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The Association of Urinary MCP-1 with Disease Activity of Lupus Nephritis

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Abstract **Original Research Article**

Background*:** The association of urinary MCP-1 (Monocyte Chemoattractant Protein-1) with disease activity in lupus nephritis (LN) has been a subject of significant interest. MCP-1 is a chemokine involved in the recruitment and activation of monocytes, which play a critical role in the pathogenesis of LN. ***Objective: To assess association of Urinary MCP-1 with disease activity of lupus nephritis. ***Method*:** This cross sectional study was conducted in the Department of Nephrology, Dhaka Medical College Hospital, Dhaka from January, 2017 to June, 2018. This cross sectional study was performed on 60 biopsy proven lupus nephritis patients and 30 age and sex matched apparently healthy control subjects. All the patients were recruited as per inclusion and exclusion criteria. Diagnosed SLE patients who had renal involvement and undergone renal biopsy for standard clinical indications were recruited by purposive sampling and divided into two groups of active and inactive LN as per operational definition. ***Results*:** During the study, The urinary MCP-1 was higher in active LN patients compared to the inactive group and both were higher than the level in the control. Plus, highest Sensitivity and specificity of uMCP-1 observed at cutoff value 433 pg/ml, where sensitivity was 0.967 and specificity was 0.900. Among 30 active lupus nephritis cases raised uMCP-1 was found in 29 cases and among 30 inactive lupus nephritis cases raised uMCP-1 was found in 3 cases. uMCP-1 showed very good agreement in diagnosis of lupus nephritis activity according to Kappa statistics. uMCP-1 in diagnosis of lupus nephritis activity showed accuracy, sensitivity, specificity, PPV and NPV were 0.933, 0.967, 0.900, 0.906 and 0.964 respectively. ***Conclusion*:** In conclusion, urinary MCP-1 holds great promise as a useful biomarker for the determination of lupus nephritis activity. Its association with disease activity, predictive value for treatment response and renal outcomes, and non-invasive nature make it an attractive candidate for clinical use. Ongoing research and validation studies are necessary to establish its precise role in disease monitoring, treatment decision-making, and improving patient outcomes in LN.

Keywords: Active lupus nephritis (LN), e urinary MCP-1, clinical status.

INTRODUCTION

Lupus nephritis (LN) is a severe manifestation of systemic lupus erythematosus (SLE) characterized by inflammation and damage to the kidneys. It significantly contributes to morbidity and mortality in SLE patients. The identification of reliable biomarkers for disease activity assessment and monitoring of LN is crucial for effective management and personalized treatment strategies. Among the emerging biomarkers, urinary monocyte chemoattractant protein-1 (MCP-1) has gained considerable attention due to its potential association with disease activity in lupus nephritis [1-4].

MCP-1, also known as C-C motif chemokine ligand 2 (CCL2), is a chemotactic cytokine primarily responsible for attracting monocytes, memory T cells, and natural killer cells to sites of inflammation. It plays a pivotal role in the recruitment and activation of

immune cells, leading to the amplification of the inflammatory response. In the context of LN, elevated MCP-1 levels have been observed in both renal tissue and urine samples of patients [5-7].

Several studies have explored the relationship between urinary MCP-1 and disease activity in lupus nephritis. It has been suggested that increased MCP-1 levels in urine correlate with the severity of renal inflammation, glomerular damage, and impaired renal function. Urinary MCP-1 has shown promise as a non-invasive biomarker for monitoring disease activity and response to treatment in LN.

The measurement of urinary MCP-1 levels can be performed using various techniques, including enzyme-linked immunosorbent assays (ELISA) and multiplex bead-based assays. These methods provide quantitative data on MCP-1 concentration, allowing for comparisons between different patient populations and monitoring changes over time. Additionally, advancements in technology have facilitated the development of point-of-care tests, enabling rapid and convenient assessment of urinary MCP-1 in clinical settings [7-9].

While urinary MCP-1 shows promise as a biomarker for lupus nephritis, further research is needed to establish its clinical utility, validate its predictive value, and determine optimal cutoff levels for disease activity assessment. Moreover, considering the heterogeneity of LN, future studies should explore the potential of combining urinary MCP-1 with other biomarkers to enhance diagnostic accuracy and improve patient stratification.

Urinary MCP-1 holds great potential as a biomarker for disease activity in lupus nephritis. Its association with renal inflammation and its non-invasive measurement make it an attractive candidate for clinical use. Further investigation and validation of its utility are warranted to better understand its role in LN management and potentially guide personalized treatment decisions [10-12].

OBJECTIVE

To evaluate the Urinary MCP-1 with disease activity of lupus nephritis.

METHODOLOGY

This cross sectional study was conducted in the Department of Nephrology, Dhaka Medical College Hospital, Dhaka from January, 2017 to June, 2018. This cross sectional study was performed on 60 biopsy proven lupus nephritis patients and 30 age and sex matched apparently healthy control subjects. All the patients were recruited as per inclusion and exclusion criteria. Diagnosed SLE patients who had renal involvement and undergone renal biopsy for standard clinical indications were recruited by purposive sampling and divided into two groups of active and inactive LN as per operational definition. Diagnosis of SLE was based on having four or more criteria according to the American College of Rheumatology (ACR) criteria for SLE (Tan *et al*., 1982). Biopsies were not done for the purposes of entry into the study but for the standard clinical indications of 24 hours UTP more than 1 gm, UTP >500mg with hematuria or cellular cast and impaired kidney function or decline in kidney functions despite appropriate therapy for SLE nephritis. Biopsies were evaluated according to the International Society of Nephrology / Renal Pathology Society (ISN/RPS) classification of lupus nephritis. The histological activity and chronicity indices were calculated.

All patients were subjected to full history taking including medication history especially immunosuppressive medications. Thorough clinical examination was performed for all patients, including vital signs, chest examination, heart examination, abdominal examination and CNS examination. All available data about LN were recorded.

Laboratory tests were carried out in the form of urine routine and microscopic examination (R/M/E), complete blood count, ESR, Serum creatinine, 24 hours UTP, anti-ds DNA Ab titre and serum C3, C4 levels. eGFR was calculated by Modification of diet in Renal Disease (MDRD) equation.

All patients were subjected to full history taking including medication history especially immunosuppressive medications. Thorough clinical examination was performed for all patients, including vital signs, chest examination, heart examination, abdominal examination and CNS examination. All available data about LN were recorded.

Assessment of disease activity of LN was carried out by the SLEDAI-2K (renal). The SLEDAI is the assessment tool for disease activity of SLE. Twenty four features that are attributed to SLE are listed with a weighted score given to any one that is present at the time of visit or within the last 10 days. The renal SLEDAI consists of four kidney related items : 1. Proteinuria (> 0·5 gm/24 hours), 2. Hematuria (> 5 red blood cells/HPF excluding stone, infection or other cause), 3. Pyuria (> 5 white blood cells /HPF excluding infection) and 4. Urinary cast (Heme-granular or red blood cell casts). The presence of each one of the four parameters takes a score of 4 points, thus the renal SLEDAI score ranged from 0 to a maximum score of 16. Active LN was considered with renal SLEDAI score ≥ 4. Statistical analysis of the study was done by the Statistical Package for Social Science (SPSS-22). The results were presented in tables, figures and diagrams. Categorical data were presented as frequency

& percentage and numerical data as mean & standard deviation.

Confidence interval was considered at 95% level. Chi square test was used for categorical data and Unpaired t test was used for numerical data. Correlation between uMCP-1 levels with relevant laboratory parameters were assessed using Pearson's correlation coefficients.

RESULTS

Table-1 shows demographic profile of the active and inactive lupus nephritis patients. Mean age of the lupus nephritis patients in active and inactive LN was 26.60 ± 8.36 years and 28.80 ± 9.18 years respectively. There was no significant difference in age between active and inactive lupus nephritis patients. Most of the patients in both groups were female. There was also no significant difference in gender between active and inactive lupus nephritis patients.

Table-1: Demographic profile of the patients, (n=60)

	Lupus nephritis		Total n(%)	p value
	Active n(%)	Inactive n(%)		
Age (years)				
≤20	10 (33.3)	6 (20.0)	16 (26.7)	
21 - 30	13 (43.4)	14 (46.7)	27 (45.0)	
31 - 40	4 (13.3)	7 (23.3)	11 (18.3)	
>40	3 (10.0)	3 (10.0)	6 (10.0)	
Total	30 (100.0)	30 (100.0)	60 (100%)	
Mean±SD	26.60 ± 8.36	28.80 ± 9.18	27.70 ± 8.78	[a]0.336
Gender				
Male	0 (0.0)	4 (13.3)	4 (6.7)	[b]0.112
Female	30 (100.0)	26 (86.7)	56 (93.3)	

[a]Unpaired t test and [b]Chi-square test was done to measure the level of significance

Figure-1 shows uMCP-1 level in active & inactive LN patients and controls. The urinary MCP-1 was higher in active LN patients compared to the inactive group and both were higher than the level in the control.

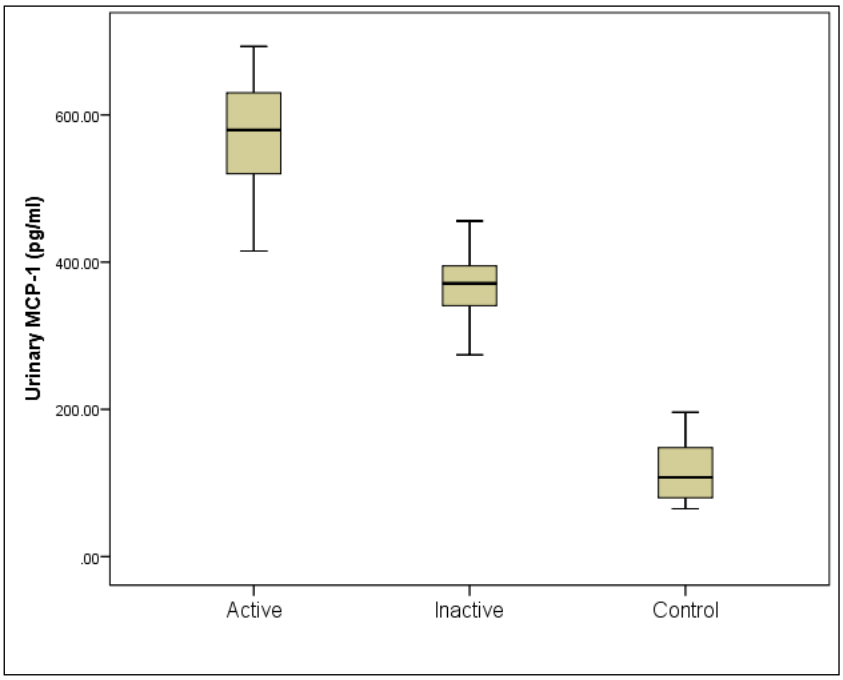

Figure 1: uMCP-1 level in active & inactive LN patients and controls

Table-2 shows Sensitivity and specificity of uMCP-1 at different cutoff value in determination of lupus nephritis activity (n=60) where highest Sensitivity and specificity of uMCP-1 observed at cutoff value 433 pg/ml, where sensitivity was 0.967 and specificity was 0.900.

Table-2: Sensitivity and specificity of uMCP-1 at different cutoff value in determination of lupus nephritis activity (n=60)

uMCP-1 (pg/ml)	Sensitivity	Specificity
413	1.000	0.867
420	0.967	0.867
433	0.967	0.900
443	0.933	0.900
448	0.933	0.933

Table-3 shows lupus nephritis patients by uMCP-1. Lupus nephritis activity was determined by SLEDAI 2K (renal). Among 30 active lupus nephritis cases raised uMCP-1 was found in 29 cases and among 30 inactive lupus nephritis cases raised uMCP-1 was found in 3 cases.

Table-3: Distribution of lupus nephritis patients by uMCP-1 cut off level (n=60)

uMCP-1	Lupus nephritis		Total
	Active	Inactive	
≥433	29	3	32
<433	1	27	28
Total	30	30	60

Table-4 shows validity parameters of uMCP-1 in diagnosis of lupus nephritis activity. uMCP-1 showed very good agreement in diagnosis of lupus nephritis activity according to Kappa statistics. uMCP-1 in diagnosis of lupus nephritis activity showed accuracy, sensitivity, specificity, PPV and NPV were 0.933, 0.967, 0.900, 0.906 and 0.964 respectively.

Table-4: Validity test of uMCP-1 in determination of lupus nephritis activity (n=60)

Statistics	Value	Low 95% CI	High 95% CI
Kappa	0.867		
Accuracy	0.933	0.821	0.965
Sensitivity	0.967	0.854	0.998
Specificity	0.900	0.788	0.932
Positive Predictive Value (PPV)	0.906	0.801	0.936
Negative Predictive Value (NPV)	0.964	0.844	0.998

Figure-2 shows ROC curve of uMCP-1 and Anti ds DNA Ab titre in diagnosis of lupus nephritis activity. Area under curve (AUC) of uMCP-1=0.992 and Anti ds DNA Ab titre = 0.901. uMCP-1 occupied more area than anti ds DNA Ab titre. so, uMCP-1 is more diagnostic than anti ds DNA Ab.

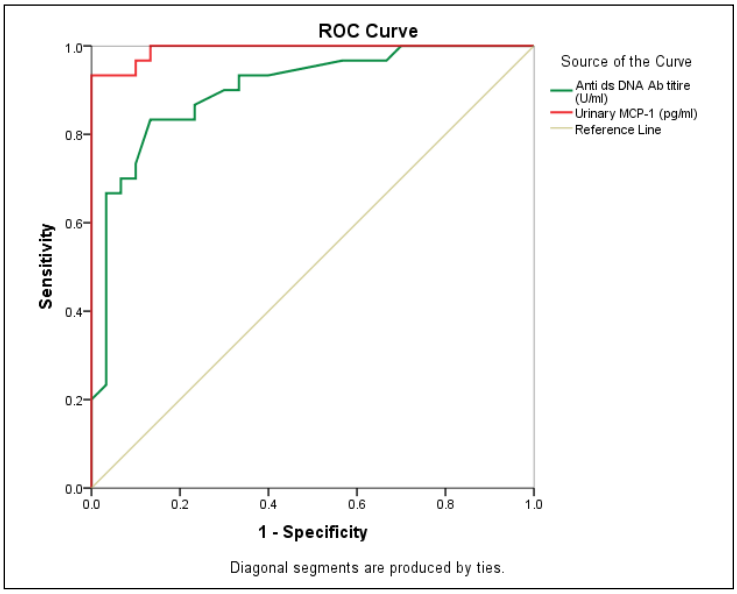

Figure 2: ROC curve of uMCP-1 and Anti ds DNA Ab titre in diagnosis of lupus nephritis activity

Figure-3 shows positive correlation of uMCP-1 with SLEDAI-2K (renal) in the study subjects.

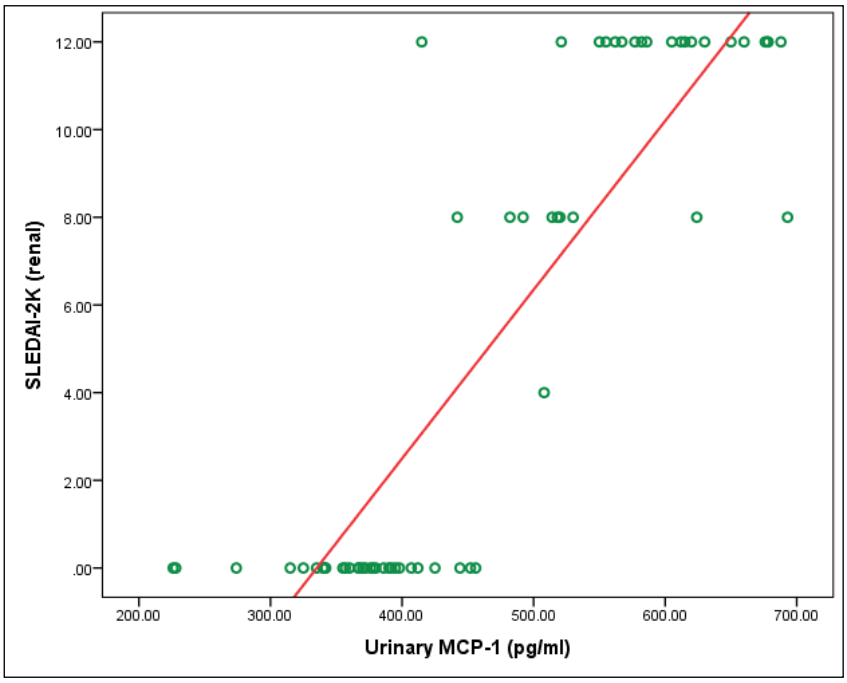

Figure 3: Positive correlation of uMCP-1 with SLEDAI-2K (renal) in the study subjects

Figure 4 shows Positive correlation of uMCP-1 with proteiuria in the study subjects.

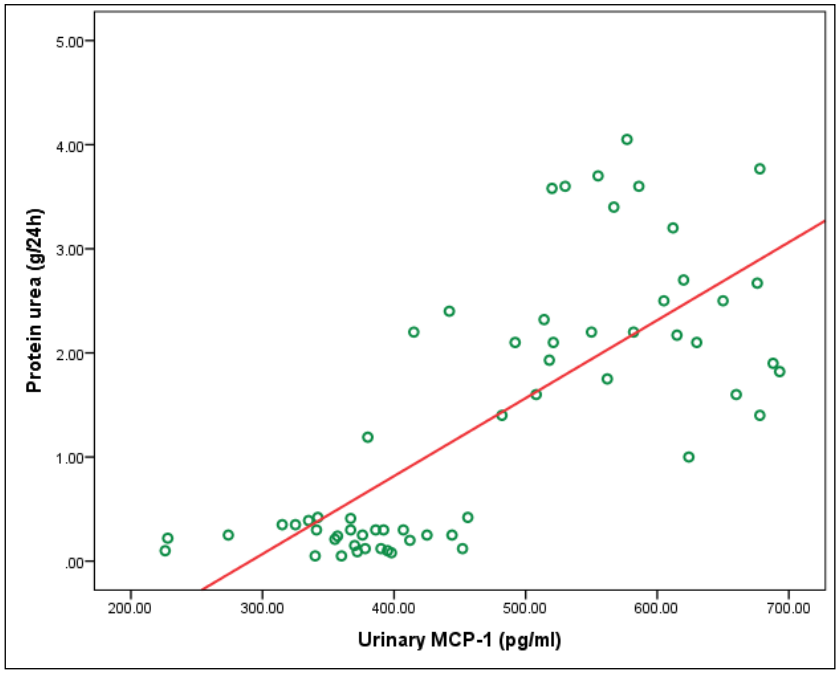

Figure 4: Positive correlation of uMCP-1 with proteiuria in the study subjects

Table-5: Urinary MCP-1 level of the patients (n=60) and the control (n=30)

Laboratory findings	Group		p value
	Lupus nephritis Mean±SD	Control Mean±SD	
uMCP-1 (pg/ml)	471.91 ± 125.44	118.13 ± 44.73	<0.001

Unpaired t test was done to measure the level of significance

Table-6: Correlation of u MCP-1 of active LN patients (n=30) with biopsy activity and chronicity index

	r value	p value
Biopsy activity index	+0.627	<0.001
Biopsy chronicity index	+0.178	0.461

Pearson's correlation test was done to measure the level of significance
Table-6 shows uMCP-1 were significantly higher in LN than that of control.

DISCUSSION

The association of urinary monocyte chemoattractant protein-1 (MCP-1) with disease activity in lupus nephritis (LN) has been a topic of significant interest in recent research. MCP-1 is a chemokine involved in the recruitment and activation of immune cells, and its elevated levels have been observed in both renal tissue and urine samples of LN patients. Understanding the relationship between urinary MCP-1 and disease activity can provide valuable insights into the pathogenesis of LN and aid in the development of effective diagnostic and monitoring strategies.

Numerous studies have investigated the association between urinary MCP-1 and disease activity in LN, with compelling findings. Several studies have reported a positive correlation between urinary MCP-1 levels and the severity of renal inflammation and damage. Higher levels of MCP-1 have been consistently observed in LN patients with active disease compared to those with inactive disease or healthy controls. This suggests that urinary MCP-1 may serve as a useful biomarker for disease activity in LN [11-13].

One study evaluated MCP-1 levels in urine samples of LN patients using enzyme-linked immunosorbent assays (ELISA). The results showed a significant increase in urinary MCP-1 levels in patients with active LN compared to those with inactive disease. Furthermore, urinary MCP-1 levels correlated with other clinical parameters, such as proteinuria and renal function. These findings suggest that urinary MCP-1 may provide valuable information regarding disease activity and renal involvement in LN [12].

In addition to its association with disease activity, urinary MCP-1 has shown promise as a predictor of treatment response and renal outcomes in LN. Several studies have demonstrated that baseline urinary MCP-1 levels can predict the response to immunosuppressive therapy and the risk of disease flare-ups. Higher baseline levels of MCP-1 have been associated with poorer response to treatment and increased risk of renal damage progression. Monitoring changes in urinary MCP-1 levels over time may provide clinicians with a tool to assess treatment efficacy and guide therapeutic decisions in LN [14, 15].

Despite the promising findings, some limitations need to be considered when interpreting the results of studies investigating the association of urinary MCP-1 with disease activity in LN. Firstly, the heterogeneity of LN patients, including variations in disease presentation and response to treatment, can influence the interpretation of results. Additionally, differences in sample collection methods, assay techniques, and cutoff values for MCP-1 levels may contribute to variability across studies. Standardization of measurement techniques and further validation studies are needed to establish the clinical utility of urinary MCP-1 as a biomarker for LN.

Future research should also explore the potential of combining urinary MCP-1 with other biomarkers to enhance diagnostic accuracy and improve patient stratification. Combinations of biomarkers reflecting different aspects of LN pathogenesis, such as immune activation, tissue damage, and fibrosis, may provide a more comprehensive assessment of disease activity and help tailor treatment strategies to individual patients.

In this study urinary MCP-1 were significantly higher in active cases 578.33 ± 74.66 pg/ml than inactive cases 365.50 ± 54.88 pg/ml. Alharazy *et al*., (2014) found elevated urinary MCP-1 ($p<0.001$) in active lupus nephritis patients than inactive. Similar findings also found significantly higher level of uMCP-1 in active LN compared to inactive LN in children [13-16].

In this study, uMCP-1 had significant positive correlation with SLEDAI-2K and proteinuria. Other studies also found positive correlation of uMCP-1 with SLEDAI-2K and proteinuria similar to our study [15, 16].

Area under curve (AUC) of uMCP-1 was 0.992 in diagnosis of lupus nephritis activity. Area under curve (AUC) of Anti ds DNA Ab titre, serum C3 and C4 was 0.901, 0.873 and 0.801 respectively. According to this study result, uMCP-1 is better than serum C3, Anti ds DNA Ab titre and serum C4 in diagnosis of lupus nephritis activity.

In this study uMCP-1 showed very good agreement in diagnosis of lupus nephritis activity according to Kappa statistics. uMCP-1 in diagnosis of lupus nephritis activity showed accuracy, sensitivity, specificity, PPV and NPV of 0.933, 0.967, 0.900, 0.906 and 0.964 respectively.

Other study reported in their study found that, sensitivity of MCP-1 for diagnosis of active LN was 0.87 with a specificity of 0.61 and the area under the curve (AUC) was 0.82. The results of both the study are similar to our study [17].

CONCLUSION

In conclusion, urinary MCP-1 holds great promise as a useful biomarker for the determination of lupus nephritis activity. Its association with disease activity, predictive value for treatment response and renal outcomes, and non-invasive nature make it an attractive candidate for clinical use. Ongoing research and validation studies are necessary to establish its precise role in disease monitoring, treatment decision-making, and improving patient outcomes in LN.

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