/high-power field), pyuria (≥ 5 leukocytes/high-power field), and urinary casts (in the absence of urinary tract infections).

Similarly patients were considered to have active central nervous system (CNS) disease if they fulfilled the following

SLEDAI-2k criteria: seizure, psychosis, organic brain syndrome, lupus headache, cerebrovascular accident, visual disturbance, or cranial nerve involvement.

Systemic Lupus International Collaborating Clinics/American College of Rheumatology/American College of Rheumatology damage index (SLICC/ACR DI) was also assessed [9].

MRI brain technique

Patients presented with neuropsychiatric lupus were subjected to open brain MRI (0.35-T Siemens Magentom Ci, Germany). The following sequences were used: axial T1-weighted image (WI) and T2-WI, fluid-attenuated inversion recovery WI, sagittal T1-WI, coronal T2-WI, with slice thickness 5 mm, and interslice interval 6 mm (to avoid gap). The patient was supine using head coil and feet lift. No contrast was given. MRI findings were expressed by a neuroradiologist (that was blinded to patients' clinical manifestations) as either normal findings, brain volume loss (cerebral atrophy) based on sulcus or ventricular enlargement, white matter ischemic lesions, area of infarctions, or the presence of hemorrhage.

Laboratory investigations

Blood samples (5 ml) were taken by venipuncture from each individual. A volume of 2 ml was used for the measurement of erythrocyte sedimentation rate, and the last 3 ml was allowed to coagulate for 30 min at room temperature; subsequently, serum was separated by centrifugation for 10 min at 3000 rpm. and stored at -70°C until biochemical analysis was performed.

Assessment of matrix metalloproteinase 3

Human serum MMP-3 (Kit from Wkea med supplies CORP, Jilin, China) concentration was determined by solid-phase enzyme-linked immunosorbent assay method according to the manufacturer's instructions, where the microtiter plate wells were coated by purified anti-human MMP-3 antibody which capture the MMP-3 of the samples. The enzyme labeled with anti-MMP-3 antibody formed antibody-antigen-enzyme-antibody complex after corresponding antigen capture. After washing completely, substrate was added forming blue color at horseradish peroxidase enzyme – catalyzed reaction that was terminated by the addition of a sulfuric acid solution and the color change was measured spectrophotometrically at a wavelength of 450 nm. The concentration of MMP-3 in the samples was determined by comparing the optical density (absorbance) of the samples with the standard curve [10].

Statistical analysis

The collected data were tabulated and analyzed using SPSS, version 16 software (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean \pm SD. Data were tested for normality using Shapiro–Wilk test, assuming normality at P value more than 0.05, as proved to be nonparametric. Mann–Whitney U -test was used to detect difference among two independent groups. Spearman's correlation coefficient (ρ) was used to assess correlation. Receiver operating characteristic curve was constructed to detect cutoff value of MMP-3 with optimum

sensitivity and specificity in prediction of nephritis among patients. The accepted level of significance in this work was stated at 0.05 ($P < 0.05$ was considered significant), where P value more than 0.05 is nonsignificant, P value less than 0.05 is significant, and P value less than or equal to 0.001 is highly significant.

RESULTS

A total of 40 patients diagnosed as having SLE (study group) participated in this study along with 20 apparently healthy volunteers (control group). They all were females. Their ages ranged from 18 to 45 years (mean \pm SD: 28.4 ± 5.6 years), whereas the duration of the disease ranged from 1 to 10 years (mean \pm SD: 4.6 ± 2.4 years). Their demographic, clinical, and laboratory data are reviewed in Table 1.

Eighteen patients (45%) showed nephritis (without any clinical evidence of current active CNS disease), depending on the presence of proteinuria, hematuria, pyuria, or cellular casts. Twelve patients (30%) presented with neuropsychiatric disease (without any laboratory evidence of current active nephritis), comprising one patient with seizures, three patients with psychosis, three patients with organic brain syndrome, and five patients with lupus headache. None of these patients fulfilled the classification criteria of antiphospholipid antibody syndrome [11].

MMP-3 level was assessed in patients and controls. It was significantly higher in patients with SLE than controls (24.93 ± 21.67 vs. 6.98 ± 1.85 $\mu\text{g/ml}$, $P < 0.001$) (Table 2) and in patients with nephritis or cerebritis than patients who presented with other clinical features (arthritis, serositis, cutaneous, and hematological) (Table 3).

Serum MMP-3 was significantly positively correlated with SLEDAI ($P = 0.001$), SLICC/ACR DI ($P = 0.02$) as well as laboratory markers of disease activity such as anti-double-stranded DNA antibodies and erythrocyte sedimentation rate ($P < 0.001$) (Table 4).

Patients with neuropsychiatric lupus showed normal MRI brain findings, except for one 21-year-old female patient who presented with psychosis, showing atrophic changes (Fig. 1a and b).

Receiver operating characteristic curve for detection of cutoff value of serum MMP-3 in prediction of nephritis in SLE is shown in Table 5. MMP-3 at cutoff of at least 26.7 $\mu\text{g/ml}$ can significantly predict patients with nephritis with sensitivity of 77.8% and specificity of 95.5%; area under the curve was 0.842.

DISCUSSION

SLE is an autoimmune disease with multiple organ involvement and chronic inflammatory response. Beside the release of inflammatory mediators, different matrix metalloproteinases have been demonstrated to be involved in the pathogenesis of SLE [12].

The aim of this work was to assess serum MMP-3 level in patients of SLE and to determine its relation to various clinical and laboratory findings.

MMP-3 was found to be higher in patients with SLE than controls and in patients with nephritis and neuropsychiatric

Table 1: Demographic, clinical, and laboratory characteristics of patients with systemic lupus erythematosus

Variables	n=40
Age (years)	
Mean \pm SD	28.4 \pm 5.6
Range	18-45
Duration (years) of disease	
Mean \pm SD	4.6 \pm 2.4
Range	1-10
Anti-double-stranded DNA antibody titer (IU/ml)	
Mean \pm SD	182.05 \pm 76.6
Range	67.5-291.2
SLEDAI	
Mean \pm SD	10.73 \pm 4.2
Range	4-20
SLICC/ACR DI	
Mean \pm SD	1.3 \pm 0.5
Range	1-3

SLEDAI, Systemic lupus Erythematosus Disease Activity Index; SLICC/ACR DI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Table 2: Comparing patients with systemic lupus erythematosus and controls regarding serum matrix metalloproteinase 3

Groups	n	Serum MMP-3 (mean \pm SD) ($\mu\text{g/ml}$)	'Z' of Mann-Whitney U	P
Patients	40	24.93 \pm 21.67	6.22	<0.001
Controls	20	6.98 \pm 1.85		(HS)

HS, highly significant; MMP-3, matrix metalloproteinase 3.

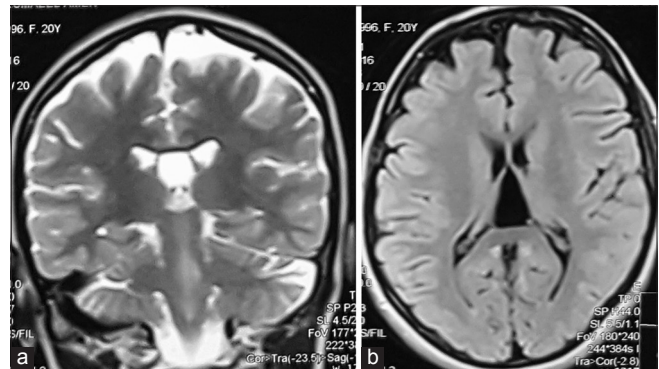


Figure 1: (a) Coronal T2-weighted image, (b) Axial T1-weighted image of a 21-year-old female patient with systemic lupus erythematosus who presented with psychosis. Brain MRI showed prominent (dilated) frontoparietal extra-axial cerebrospinal fluid spaces with normal sized ventricles, indicating mild brain atrophic change

Table 3: Serum level of matrix metalloproteinase 3 in patients with systemic lupus erythematosus presenting with various clinical manifestations

Variable	n	MMP-3 (µg/ml)		'Z' of Mann-Whitney U	P
		Mean ±SD	Range		
Nephritis					
No	22	18.1	6.29	11-29.1	2.61
Yes	18	34.3	23.05	10.3-98.9	
Neuropsychiatric manifestations					
No	28	21.4	12.03	10.3-46.3	2.36
Yes	12	34.7	25.36	15.2-98.9	
Cutaneous manifestations					
No	16	27.2	21.98	10.3-98.9	0.35
Yes	24	24.2	14.95	11-70.7	
Arthritis					
No	18	25.7	16.4	11-70.7	0.45
Yes	22	25.1	19.37	10.3-98.9	
Serositis					
No	34	26.6	18.96	10.3-98.9	0.74
Yes	6	18.8	7.76	11.5-29.4	
Hemolytic anemia					
No	26	23.6	13.55	10.3-70.7	0.28
Yes	14	28.8	24.24	11-98.9	
Thrombocytopenia					
No	28	23.6	14.18	10.3-70.7	0.044
Yes	12	29.7	24.73	11.8-98.9	
Leucopenia					
No	29	24.3	14.3	10.3-70.7	0.58
Yes	11	28.4	25.7	11.8-98.9	
Patients with either nephritis or CNS disease					
No	10	15.74	6.39	11-26.13	2.62
Yes	30	32.4	23.6	10.22-98.95	

CNS, central nervous system; MMP-3, matrix metalloproteinase 3; S, significant.

Table 4: Correlation between matrix metalloproteinase 3 and the studied variables among the patient group

Variables	MMP-3 (n=40)	
	ρ	P
Age	-0.077	0.63
Duration (years)	-0.066	0.68
SLEDAI	0.488	0.001 (HS)
SLICC/ACR DI	0.36	0.02 (S)
Anti-dsDNA antibodies	0.673	<0.001 (HS)
ESR first hour	0.944	<0.001 (HS)

Anti-dsDNA, anti-double-stranded DNA; ESR, erythrocyte sedimentation rate; HS, highly significant; S, significant; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR DI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

manifestations than patients presented with other clinical features. MMP-3 level correlated positively with SLEDAI, SLICC/ACR DI, and laboratory markers such as anti-double-stranded DNA antibodies.

In concordance with these data, a previous Egyptian study conducted by Gheita *et al.* [13] found a significant relation

between MMP-3 and disease activity and patients with SLE presented with nephritis, arthritis, and hematologic disorders showed higher level of MMP-3. Moreover, MMP-3 expression was different among classes of lupus nephritis, being more relevant to class IV.

Regarding CNS manifestations in patients with lupus, Gheita *et al.* [13] did not find any correlation between neuropsychiatric lupus and MMP-3, which is against the findings of this work.

Regarding disease activity, in contrary to this study, Zucker *et al.* [14] failed to find a relation with disease activity while exhibiting increased level of MMP-3 in contrast to other MMPs such as collagenase-1 and gelatinase A.

Despite that the MMP-3 level was elevated in patients with SLE than healthy controls in several studies, no relation to disease activity was reported, suggesting that MMP-3 may be related to later process of tissue repair rather than initial inflammatory and destructive process. Depending on these data, the use of MMP-3-manipulating drugs is not recommended, as it may have hazardous effects owing to blocking the beneficial healing function of MMP-3 [15].

Table 5: Cutoff value of serum matrix metalloproteinase 3 in prediction of nephritis among the patient group

MMP-3	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC	95% CI
≥26.7	77.8	95.5	93.3	84	87.5	0.842	0.69-0.99

AUC, area under the curve; CI, confidence interval; MMP-3, matrix metalloproteinase 3; NPV, negative predictive value; PPV, positive predictive value.

In this study, MMP-3 was higher in patients who presented with clinical and laboratory markers of active nephritis such as proteinuria, urinary casts, and anti-double-stranded DNA antibodies. These results are in agreement with Kotajima *et al.* [5], who also found a correlation with other laboratory tests like serum uric acid and triglycerides. This pointed to the role of this MMP in different pathological mechanisms of the disease.

Higher level of MMP-3 is closely related to tissue destruction in lupus nephritis. Therefore, balance between MMP-3 and tissue inhibitors of metalloproteinases should be present. Changes in cellularity is a major characteristic of many glomerular diseases, which in turn will affect the structural of glomerular ECM and turnover. MMPs will affect the glomerular cell behavior as well as matrix turnover by influencing certain growth factors like protein binding of insulin-like growth factor-1 [16].

In this work, 12 of the 40 patients enrolled had neuropsychiatric lupus. MMP-3 level was higher in those patients than others who showed other clinical manifestations, which refers to its possible role in the development of CNS disease in SLE. MMP-3 was proven to cause disruption of blood–brain barrier (BBB) through studies performed on traumatic brain injury, where trauma and inflammation induce MMP-3 production [17].

Studying the level of MMP-3 in both MMP-3 wild-type and knockout mice showed increase permeability of BBB following induced trauma. Wild-type mice showed lower level of the proteins that form the tight junction between the cells such as claudin-5, occludin, and laminin- α 1 suggesting the important role of MMP-3 in destruction of tight junction and basal lamina protein of BBB [18].

Similarly, MMP-3 was found to play a role in destruction of blood–spinal cord barrier after spinal cord injury, as it increase the permeability of that barrier owing to damage of ZO-1 besides claudin-5 and occludin [19], which provides easy axis for inflammatory cells to invade the tissues, among them neutrophils that carry MMP-9, bringing more MMPs to cause exaggerated inflammatory response [20,21].

This may give a clue for explaining the results of this work with higher level of MMP-3 in patients with clinical CNS disease, although poor correlation with radiological findings was found.

In addition to the role of MMP-3 in destruction of several types of collagen and proteoglycans as well as other matrix proteins, it influences the activity of other MMPs such as MMP-1, MMP-7, and MMP-9 [22].

MMP-3 stimulates the release of tumor necrosis factor α and prostaglandin E2 (through activation of cyclooxygenase-2)

from macrophages which in turn increase the release of MMP-9 [23].

Previous data insisted on amplification circuit between MMP-3 and other MMPs. Plasmin generates active MMP-3 from its zymogen and subsequently MMP-3 causes cleavage of pro-MMP-9 (92 kDa) into active enzyme (82 kDa) [24].

So MMP-3 plays a role in pathogenesis of SLE through its direct effects and indirectly through activation of other MMPs like MMP-9, which is reported to be increased in the sera from patients with SLE more than controls, and higher level was found in patients presented with discoid rash, Raynaud's phenomenon, mucosal ulcers, pneumonitis, and phospholipid antibodies positivity, although no correlation with disease activity parameters was found [25].

MMP-9 was also found to be related to anti-double-stranded DNA antibodies and other markers of lupus nephritis in another study [26]. It was related to development of epileptic focus by recruitment of inflammatory cells to that site and by modulating effects on neurotransmitters such as glutamate [27].

Intrathecal MMP-9 was found to be increased in patients with neuropsychiatric lupus than in patients without CNS involvement and was significantly correlated with IL-6 and IL-8 levels, suggesting that cytokine-induced MMP-9 may contribute to CNS tissue involvement in SLE [28].

MMP-3 also increases MMP-7 expression which was elevated in advanced stage of SLE with renal and neuropsychiatric activity [29,30].

CONCLUSION

From the previous data, we concluded that MMP-3 is reported to be higher in patients with SLE than controls and patients presented with either nephritis or neuropsychiatric symptoms showed elevated level of MMP-3 than patients presented with other clinical manifestations. In addition to its proven role in development of lupus nephritis, this study highlighted the possible role of MMP-3 in neuropsychiatric disease, but larger studies are needed to confirm these data.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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