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ORIGINAL ARTICLE

The association of urinary plasmin level with renal involvement and disease flare among systemic lupus erythematosus patients

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ABSTRACT

Objectives: To explore the ability to use urinary level of plasmin as an indicator for renal affection and activity in systemic lupus erythematosus (SLE) patients.

Patients and methods: Between April 2020 and October 2020, urine samples from 50 SLE patients (2 males, 48 females; mean age: 35.5±8.1 years; range, 22 to 39 years) and 20 age- and sex-matched healthy controls (2 males, 18 females; mean age: 34.1±6.5 years; range, 27 to 38 years) were collected. The patients were divided into two groups according to the presence or absence of renal manifestations as those with renal disease (n=28) and those without renal disease (n=22). The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), renal activity (rSLEDAI), and Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI) scores were calculated. Renal biopsy was performed to patients with active lupus nephritis (LN). The activity index (AI) and Chronicity Index (CI) were scored.

Results: There was a highly statistically significant difference in the mean urinary plasmin levels between SLE cases and the control group (88.9±42.6 ng/mL *vs.* 21.3±26.8 ng/mL, respectively; p<0.001). A significant elevation was observed (p<0.05) in patients with LN (97.9±46.6 ng/mL) than without (42.7±12.7 ng/mL), particularly in patients with active renal involvement (82.9±26.6 ng/mL) than patients with inactive renal disease (63.2±15.5 ng/mL). There were significant positive correlations between the mean urinary plasmin levels and inflammatory markers, SLEDAI, and rSLEDAI scores.

Conclusion: Urinary level of plasmin is significantly elevated among SLE cases, particularly in those with active LN. The remarkable association between urinary plasmin level and various activity status implies that urinary plasmin can be used as a beneficial marker to monitor lupus nephritis flare.

Keywords: Disease activity, lupus nephritis, systemic lupus erythematosus, urinary plasmin.

Systemic lupus erythematosus (SLE) is a chronic inflammatory multifactorial autoimmune disorder. Inflammation with the presence of hyperactive B cells is the crucial factor in the pathogenesis of SLE giving a head for production of anti-nuclear antibodies (ANAs) by plasma cells associated with the lack of B-cell tolerance.[1]

Lupus nephritis (LN) is a serious and frequent condition complicated SLE that may develop end-stage renal disease.[2] Treatment of LN is usually based on kidney biopsy findings which is considered the gold standard in the diagnosis, classification and prognosis of LN. However, it is an invasive, costly, risky procedure, not

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applicable for all cases as a routine tool for follow up of disease flare and lacks the capability to predict patients that will respond well to immunosuppressive drugs.[3]

In addition to these limitations, certain histological findings including thrombotic microangiopathy, vasculitic lesions, and lupus vasculopathy are not included in the present classification of LN which can change the management decision and be associated with a poorer renal prognosis.[4] Thus, researches have focused on other non-invasive, site-specific, and immune process-related biomarkers for initial diagnosis and monitoring of response to treatment.[5]

Subsequently, numerous urinary and serum biomarkers have been considered in SLE patients for the study of LN. The advantage of urine over serum samples is that they can be easily collected and may reflect more accurately the underlying renal inflammation and injury.[4]

Some authors have reported a significant elevation of urinary levels of transferrin, alpha-1-acid glycoprotein (AGP-1), monocyte chemoattractant protein 1 (MCP-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) in active LN patients compared to those with inactive disease and control.[5] Others have reported a significant elevation of serum and urine pentraxin 3 levels in lupus patients with renal involvement than in non-renal lupus patients.[6] Nevertheless, no association between serum pentraxin 3 and renal disease in childhood-onset SLE has been found.[7,8]

In the mammalian body, plasmin, primarily a blood protein, acts a diversity of physiological functions.[9] It has been highlighted that the formation of plasmin at the site of tissue damage would facilitate the proinflammatory response, enhance recruitment of phagocytes, and augment clearance of debris by phagocytes.[10] Moreover, plasmin plays a role in the fibrinolytic mechanism to dissolve blood clots, whether formed regularly in cases of injury or unusually in cases of thrombosis.[11]

In the present study, we aimed to explore the ability to use urinary level of plasmin as an indicator for renal affection and disease activity in SLE patients.

PATIENTS AND METHODS

This case control study was conducted at Benha University Hospitals, Rheumatology, Rehabilitation and Physical Medicine Department between April 2020 and October 2020. Urine samples (5 mL) from 50 SLE patients (2 males, 48 females; mean age: 35.5±8.1 years; range, 22 to 39 years) fulfilling the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria[12] and 20 age- and sex-matched healthy controls (2 males, 18 females; mean age: 34.1±6.5 years; range, 27 to 38 years) were collected. The SLE patients were divided regarding the presence or absence of renal involvement into: those with renal involvement and those with non-renal involvement. Patients aged <16 years, suffering from other autoimmune disease, congenital renal disease or any risk factors for renal insult, renal replacement therapy, pregnant females, active infection (urinary tract or systemic infection) which was confirmed to be free of infection by negative urine bacterial culture and by the absence of any features suggestive of infection upon follow-up in the absence of antibiotic treatment were excluded.

Diagnosis of LN was done based on laboratory findings (proteinuria >500 mg/day and/or cellular casts [red blood cells, granular, tubular or mixed]) and the diagnosis was confirmed by renal biopsy either collected from patients' data or recently performed.

Full history including medication history was obtained and clinical examination was performed. Disease activity of SLE patients was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[13] ranging from 0 to 20 with a score of 0 indicating no activity, mild activity from 1-5, moderate activity from 6-10, high activity from 11-19, and a score of 20 indicates very high activity. The renal SLEDAI (rSLEDAI) score[14] includes four kidney-related parameters: hematuria, pyuria, proteinuria and urinary casts. The SLE patients were, then, classified as having either active LN where there was active urine sediment or proteinuria (rSLEDAI >0) or inactive LN (inactive urine sediment and no proteinuria [rSLEDAI=0]). The presence

of each one of the four parameters takes a score of 4 points with a maximum activity score of 16. Organ damage was determined by the Systemic Lupus International Collaborating Clinics Damage Index (SLICC-DI) score.[15]

Renal biopsy was obtained ultrasound guided using a tru-cut needle biopsy, from SLE patients with active LN based on parameters of renal SLEDAI score and, then, analyzed and graded using the International Society of Nephrology/Renal Pathology Society classification.[16]

Venous blood samples from all participants were collected and the following laboratory parameters were ordered: complete blood count (CBC) using a Sysmex 5000 counter; erythrocyte sedimentation rate (ESR) determination using the Wintergreen method and C-reactive protein (CRP) by latex agglutination slide test, kidney function tests (serum creatinine, blood urea nitrogen [BUN], creatinine clearance), ANA by indirect immunofluorescent test using HEP-2 substrate, (IMMCO Diagnostics Inc., NY, USA), anti-double stranded deoxyribonucleic acid (anti-dSDNA) antibodies by EIA (the Binding Site, Birmingham, U.K), Complement (C3&C4) by immunodiffusion plate method, complete urine analysis, 24-h urinary protein and protein-to-creatinine ratio (P/C ratio). As a preparatory step for renal biopsy, prothrombin time (PT), partial thromboplastin time (PPT), and international normalized ratio (INR) were determined on Diagnostica Stago (Asnières-sur-Seine, France).

Urine samples (5 mL) were collected in the same time with serum samples from all participants and, then, centrifuged (at 2,000 to 3,000 RPM) for approximately 20 min. Supernatants carefully collected by sterile tube and stored at -20°C. The plasmin was measured by enzyme-linked immune sorbent assay (ELISA) (Cat.No: E1136Hu, Shanghai Korain Biotech Co., Ltd. Shanghai, China) according to the manufacturer's instructions.

Statistical analysis

Statistical analysis was performed using the SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The Student t-test, analysis of variance (ANOVA) (F value), chi-square test (χ^2), and Fisher exact test were used to examine the significance of differences according to type of data. The correlation between quantitative variables were done using Spearman correlation analyses and receiver operating characteristics (ROC) analysis detected the validity of urinary plasmin in prediction of cases. A p value of <0.05 was considered statistically significant (*) and of <0.001 considered highly statistically significant (**).

RESULTS

Both SLE and control groups were comparable in terms of age and sex (p=0.47, 1.0 respectively). The SLE patients were further divided into two groups as SLE patients with LN (n=28) and SLE patients without LN (n=22). Baseline characteristics of patients and control groups were summarized in Table 1.

The mean urinary plasmin levels tended to be significantly higher in patients (88.9±42.6 ng/mL) than in controls (21.3±26.8 ng/mL) (p<0.001). No significant difference was found between urinary plasmin and the sex of SLE patients (p=0.69). Comparison between SLE patients with and without LN and the healthy control group in terms of the mean urinary plasmin level was shown in Figure 1. Table 2 shows the mean urinary plasmin levels in SLE patients according to the presence and absence of some clinical manifestations. Among the studied LN patients (28/50), there were 10 (35.7%) cases with inactive renal disease (renal SLEDAI=0) and 18 (64.3%) were considered active (renal SELEDAI ≥4). A significant difference was observed between active and inactive LN patients in terms of the mean urinary plasmin levels (p=0.02) (Table 3). The active LN patients (18/28) were subjected to renal biopsy with six cases classified as Grade II, four cases with Grade III, five cases with Grade IV, and three cases with Grade V with a mean activity index score of 6.2±4.9 and a mean chronicity index score of 3.4±0.1. The relationship between the mean urinary plasmin level among SLE

Table 1. Baseline characteristics of patient and control groups

	SLE with LN (n=28)			SLE without LN (n=22)			Healthy control (n=20)			
Variables	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			26.5±4.1			28.1±3.2			34.1±6.5	0.39
Disease duration (year)			7.8±4.8			6.3±4.1			-	0.83
Sex										0.45
Male	2	7.1		0	0		2	10.0		
Female	26	92.9		22	100		18	90		
Hemoglobin % (gm/dL)			10.1±1.9			10.3±.2.1			13.1±0.8†‡	<0.001**
RBCs ($\times 10^6$) (Cell/uL)			4.1±0.5			4.2±0.5			5.9±0.7†‡	0.003*
Platelets ($\times 10^3$) /mcL			247.3±66.8			264.3±54.8			278.6±49.3	0.63
TLC ($\times 10^6$) Cell/uL			6.7±4.0			7.7±1.1			8.3±1.2	0.65
ESR 1st hour (mm/h)			82.9±33.2			74.9±33.2			16.3±4.3†‡	<0.001**
CRP mg/L			30.5±4.4			25.5±3.3			4.2±0.5†‡	<0.001**
Serum creatinine (mg/dL)			1.0±0.5			0.8±0.2			0.7±0.1	0.15
Proteinuria (gm/24 h urine)			1.3±0.8			0.2±0.1†			0.2±0.1†	<0.001**
P/C ratio Mg protein/mg creatinine			24.0±6.5			0.1±0.0†			0.0±0.0†	<0.001**
Creatinine clearance			75.1±46.1			109.3±12.6†			111.5±3.1†	0.04*
C3 (mg/dL)			82.1±41.1			95.4±52.8†			129.9±43.7†‡	<0.001**
C4 mg/dL			14.9±8.2			22.7±12.5			32.3±12.3†‡	<0.001**
Blood urea			23.2±9.2			27.5±2.1			25.5±1.7	0.18
ANA										<0.001**
Positive	28	100		22	100		†‡0	0.0		
Negative	0	0		0	0		20	100.0		
Anti dsDNA										<0.001**
Positive	17	0.60		12	0.55		†‡0	0.0		
Negative	11	0.40		10	0.45		20	100.0		
SLEDAI			12±4.1			5.6±4.2†			-	0.03*
rSLEDAI			5.9±5.2			-			-	-

SLE: Systemic lupus erythematosus; SD: Standard deviation; RBCs: Red blood cells; TLC: Total leucocyte count; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; C: Complement; ANA: Anti-nuclear antibodies; ds-DNA: Double stranded deoxyribonucleic acid; SLEDAI: Systemic lupus erythematosus disease activity score; † Significant differences compared to SLE patients with LN; ‡ Significant differences compared to SLE patients without LN; * p<0.05 significant; ** p<0.001 highly significant.

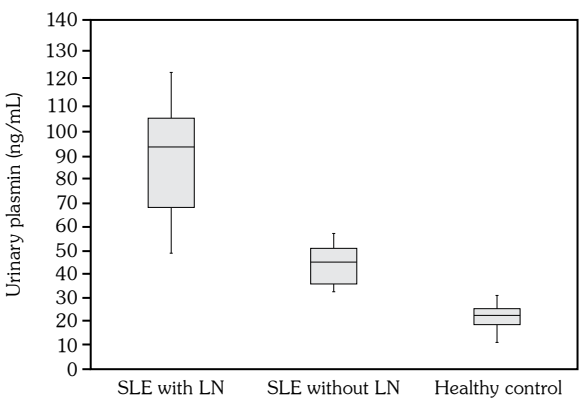

Figure 1. Comparison between SLE patients with & without LN and the healthy control group as regard mean urinary plasmin level.

SLE: Systemic lupus erythematosus; LN: Lupus nephritis.

patients and different grade of renal biopsy was expressed in Table 4.

The mean urinary plasmin levels among SLE patients with positive ds-DNA antibodies in 29/50 (58%) was found to be higher than negative patients (79.1±42.2 ng/mL *vs.* 52.5±48.8 ng/mL, respectively).

Regarding drugs received by SLE cases, there were 29 cases (58.0%) on regular corticosteroids, 27 cases (54.0%) received chloroquine, 26 cases (52.0%) received mycophenolate mofetil, 15 cases (30%) received azathioprine, five cases (10%) received leflunomide, and four cases (8%) received cyclosporine.

Table 2. Mean urinary plasmin levels according to disease manifestations

Clinical manifestation	n	%	Mean±SD (ng/mL)	*p*
Mucocutaneous manifestations				
Yes	45	90	43.1±5.7	0.1
No	5	10	39.1±5.2	
Eye				
Yes	7	14	37.2±78.1	1.0
No	43	86	42.3±1.3	
Arthritis				
Yes	5	10	31.2±21.1	0.21
No	45	90	28.1±35.2	
Renal manifestations				
Yes	28	56	97.9±46.6	0.03*
No	22	44	42.7±12.7	
Pulmonary manifestations				
Yes	12	24	37.8±12.6	2.3
No	38	76	26.3±11.4	
Cardiac manifestations				
Yes	7	14	22.1±18.2	1.6
No	43	86	32.1±8.6	
CNS manifestations				
Yes	6	12	13.6±4.2	3.4
No	44	88	17.1±0.2	

SD: Standard deviation; CNS: Central nervous system manifestations; * p<0.05 significant; ** p<0.001 highly significant.

Table 3. Comparison between active LN cases and inactive LN cases according to mean urinary plasmin levels

	Active LN (n=18)	Inactive LN (n=10)	
Variable	Mean±SD	Mean±SD	*p*
Urinary plasmin level (ng/mL)	82.9±26.6	63.2±15.5	0.02*

LN: Lupus nephritis; SD: Standard deviation; * p<0.05 significant.

Table 4. Comparisons of mean urinary plasmin levels in active LN patients according to renal biopsy grading

		Urinary plasmin level (ng/mL)	
LN grading	n	Mean±SD	*p*
SLE patients with LN class II/III	10	75.3±9.7	0.06*
SLE patients with LN class IV/V	8	84.1±4.2	

LN: Lupus nephritis; SD: Standard deviation; SLE: Systemic lupus erythematosus; * p<0.05 significant.

Table 5 shows the correlations of mean urinary plasmin among SLE cases with different disease parameters. The diagnostic performance of urinary plasmin in SLE is expressed in Table 6.

DISCUSSION

About 30 to 60% of adult SLE patients and up to 70% of juvenile cases suffer from renal involvement which causes higher morbidity and

Table 5. Correlations of mean urinary plasmin levels among SLE cases with different disease variables

Case group (n=50)	Statistical test (r)	*p*
Age	0.13	0.37
Disease duration	0.362	0.01*
Hemoglobin %	0.315	0.26
Red blood cells	0.076	0.60
Platelets	0.261	0.067
Total leucocyte count	0.239	0.095
Erythrocyte sedimentation rate 1st h	0.560	<0.001**
C-reactive protein	0.804	<0.001**
24 h urinary proteins	0.237	0.004**
Serum creatinine	0.041	0.02*
Blood urea	0.728	<0.001**
Anti double stranded deoxyribonucleic acid	0.085	0.559
Anti-nuclear antibodies	0.223	0.12
Complement 3	-0.133	0.03*
Complement 4	-0.320	0.02*
Systemic lupus erythematosus disease activity score	0.631	<0.001**
Systemic lupus international collaborating clinic damage index	0.339	0.016*
Renal systemic lupus erythematosus disease activity score	0.341	0.015*
Renal pathology staging	0.023	0.41
Activity index	0.188	0.01*
Chronicity index	-0.222	0.12

SLE: Systemic lupus erythematosus; * p<0.05 significant. ** p<0.001 highly significant.

Table 6. Diagnostic performance of urinary plasmin

	Case group (n=50)		Control group (n=20)			
Urinary plasmin	n	%	n	%	Statistical test	*p*
≥40.31	42	84.0	7	23.0	7.83	**0.005****
<40.31	8	16.0	13	77.0		
AUC (95% CI)	0.591 (0.461-0.721)					
Cutoff point	40.31					
Sensitivity	84					
Specificity	65.0					
Positive predictive value	85.71					
Negative predictive value	61.9					
Accuracy	87.7					

AUC: Area under the curve; CI: Confidence interval; P value <0.05 (S).

lower survival rates.[4] In general, LN patients and murine LN cases have a greater risk for hypercoagulability[17-19] and coagulation system disorders[17] with intra-renal microthrombosis, associated with more advanced renal pathology and severe clinical disease.[20,21]

Many proteins are involved in the coagulation system and fibrinolysis. Plasmin, one key fibrinolytic protein, circulates in the blood as plasminogen, an inactive protein.[22] Systemic activity reflected on serum biomarkers may not be specific for nephritis. Therefore, recently, the focus has shifted in numerous studies searching for new urinary biomarkers with promising results.[23,24]

In the current study, the mean urinary plasmin level was significantly higher in LN than non-LN patients and healthy controls ($p<0.001$). However, contradicting results have been reported in studies investigating circulating levels of plasminogen/plasmin in SLE patients; some have described elevated plasminogen/plasmin levels compared to healthy controls,[25,26] although others have reported no change in SLE patients' serum levels.[27,28] These opposing outcomes may be related to variable disease activity status at the time of testing, as plasminogen is considered a part of the acute phase response.[29]

There is a limited number of evidence in previous reports suggesting the systemic origin of elevated urine plasmin in LN patients.[2] However, some authors have proposed that angiostatin, the autocatalytic product of plasmin, is extensively expressed inside the kidneys in LN patients.[30]

Production and deposition of autoantibodies together with complement and associated inflammation in the involved organs is a hall mark of SLE.[31] In the current study, there was a highly statistically significant difference between the anti-ds-DNA-positive and negative cases in terms of the mean urine plasmin levels ($p<0.01$).

Concerning treatment of LN, it usually depends on findings of kidney biopsy and assessment of disease flare; however, the repetition of biopsies is infrequently performed.[4] Thus, identification of biomarkers in urine that can differentiate classes of LN and distinguish LN from non-lupus glomerular diseases are requested.[32]

In the present study, there was a statistically non-significant difference in the mean urinary plasmin levels between active LN cases with different histopathological grading ($p<0.06$), although it was correlated with activity index ($p=0.01$), but not with chronicity index ($p=0.12$). However, other authors have documented that urinary angiostatin levels are strongly related to the chronicity index obtained from renal histopathology, supporting the association between urinary plasmin and renal chronicity.[2]

A study investigating the origin of plasmin in murine hypothesized that urinary plasmin originates basically from the kidneys in patients with LN.[33] The authors concluded that tubular urokinase-type plasminogen activator could activate plasminogen and convert to plasmin in nephrotic urine.

Biomarkers are required to differentiate between lupus disease activity and non-lupus-related complaints.[34] In this study, the mean urinary plasmin level was significantly higher in active LN patients than inactive LN ($p=0.03$). Also, urine plasmin levels were significantly correlated with the SLEDAI score ($r=0.63$, $p=0.001$), rSLEDAI score ($r=0.34$, $p=0.015$), and SLICC damage index ($r=0.33$, 0.016). These findings were compatible with previous studies.[2]

There are some reports proving that plasmin has a protective role against crescentic nephritis by limiting glomerular fibrin, collagen, and matrix accumulation in renal fibrosis;[35,36] therefore, plasminogen deficiency is associated with severe functional and histological exacerbation of glomerular injury.[35] Nevertheless, it performs a pathogenic role in renal disease by increasing leukocyte recruitment, converting transforming growth factor-beta (TGF-β) to its active form with subsequent stimulation of renal fibrosis.[37,38]

In the present study, there were significant positive correlations of the mean urinary plasmin level with disease duration ($r=0.36$, $p=0.01$), ESR ($r=0.56$, $p=0.001$), CRP ($r=0.804$, $p=0.001$), 24-h urinary proteins ($r=0.23$, $p=0.004$), serum creatinine ($r=0.04$, $p=0.02$), and BUN ($r=0.72$, $p=0.001$). In addition, there were significant negative correlations with C3 ($r=-0.13$, $p=0.03$) and C4 ($r=-0.32$, $p=0.02$).

The performance of plasmin in the present study showed 84% sensitivity and 65% specificity with a positive predictive value (PPV) of 85.71, consistent with previous findings.[2]

The main limitations of this study are the lack of correlation of the hematological manifestations, the medications received of

the included patients with urine plasmin level, and the limited number of the obtained renal biopsy. Therefore, further comparative studies on different racial groups are required to measure urinary plasmin level before and after treatment of active LN patients to further prove its role in LN and disease flare.

In conclusion, urinary level of plasmin is significantly elevated among SLE cases, particularly in those with active LN. The remarkable association between urinary plasmin level and various activity status implies that urinary plasmin can be used as a beneficial marker to monitor LN flare.

Ethics Committee Approval: The study protocol was approved by the local department committee and the faculty post graduate research committee in January 2020. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient and/or legal guardians

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Cases and data collection, writing, revision: R.F.; Revision: M.S.; Writting and revision: A.S.; Laboratory: S.E.; Cases collection examination: S.M.

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