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Original Article.

The Possible Role of Urinary Matrix Metalloproteinase 7 as an Early Predictor of Lupus Nephritis Flares in Systemic Lupus Erythematosus Patients

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ABSTRACT

Background: Systemic lupus erythematosus **(**SLE) is a multisystemic autoimmune disorder characterized by an excessive and chronic inflammatory response which is a result of abnormalities in the immune responses that cause the formation of harmful autoantibodies and inflammatory cells infiltration in target tissues. **Aim:** to investigate the possible role of urinary matrix metalloproteinase 7 (MMP7) as an early predictor of lupus nephritis (LN) flares in SLE cases by comparing the level of urinary MMP7 in SLE cases without LN, SLE cases with LN and control apparent healthy people. **Methods:** This case-control study was subjected to 60 cases, Group I (SLE group) included 20 cases with SLE without nephritis. Group II (LN group) included 20 patients with LN. Group III (control group) included 20 healthy volunteers. All cases were subjected to clinical examination and laboratory tests including CBC, urine analysis, Kidney function tests, 24-hour proteinuria, C3, C4, ANA, and Anti dsDNA antibodies. Urinary and Serum MMP7 levels were detected by ELISA.**Results:** A highly remarkable variance was found between the three groups regarding serum and urinary MMP7. Regarding serum MMP7, it was notably higher in both SLE patient groups ($p<0.001$) than the control group. Regarding urinary MMP7, it was markedly elevated in both SLE cases groups ($p<0.001$) than in group III, also, remarkably higher in SLE cases with LN than in cases without LN ($p <0.001$). 24hs protein in urine showed a high remarkable positive association with urinary MMP7 in lupus patients with nephritis ($p<0.001$) and without nephritis ($p=0.048$) . Anti dsDNA showed a positive relationship with u MMP7 in lupus nephritis cases ($p= 0.026$).
Conclusion: Our study evaluates the role of urinary MMP7 in SLE patients as a noninvasive biomarker which can be useful as a marker of prediction of LN flares.
Keywords: Systemic lupus erythematosus; matrix metalloproteinase 7 (MMP7) ; Lupus nephritis.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune illness featuring extensive immune complex development in multiple organs, culminating in multisystem diseases. Joints, skin, blood cells, lungs, heart, kidneys, and the neurological system are all involved. Although the exact reasons causing

the pathogenesis of SLE and its progression have not yet been identified, genetic, hormonal, and environmental factors are considered etiological factors. While SLE is a cyclical in nature, its flares and remissions are difficult to predict. As a result, it is critical to establish an appropriate biomarker to assess the activity of SLE [1].

SLE is characterized by immune complexes and nuclear autoantigens forming, causing inflammation. SLE can have a variety of clinical manifestations, involve one or more organs, and be chronic or recurrent. SLE affects all elements of the patient's life, including physical, social, and psychological wellness, and significantly influences quality of life, with greater mortality rates [2].

The hyperactive B cells and defective T cells caused damage to tissue and organs resulting from autoantibodies being produced, complement being activated, and immune complexes being formed and deposited [3].

Adaptive and innate immunological dysregulation have a potential role in SLE pathogenesis, and particular cytokines have been correlated to SLE development [4]. Lupus nephritis (LN) is the causative factor of death in SLE cases [5]. Studies held to assess the activity of renal disease may offer the opportunity to enhance SLE patients survival [6].

Matrix metalloproteinases (MMPs) are zinc-containing proteinases that are essential for tissue growth and integrity [7]. MMP-7 is one of the MMP family's smallest expressed members. MMP-7 expression could elevate the expression of other MMPs, which have been proposed as possible indicators for disease development in LN [8].

The present study aims to Predict lupus nephritis flares by using the relation between urinary MMP-7 and disease activity in LN.

METHODS

Patients:

This case-control study was done on 20 SLE cases with nephritis and 20 SLE patients without nephritis in the outpatient and inpatient clinics of the Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig University hospitals, and 20 healthy age and sex-matched participants. Informed consent was obtained from all participants after an explanation of the procedure and medical research. The research was conducted under the World Medical Association's Code of Ethics (Helsinki Declaration) for human research. This study was carried out after the approval of the Institutional Review Board (IRB).

Cases were allocated into; Group I: It included 20 patients with SLE without nephritis, who fulfilled the ACR/SLICC characteristics of SLE [9]. Group II: It included 20 patients with lupus nephritis who were diagnosed clinically according to ACR criteria as LN patients. Group III: included 20 healthy participants.

Participants were labelled as having SLE if they had biopsy-proven LN and ANA or anti dsDNA autoantibodies. Four of the requirements are present in the case, involving at least one immunologic and one clinical condition.

Patients were excluded if any of the following conditions were present:

Cases with other autoimmune diseases, kidney transplantation. Cases of kidney diseases are associated with other causes such as infection, Diabetes mellitus and essential hypertension, and patients undergo renal dialysis.

Methods:

Cases were subjected to full history taking, general and local examination (inspection, palpation, and range of motion).

Laboratory examination:

Routine laboratory examination was assessed only for the SLE patients groups, and ESR was assessed by using the Westergren method recorded mm/hr [11]. Complete blood count (CBC) using Cell Dyn-Ruby apparatus. C-reactive protein (CRP) by BN prospect nephelometer semines [12], with normal range (1-6 mg/dl). Kidney function tests: BUN and serum creatinine by Cobas 8000 auto analyser (Roch, German). Creatinine, protein in 24hours urine collection, and urine analysis (R.B.Cs, W.B.Cs, Casts and Proteinuria) were assessed. Anti-nuclear antibodies (ANA):

Immunofluorescence was evaluated [13]. Anti double strand deoxyribonucleic acid (Anti dsDNA) titre was assessed. Complement 3 &4 (C3 & C4): by use of immunophlometry using BN pro-spec (DADE BEHRING, New York, USA).

MMP-7: MMP7 was assessed by specific sandwich ELISA according to the instruction of the manufacturer. (SunRed, Shanghai). SLE patients activity was evaluated by SLEDAI score [10].

STATISCAL ANALYSIS

Data was analyzed statistically with IIBM SPSS, version 23.0 (IBM Corporation, Armonk, New York). Quantitative data were described utilizing the mean, standard deviation, and range, while qualitative data were expressed using the number and percentage. To compare two groups of normally distributed variables, the t-test was used. When applicable, the Chi-square test was employed to compare percentages of categorical variables. One-way ANOVA was used to compare quantitative data between the two groups. The Pearson correlation coefficient (r) is a method of determining the degree and direction of a linear association between two variables. The ROC curve was utilized in the diagnosis of a health condition to determine the optimal cutoff for a certain quantitative parameter. All of the tests were two-sided. A p-value < 0.05 considered significant.

RESULTS

Age varied significantly between the two diseased groups being more young in the SLE group with LN (P=0.002) **(Table 1).**

There was a remarkable variance between the two diseased groups regarding malar rash (p=0.003), hair loss (p=<0.001) and pleurisy (p=0.027) being more present in LN patients than in patients without nephritis, the neurological manifestations; headache (p=0.011) and seizures (diagnosed by EEG) (P=0.011) were significantly high in lupus without nephritis. Some clinical manifestations were equally distributed in both groups like arthritis, pericarditis, and leukopenia **(Table 2).**

Laboratory data showed that regarding CBC there was a significant variance between the two groups in TLC and hemoglobin (p=0.038) and (p=0.027) respectively. The laboratory tests showed a notable variation between the two groups in 24 h protein in urine, C3, C4, and Anti dsDNA (p<0.001) **(Table 3).**

A highly remarkable variation was detected between the three groups regarding serum and urinary MMP7. Regarding serum MMP7, it was remarkably higher in both SLE patient groups (p<0.001) than the control group. Regarding urinary MMP7, it was markedly higher in both SLE patient groups (p<0.001) than the control group, also higher in SLE cases with LN than in cases without LN (p<0.001) **(Table 4).**

Out of the measured laboratory variables, only two variables showed a significant relationship with serum MMP7. Hemoglobin showed a positive correlation with serum MMP7 in lupus patients without nephritis (r=0.517, p<0.001) and C3 revealed a positive relationship with s MMP7 in lupus nephritis cases (r=0.362, p= 0.002) **(Table 5).**

Urinary MMP7 revealed a good correlation with Anti-dsDNA in SLE cases with nephritis (p=0.026), and a significant correlation with hemoglobin in the same group. 24h urinary protein showed a positive correlation with urinary MMP7 in SLE cases without nephritis (r=0.447, p=0.048) and a highly marked positive correlation with urinary MMP7 in LN patients (r=0.622, p=<0.001) **(Table 6).**

At the cut-off point (1.628 ng/ml), the serum MMP7 to distinguish between SLE cases with LN and without LN. MMP7 showed sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 65, 35, 50, and 50% respectively. At the cut-off point (3.135 ng/ml), the urinary MMP7 to distinguish between SLE cases with nephritis and without LN. MMP7 showed sensitivity, specificity, PPV, and NPV of 75, 45, 57.62, and 64.29% respectively **(Table 7).**

Table 1: Comparison between the studied groups regarding demographic characteristics and duration of disease:

Demographic characteristics		Groups			P
		Lupus without nephritis group	Lupus with nephritis group	Control group	
		N=20	N=20	N=20	
Gender	**Female**	**18 (80 %)**	**20 (100 %)**	**19 (95%)**	**0.122# (NS)**
	Male	**2 (10%)**	**0 (0 %)**	**1 (5 %)**	
Age (years)	**Mean ± SD**	**37.25±12.35[a]**	**28.55±9.94[bc]**	**32.7±10.44[ab]**	**0.002* (HS)**
	Range	**20 - 64**	**18 – 49**	**18 – 55**	
	Median	**34**	**26**	**35**	
Duration of disease (years)	**Mean ± SD**	**7.45±5.48**	**5.87±4.05**	-	**0.566•**
	Range	**1 – 20**	**1 -15**	-	
	Median	**5.5**	**7**	-	

#chi square&*One-Way ANOVA tests are used to analyze the difference between the groups. Means with different superscripts (a, b, c) are significantly different at P<0.05. **•Student t test** is used to analyze the difference between the two groups. P <0.05 was defined as statistically significant.

Table 2: Distribution of the studied patients according to clinical manifestations:

Clinical manifestations		Groups		P
		Lupus without nephritis group N=20	Lupus with nephritis group N=20	
Constitutional	Fever	2 (10%)	1 (5%)	0.548
Mucocutaneous	Malar rash	16 (80%)	20(100%)	0.003 (S)
	Hair loss	15 (75%)	20 (100%)	<0.001 (HS)
	Oral ulcers	8 (40%)	7 (35%)	0.644
Musculoskeletal	Arthritis	17 (85%)	17 (85%)	1.00
	Myositis	4 (20%)	2 (10%)	0.210
Vascular	Vasculitis	5 (25%)	1 (5%)	0.012 (S)
Neurological	Headache	3 (15%)	0 (0%)	0.011 (S)
	Seizures	3 (15%)	0(0%)	0.011 (S)
Serositis	Pleurisy:	6 (30%)	13 (65%)	0.027 (S)
	Pericarditis:	1 (5%)	1 (5%)	1.00
Hematological	Anemia	12 (60%)	15 (75%)	0.311
	Leukopenia	1 (5%)	1 (5%)	1.00

Chi square test is used to analyze the difference between the two groups.P <0.05 was defined as statistically significant **S:** significant, **HS;** highly significant.

Table 3: Laboratory data and SELDAI score of the studied patients in diseased groups

Parameters		Groups		P
		Lupus without nephritis group N=20	**Lupus with nephritis group N=20**	
TLC (10^3/mm^3)	Mean±SD	5.64±1.94	6.57±2.06	0.038• (S)
	Range	2.7 - 9.7	2.1-11	
	Median	5.2	6.6	
Hemoglobin (g/dl)	Mean±SD	11.59±1.0	11.02±1.29	0.027• (S)
	Range	9.5 – 13	8.9-14.3	
	Median	11.8	10.8	
Platelet count (10^3/mm^3)	Mean±SD	242.75±69.42	266.35±103.45	0.229•
	Range	140-395	160-470	
	Median	229.5	217.5	
CRP (g/dl)	Mean±SD	7.81±11.98	7.77±13.38	0.998•
	Range	1 – 55	0.8-55.8	
	Median	5	3	
ESR (mm/hr.)	Mean±SD	32.0±20.56	36.85±26.35	0.355•
	Range	7 – 94	5-109	
	Median	29	31.5	
BUN (mg/dl)	Mean±SD	16.07±10.1	13.39±3.36	0.109•
	Range	9.6 – 57	8.2-23.4	
	Median	13.75	12.8	
S. Creatinine (mg/dl)	Mean±SD	0.72±0.21	0.76±0.39	0.622•
	Range	0.4 – 1.08	0.3-1.7	
	Median	0.65	0.6	
24h Protein in urine (mg/24 h)	Mean±SD	165.66±95.67	2038.05±2005.58	<0.001 (HS)
	Range	62–368.2	535-6703.5	
	Median	110.5	984.5	
RBCs	Absent	11 (55%)	11(55%)	0.589#
	1-5	8 (40%)	9 (45%)	
	6-10	1 (5%)	0 (0%)	
Pus cells	Absent	8 (40%)	8 (40%)	0.676#
	2-5	8 (40%)	5 (25%)	
	6-30	3 (15%)	5 (25%)	
	>30	1 (5%)	2 (10%)	
Casts	Absent	20 (100%)	20(100%)	-
C3 (o.75 to 1.75) (g/l)	Mean±SD	1.36±0.3	1.1±0.36	<0.001• (HS)
	Range	0.7- 1.7	0.61-1.6	
	Median	1.45	1.1	
	N.hypocomp-lementemia	1 (5%)	5 (25%)	
C4 (0.15 to 0.45) (g/l)	Mean±SD	0.23±0.08	0.16±0.09	<0.001• (HS)
	Range	0.06- 0.32	0.03-0.29	
	Median	0.27	0.16	
	N.hypocompl-ementemia	3 (15%)	7(35%)	
ANA titer:	Positive	20(100%)	20(100%)	-
Anti-dsDNA:	Negative	13 (65%)	3 (15%)	<0.001# (HS)
	Positive	7 (35%)	17 (85%)	
SLEDAI	Mean±SD	13.35±4.72	16.40±3.30	<0.001• (HS)
	Range	(6 – 26)	(10 – 24)	
	Median	12	16	

•**Student t and** #**chi square tests** are used to analyze the difference between the two groups. P <0.05was defined as statistically significant. **S:** significant, **HS:** highly significant.

Table 4: Comparison between the studied groups regarding to serum and urinary MMP7

MMP7 (ng/ml)		Groups			P
		Lupus without nephritis group	**Lupus with nephritis group**	**Control group**	
		N=20	**N=20**	**N=20**	
serum	Mean ± SD	**1.89±0.5[a]**	**1.79±0.6[ab]**	**1.24±0.32[c]**	**<0.001* (HS)**
	Range	**1.20 – 3.049**	**0.95 – 3.218**	**0.721 – 1.801**	
	Median	**1.865**	**1.751**	**1.195**	
Urinary	Mean ± SD	**3.49±1.04[a]**	**4.32±1.49[b]**	**0.55±0.32[c]**	**<0.001* (HS)**
	Range	**2.125 – 6.033**	**2.425 –7.418**	**0.201 – 0.981**	
	Median	**3.2955**	**3.9265**	**0.471**	

*__One-Way ANOVA__ is used to analyze the difference between the groups. Means with different superscripts (a, b, c) are significantly different at P<0.05. **(HS)** highly significant.

Table 5: Correlation between serum MMP7 and laboratory findings

		Serum MMP7			
		Lupus without nephritis N=20		**Lupus with nephritis N=20**	
		r	**P**	**r**	**P**
CBC	Hemoglobin	0.517	<0.001 (HS)	-0.195	0.227
	TLC	0.12	0.943	-0.248	0.123
	PLTs	-0.296	0.063	-0.087	0.592
Acute phase reactant	CRP	0.177	0.273	-0.066	0.686
	ESR	0.313	0.050	0.089	0.587
KFTs(kidney function tests)	S. creatinine	-0.152	0.348	-0.002	0.991
	BUN	0.058	0.724	-0.227	0.159
	24h protein in urine	0.041	0.865	-0.285	0.074
Urine analysis	Hematuria	0.366	0.113	-0.228	0.335
	Pyuria	0.107	0.664	-0.093	0.695
Immunologic data	C3	0.52	0.752	0.362	0.002 (S)
	C4	0.199	0.219	0.291	0.069
	AntidsDNA	Serum MMp7 (ng/ml)			
		Lupus without nephritis N=20			Lupus with nephritis N=20		
		Present	Absent	P•	Present	Absent	P•
		1.86±0.18	1.91±0.61	0.801	1.85±0.63	1.46±0.40	0.332

Correlation between urinary MMP7 and variables is analyzed using **Pearson correlation coefficient**.•**Student t test** is used to analyze the difference between the two groups. P <0.05 was defined as statistically significant.**S:** significant, **HS:** highly significant.

Table 6: Correlation between urinary MMP7 and laboratory variables:

Parameters		Urinary MMP7			
		Lupus without nephritis		Lupus with nephritis	
		r	P	r	P
CBC	Hemoglobin	0.019	0.935	0.510	<0.001 (HS)
	TLC	0.161	0.320	0.242	0.304
	PLTs	-0.122	0.452	0.084	0.607
Acute phase reactant	CRP	-0.185	0.253	-0.169	0.296
	ESR	0.155	0.340	-0.474	0.112
KFTs(kidney function tests)	S. creatinine	-0.370	0.119	-0.192	0.235
	BUN	0.298	0.202	0.300	0.060
	24h protein in urine	0.447	0.048 (S)	0.622	<0.001 (HS)
Urine analysis	Hematuria	0.139	0.559	-0.049	0.838
	Pyuria	-0.060	0.801	-0.006	0.980
Immunologic data	C3	0.081	0.620	-0.261	0.104
	C4	-0.015	0.924	-0.142	0.382
		Urinary MMp7 (ng/ml)			
		Lupus without nephritis N=20		Lupus with nephritis N=20	
		Present	Absent	P*	Present	Absent	P*
	AntidsDNA	4.09±1.08	3.16±0.90	0.540	4.03±1.12	5.94±2.56	0.026 (S)

Correlation between urinary MMP7 and variables is analyzed using **Pearson correlation coefficient.*Student t test** is used to analyze the difference between the two groups. P <0.05 was defined as statistically significant. **S:** significant, **HS:** highly significant.

Table 7: Performance of serum and urinary MMP7 in prediction of lupus nephritis patients among the studied patients

Cut-off (ng/ml)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR	-LR	P
Serum MMP7								
1.628	0.418	65	35	50	50	1.00	1.00	0.223
Urinary MMP7								
3.135	0.660	75	45	57.62	64.29	1.36	0.56	0.008
AUC; area under the curve, **PPV:** positive predictive value, **NPV:** negative predictive value, **+LR:** positive likelihood ration, **-LR:** negative likelihood ratio.**P**<0.05 is significant.								

DISCUSSION

SLE is a multisystem autoimmune illness. It is multifactorial and primarily causes both innate and adaptive immunity to become activated, which in turn causes autoreactive B cells to be activated by T cells and immune complexes to accumulate in tissues, which sets off an autoimmune cascade that may only affect a single organ or may result in frequent systemic involvement. SLE has a variety of clinical presentations that can range from clinically minor, quickly going away symptoms to serious, critical organ involvement. Critical aspects of SLE include clinical and serological heterogeneity [14].

SLE is a prolonged inflammatory disease caused by many factors and negatively affects the majority of body systems. It occurs when the immune system destroys healthy body tissues through unintentional error. Lupus is unpredictable, with periods of aggravation and remission. According to

WHO, females are 10 times more likely than males to have lupus. [15].

Even though the disease impacts many systems, each individual's course may differ based on the disease's severity, the frequency of flare-ups, and periods of remission. The involvement of key organs, such as the kidneys, determines the disease's severity and course of action. LN is one of the most frequent SLE clinical manifestations. It is one of the initial SLE symptoms and affects about 50% of cases [16].

Biomarkers are essential for identifying SLE, monitoring disease progression, and categorizing consequences. However, it is difficult for a single biomarker to adequately reflect the state of the disease due to the clinical heterogeneity of the pathophysiology of SLE. A mix of biomarkers reflecting various disease symptoms may be more useful in assessing SLE because no single biomarker has demonstrated the appropriate SLE specificity and sensitivity [17].

One of the tiniest MMP family members to be secreted is MMP-7. The activity of other MMPs that have been proposed as possible indicators for disease development in LN could be increased by the activation of MMP-7 [18].

The level of uMMP-7 is crucial to be utilize as a non-invasive biomarker of renal disease. MMP-7 is increased in a variety of kidney illnesses, and its protein is mainly localized in the apical area and lumen fluids of the cells of renal tubules, implying that this protein could be released into the urine [19].

So, the present investigation aimed to evaluate the possible role of urinary matrix metalloproteinase7 (MMP7) as an early predictor of LN flares in SLE cases at Zagazig University Hospitals, by comparing the level of urinary MMP7 in SLE cases without LN and SLE patients with LN and control apparent healthy people.

This study included 60 participants, 40 of them were suffering from SLE and 20 were healthy volunteers. an overall 90% of SLE cases were females. That was in agreement with **Abd Elazeem et al.,** [20] who illustrated as The X chromosome may contribute to the disease's severity by raising the incidence of SLE among women, which is also influenced by sex and hormonal factors through unidentified processes.

Our research revealed that there is not a noticeable distinction in gender across the tested groups (P=0.122) and the duration of the disease (P=0.566), these results agreed with **Vira et al.,** [21] who found no statistically substantial association was observed between the two groups of SLE patients regarding sex, and disease duration.

In the present study, comparing the diseased groups we found that age varied significantly being younger in the SLE group with nephritis (P=0.002) which is against **Vira et al.,** [21] who found no marked correlation was observed between the two studied groups concerning age as he studied larger sample size, for this study, 150 SLE cases and matching normal controls were enrolled.

Our study showed that mucocutaneous manifestations (malar rash, hair loss) were significantly higher in LN (p=0.003, p<0.001 respectively), and no marked variance between both diseased groups in haematological and cardiovascular manifestations that were in agreement with **Elsayed, et al.,** [22].

Our study found that pleurisy was substantially higher in LN (p=0.027) and the neurological manifestations; headache (p=0.011) and seizures (diagnosed by EEG) (P=0.011) and vasculitis (P=0.012) were notably high in lupus without nephritis and no remarkable variance in musculoskeletal manifestations between both diseased groups, that was against **Elsayed, et al.,** [22] who found no variance between both diseased groups in pleurisy, neurological manifestation and vasculitis but musculoskeletal manifestations highly significant in LN, as his research was cohort study on SLE patients.

In our research regarding CBC there was a marked variance between the two diseased groups in TLC and haemoglobin (p=0.038) and (p=0.027) respectively, lower in SLE without nephritis that is against **Elsayed, et al.,** [22] who found them significantly lower in LN, that was could be attributed to a different number of cases in that study (LN=102) and (SLE without nephritis=88).

Regarding ESR **Abozaid, et al.,** [23] were in agreement with our results that there was no marked variance between the diseased groups may be due to its lack of specificity as an accurate indicator of SLE activity.

24h protein in urine and anti dsDNA were substantially elevated in LN cases which is in harmony with **Elsayed, et al.,** [22] and **Yu, et al.,** [24] as anti-dsDNA is positively association with LN which is measured by proteinuria, can also determine disease course and guide early treatment.

Regarding C3 and C4 levels we found them markedly lower in LN Though **Abozaid, et al.,** [23] were against our results as they found no remarkable variance between both diseased groups as C3, C4 levels are not only considered a marker of renal affection.

Our study results showed that SLEDAI was substantially higher in LN cases than in SLE cases without nephritis (p=0.001)

These results were followed by **Vira et al.,** [21] who studied SLE patients and divided them according to SLEDAI into 2 groups active and inactive and found 55% of renal affection found in active one.

Regarding serum MMP7, Our results showed serum MMP7 remarkably higher in SLE cases than in controls that were followed by **Vira et al.,** [21] and **Wang et al.,** [18].

Our study results showed no marked variance regarding serum MMP7 between both diseased groups in SLEDAI or clinically, as MMP7 acts as a pro-inflammatory marker and has a role in cell proliferation and inflammation not specific to certain organs.

We also detected that serum MMP7 was positively related to serum C3 agreed with **Goletti et al.,** [25] but incompatible with him as we found no correlation with serum MMP7 and Anti-dsDNA or 24h protein in urine and that may be illustrated as Serum MMP7 levels were substantially greater in cases with an eGFR of 50 mL/min/1.73 m^2 compared to individuals with an eGFR of >50 mL/min/1.73 m^2 and that classification was not present in our study may be established in further researches.

Urinary MMP7 levels were considerably greater in both SLE patient groups (p=0.001) than in the control group, and in SLE cases with LN than in cases without LN (p=0.001) and that is in harmony with **Wang et al.,** [18] who found patients with LN had elevated urinary MMP7 compared with healthy volunteers and SLE without nephritis cases.

Our study showed a positive relationship between urinary MMP7 and Anti dsDNA in SLE patients with nephritis (p=0.026) and 24h protein in urine in both diseased groups that are in agreement with **Wang et al.,** [18] and **Afkarian et al.,** [26] suggesting that MMP7 has a role in kidney pathology.

However, no significant correlation with clinical manifestations or SLEDAI suggests that MMP7 may be related to kidney pathology more than other pathological changes in SLE.

Conclusion

Our study evaluates the role of urinary MMP7 in SLE patients as anon invasive biomarker which can be useful as a marker for the prediction of LN flares.

Conflicts of interest: None

Financial disclosures: None

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Supplementary data

Table 1: Correlation of Serum MMP7 with demographic data and disease activity index (SLEDAI):

	Serum MMP7			
	Lupus without nephritis		Lupus with nephritis	
	r	P	r	P
Age	0.055	0.735	-0.252	0.117
Duration of disease	0.089	0.709	-0.220	0.350
SLEDAI	0.407	0.649	0.033	0.841

Correlation between Serum MMP7 and variables is analyzed using **Pearson correlation coefficient**. P <0.05 was defined as statistically significant.

Table 2: Correlation of serum MMP7 with clinical manifestations

Clinical manifestations		Serum MMP7 (ng/ml)					
		Lupus without nephritis N=20			Lupus with nephritis N=20		
		Absent	Present	P*	Absent	Present	P*
Constitutional	Fever	1.86±0.51	2.20±0.48	0.379	-	-	-
Hematological	Anemia	2.12±0.61	1.75±0.66	0.104	1.55±0.94	1.87±0.48	0.318
	Leucopenia	1.92±0.49	1.36±0.00	0.282	1.79±0.61	-	-
	Thrombocyto-penia	1.89±0.5	-	-	1.79±0.61	-	-
Neurological	Seizures	1.94±0.5	1.65±0.51	0.365	-	-	-
	Headache	1.93±0.50	1.7±0.50	0.480	-	-	-
Vascular	Vasculitis	1.88±0.5	1.92±0.54	0.876	-	-	-
Musculoskeletal	Arthritis	1.87±0.33	1.9±0.53	0.936	1.32±0.18	1.87±0.62	0.154
	Myositis	1.9±0.50	1.9±0.54	0.948	1.81±o.64	1.64±0.22	0.314
Serositis	Pleurisy	1.9±0.52	1.87±0.50	0.907	1.54±0.52	1.93±0.63	0.186
Mucocutaneous	Malar rash	2.05±0.45	1.86±0.85	0.512	-	-	-
	Hair Loss	2.03±0.37	1.85±0.54	0.510	-	-	-
	Oral ulcers	2.01±0.51	1.73±0.46	0.227	1.67±0.41	2.02±0.87	0.341

Student t test is used to analyze the difference between the two groups.P <0.05 was defined as statistically significant.

Table 3: Correlation of urinary MMP7 with demographic data and SLE disease activity index (SLEDAI)

	Urinary MMP7			
	Lupus without nephritis		Lupus with nephritis	
	r	P	r	P
Age	0.288	0.219	-0.076	0.749
Duration of disease	0.165	0.486	-0.033	0.889
SLEDAI	0.102	0.668	-0.397	0.083

Correlation between Serum MMP7 and variables is analyzed using **Pearson correlation coefficient**. P <0.05 was defined as statistically significant.

Table 4: Correlation of urinary MMP7 with clinical manifestations

Clinical manifestations		Urinary MMP7 (ng/ml)					
		Lupus without nephritis N=20			Lupus with nephritis N=20		
		Absent	Present	P*	Absent	Present	P*
Constitutional	Fever	3.52±1.03	3.18±1.50	0.676	-	-	-
Hematological	Anemia	3.47±1.1	3.5±1.05	0.953	5.33±2.15	3.98±1.11	0.081
	Leucopenia	3.42±1.03	4.7±0.00	0.241	4.38±1.51	3.19±0.00	0.453
	Thrombocy-topenia	3.49±1.04	-	-	4.32±1.49	-	-
Neurological	Seizures	3.57±1.11	3.01±0.17	0.065	-	-	-
	Headache	3.54±1.11	3.17±0.46	0.523	-	-	-
Vascular	Vasculitis	3.85±1.15	3.2±0.36	0.277	-	-	-
Musculoskeletal	Arthritis	3.2±0.25	3.5±1.12	0.290	5.14±0.85	4.17±1.55	0.314
	Myositis	3.2±0.85	4.6±1.08	0.012 (S)	4.28±1.54	4.65±1.35	0.753
Serositis	Pleurisy	3.4±1.16	3.69±0.74	0.589	4.86±1.96	4.03±1.16	0.332
Mucocutaneous	Malar rash	3.57±1.05	3.47±1.07	0.862	-	-	-
	Hair Loss	3.71±0.57	3.41±1.16	0.593	-	-	-
	Oral ulcers	3.59±1.07	3.34±1.04	0.622	4.42±0.96	4.12±2.27	0.748

*__Student t test__ is used to analyze the difference between the two groups.P <0.05 was defined as statistically significant. **S:** significant.

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