Original Article

Serum complement levels as prognostic marker for monitoring treatment response in lupus nephritis

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ABSTRACT

Background: *Lupus nephritis (LN) is one of the most common and serious manifestations of systemic lupus erythematosus (SLE) that causes significant morbidity and mortality. Certain biomarkers for LN are sometimes able to assess treatment response in lupus nephritis. This study aimed to compare serum complement levels (C3 and C4) as markers of treatment response of LN and their relation to the LN class in renal biopsy.*

Methods: *This prospective observational study was conducted in the Department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from July 2018 to August 2019. Twenty seven patients who were diagnosed with LN after kidney biopsy were included in this study. Serum complement levels (C3 and C4), 24 hours urinary total protein (24-hr UTP) and anti-double-stranded DNA (anti-ds DNA) were measured in all patients at baseline, 3 months and 6 months after treatment initiation. These biomarker values before and after treatment were compared between the proliferative and non-proliferative LN patients.*

Results: *Serum C3 levels were significantly different between patients with proliferative LN (Class III and Class IV) and non-proliferative LN (Class V) at baseline (0.47 ± 0.32 g/l versus 0.89 ± 0.43 g/l, p=0.009) and levels changed significantly 6 months after treatment initiation (p<0.001) and likewise for serum C4 levels (0.10 ± 0.06 g/l versus 0.24 ± 0.26 g/l, p=0.040). The values of 24-hr UTP and anti-ds-DNA were significantly different 6 months after treatment with p value <0.05 in both groups but C3 (p<0.001) and renal Systemic Lupus Erythematosus Disease Activity Index (rSLEDAI) (p<0.001) were only significant in the proliferative group. On the other hand, after 6 months treatment, C4 levels became relatively higher but that was not significant in both groups (p>0.05).*

Conclusion: *After 6 months of treatment, serum C3 and C4 levels increased towards normal in both LN groups. Serum C3 and C4 levels in patients with LN correlate with disease activity. Therefore, serum complement (C3 and C4) levels may be utilized as serological biomarkers for treatment response of LN.*

Key words: *lupus nephritis, serum complements, systemic lupus erythematosus.*

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune disease which affects almost every system in the body with different degrees of severity.[1] The clinical features of this chronic disease may vary from person to person; ranging from mild joint pain and skin involvement to severe, life-threatening internal organ damage.[2,3] Renal involvement in SLE termed as lupus nephritis (LN) is one of the most common manifestations of SLE and continues to be a major contributor to morbidity and mortality.[4] The pathogenesis of LN is a complicated process; including glomerular deposition of autoantibodies, complement activation, cellular proliferation, release of chemokines and proinflammatory cytokines leading to inflammation and fibrosis.[5,6,7]

Up to 50% of SLE patients will have clinically evident kidney disease at presentation; during follow-up, renal involvement will occur in 60% of patients.[8] Clinical course ranges from asymptomatic urinary occult blood to nephrotic syndrome or acute kidney injury since kidney injuries in LN are so variable.[9]

All four renal compartments glomeruli, tubules, interstitium and blood vessels may be affected in LN.[10] In addition, if LN develops early in the course of SLE, it becomes a major predictor of poor prognosis.[11] It has been reported that, in spite of remarkable progression in treatment, up to 25% of SLE patients progress to end-stage renal failure (ESRD) 10 years after the onset of renal damage and the 5-year survival of nephritis patients is 82%, whereas 5-year survival for those without nephritis is 92%.[10,12,13]

Despite the fact that several efficacious therapies have been used to treat lupus nephritis, the incidence of ESRD from LN increased day by day. This may reflect the limitations of our current treatment options, poor access to health care, late diagnosis, delay in treatment and lack of follow-up the response of treatment.[14] Earlier treatment has a beneficial effect on the prognosis of LN and it has been shown that late diagnosis of LN is correlated with a higher frequency of renal insufficiency.[14,15] Moreover, delayed diagnosis is associated with an increased incidence of ESRD.[15]

Certain laboratory markers which may be used for assessment of LN are proteinuria, urine protein creatinine ratio (PCR), creatinine clearance, anti-double-stranded DNA (anti-dsDNA) antibodies, and complement levels.[16] It was observed, however, that these parameters, namely anti-dsDNA antibodies, complement levels, proteinuria, creatinine clearance and urinary sediment are not specific enough to detect disease activity in renal involvement and nephritis relapse.[17] Anti-dsDNA antibodies are necessary but not sufficient for the development of LN exacerbations.[18]

Anti-dsDNA antibody assays can be negative early in disease, after treatment or when the patient is in clinical remission; therefore, not all patients with SLE are seropositive at any one time.[19] However, these traditional markers are often not as specific as desired in situations of diagnostic dilemma.[16] Repeat kidney biopsy, though useful, is an invasive procedure with its own complications.[5] Previous reports have demonstrated that focal, diffuse proliferative and membranous nephritides (World Health Organization LN classes III, IV, V) have poor prognosis, especially class IV LN and they usually require active interventions to inhibit their progression to renal failure.[20]

To date, studies have produced controversial reports regarding correlation of serum C3 and C4 levels in such patients with renal disease activity and prognosis.[20] Assessment of response to treatment using proteinuria as the sole biomarker has also not correlated well with renal functional recovery. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) is a global index that stratifies severity of SLE.[21] The renal SLEDAI (rSLEDAI) score consists of the four kidney-related parameters: hematuria, pyuria, proteinuria, and urinary casts.[21] Each parameter consists of 4 point. Scores for the rSLEDAI can range from 0 (inactive renal disease) to a maximum of 16. Active lupus nephritis was those with an rSLEDAI score of 4 or more. This study aims to compare serum complement levels (C3 & C4) as markers of treatment response of LN and their relation to the LN classes.

METHODS

This prospective observational study was conducted in the Department of Nephrology and Department of Rheumatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from July 2018 to August 2019 among 27 patients, who were diagnosed with LN after kidney biopsy. The study was approved by the Ethical Review Committee, BSMMU, Dhaka, Bangladesh. Informed written consent from the participants was obtained prior to the enrollment in the study.

Adult SLE patients, diagnosed as LN admitted in the Nephrology department with urinary total protein > 0.5 gm were included in this study. Pregnant women and lactating mothers, patients with malignancy, patients with active infection, patients with autoimmune disease other than SLE and ESRD patients were excluded from the study.

The renal histology was classified according to the International Society of Nephrology/Renal Pathology Society.[22] According to the abbreviated version of the classification; combined classes III/V or IV/V were considered as class III or IV, respectively. Out of those patients who were class III, IV and V LN diagnosed histologically without any features of exclusion criteria and willing to participate in this study were finally enrolled for this study. rSLEDAI was used to assess kidney disease activity.[21]

Before starting the treatment base line levels of complete blood count (CBC), Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urine routine microscopic examination (urine- R/M/E), 24-hour urinary total protein (24-hr UTP), serum creatinine, serum electrolytes, serum alanine aminotransferase (ALT), antinuclear antibody (ANA), serum anti-dsDNA antibody and serum levels of complement components 3 and 4 (C3 & C4) were measured in study patients. After initiation of treatment, CBC, ESR, urine R/M/E, 24-hr UTP, serum creatinine, anti-dsDNA and serum levels of C3 & C4 were again measured at 3rd month and 6th month. Each study patient received either intravenous cyclophosphamide (NIH protocol[23]) or mycophenolate mofetil (MMF -2 gm/day[24]) as induction therapy for 6 months.

Statistical analysis

Statistical analyses were performed by using windows based computer software with Statistical Packages for Social Sciences (SPSS) version-23 (Armonk, NY: IBM Corp). Level of significance was examined by paired 't'-test, unpaired 't'-test and Chi-square test. For all statistical tests, we considered p value <0.05 as statistically significant.

RESULTS

A total of 27 patients were evaluated over the study period. Majority of the study patients (44.4%) were in the age group of 21 – 30 years. Females were predominant to males (24 versus 3) and most patients were in class IV group [13 (48.1%)] [Table I]. Table II shows urine routine microscopic examination (RME) findings of 27 lupus nephritis patients at baseline, after 3 months and after 6 months. Table III shows urine abnormalities at baseline according to different classes of lupus nephritis.

Table I Baseline characteristics of the study subjects (N = 27)

	Frequency	Percentage
Age		
< 20	8	29.6
21 – 30	12	44.4
> 30	7	25.9
Gender		
Male	3	11.1
Female	24	88.9
ISN/RPS classification		
Class III	5	18.5
Class IV	13	48.1
Class V	9	33.3

Table II Urine R/M/E of the study subjects at baseline, after 3 months and 6 months of treatment

	Baseline	After 3 months	After 6 months
Mean Pus cells (per HPF) ± SD	13.74 ± 15.38	5.62 ± 5.73	3.37 ± 1.33
Mean RBC (cells per HPF) ± SD	41.07 ± 51.49	4.29 ± 7.22	2.11 ± 3.60
Patients with Casts, n (%)	6 (22.2 %)	Nil	Nil
Patients with proteinuria,	16 (59.3%), 3+	15 (55.5%), 2+	11 (40.7 %), 1+
n (%), amount of proteinuria	11 (40.7%), 2+	12 (44.5%), 1+	16 (59.3%), trace

SD: Standard deviation, R/M/E: Routine microscopic examination, HPF: High power field.

Table III Urine abnormalities at baseline according to classes of lupus nephritis

		Class III	Class IV	Class V	p-value
Proteinuria (24-hour UTP)	500 mg/day -3 gm/day	4 (80.0)	7 (53.8)	0 (0.0)	0.006
	>3 gm/day	1 (20.0)	6 (46.2)	9 (100.0)	0.001
RBC	>5/HPF	5 (100.0)	13 (100.0)	2 (22.2)	0.001
	<5/HPF	0 (0.0)	0 (0.0)	7 (77.8)	0.001

UTP: Urinary total protein, HPF: High power field. Chi-square test was performed to examine the level of significance

Table IV Laboratory parameters of the study subjects at baseline

Parameters	Proliferative (class III+IV) n=18	Non-proliferative (class V) n=9	p-value
C3 (g/l)	0.47 ± 0.32	0.89 ± 0.43	0.009
C4 (g/l)	0.10 ± 0.06	0.24 ± 0.26	0.040
24-hr UTP (gm/day)	2.84 ± 1.00	5.07 ± 2.06	0.001
S. Creatinine (mg/dl)	1.15 ± 0.37	0.86 ± 0.15	0.036
Anti ds DNA	162.45 ± 146.00	95.83 ± 74.31	0.212
Renal SLEDAI	12.22 ± 3.21	5.33 ± 2.83	<0.001
SLEDAI	21.33 ± 4.34	10.44 ± 5.64	<0.001

Unpaired 't' -test was done to examine the level of significance

Table V Biomarkers at baseline and after 6 months in proliferative and non-proliferative patients

	Proliferative (Class III+IV) n=18	Non-Proliferative (Class V) n=9
24-hr UTP		
Baseline	2.84 ± 1.00	5.07 ± 2.06
After 6 months	1.53 ± 1.50	1.37 ± 1.12
% change	46.12 ± 47.94	72.89 ± 24.76
p-value	0.003	<0.001
Anti ds DNA		
Baseline	162.45 ± 146.00	95.83 ± 74.31
After 6 months	68.90 ± 73.54	33.32 ± 33.28
% change	41.78 ± 42.05	48.17 ± 33.72
p-value	0.002	0.031
C3		
Baseline	0.47 ± 0.32	0.89 ± 0.43
After 6 months	0.85 ± 0.22	0.99 ± 0.18
% change	-129.46 ± 101.66	-29.43 ± 48.11
p-value	<0.001	0.385
C4		
Baseline	0.10 ± 0.06	0.24 ± 0.26
After 6 months	0.31 ± 0.58	0.44 ± 0.81
% change	-339.74 ± 976.55	-139.04 ± 236.71
p-value	0.141	0.476
rSLEDAI		
Baseline	12.22 ± 3.21	5.33 ± 2.83
After 6 months	4.22 ± 3.99	3.11 ± 1.76
% change	64.81 ± 31.26	35.19 ± 44.45
p-value	<0.001	0.051

Paired 't' -test was performed to examine the level of significance

Table IV shows laboratory parameters of the study subjects at baseline. At baseline Serum C3 (p=0.009) and C4 (p=0.040) levels were significantly lower and 24-hr UTP was significantly higher (p=<0.001) in membranous/non-proliferative lupus nephritis (class V) then proliferative lupus nephritis (class III+IV).

Table V shows pre-treatment (at baseline) and post-treatment (after 6 months) value of different parameters in proliferative (Class III & Class IV) and non-proliferative/membranous (Class V) lupus nephritis. The values of 24-hr UTP and Anti ds DNA were significantly different before and after (6 months) treatment with p value <0.05 in both groups but C3 (p<0.001) and rSLEDAI (p<0.001) were only significant in the proliferative group. On the other hand, C4 levels were became relatively higher (improved) after treatment but that was not significant in both groups (p>0.05).

DISCUSSION

LN is an immune-mediated glomerulonephritis that is a common consequence in patients with SLE. SLE is an autoimmune disorder caused by loss of tolerance to self-antigens, the production of autoantibodies and deposition of complement-fixing immune complexes (ICs) in injured tissues. Complement is centrally involved and plays key roles in the pathogenesis of SLE; the complement system consists of three pathways and is

tightly controlled by a set of regulatory proteins to prevent injudicious complement activation on host tissues. The involvement of the complement system in the pathogenesis of SLE is well accepted.[25]

In this study it was observed that most of the study subjects (88.9%) were females and maximum (44.4%) were in the age group of 21 – 30 years. These findings were consistent with previous studies.[24,26,27] This can be explained by the fact that lupus nephritis is more common in young females.

Renal biopsy was done in all study patients. Among 27 lupus nephritis patients, the most common histopathological type was class IV (48.1%) followed by class V (33.3%) and class III (18.5%). Near similar findings were observed in a study done by Sharma et al.[28] where the most common histopathological type was class IV (50%), followed by class III (17.6%) and class V (9%) and in another study by Gupta et al.[5] where proliferative glomerulonephritis (class III and IV) was detected in 31 (68.8%) patients and class II and class V LN was detected in seven (15.5%) patients each. In both study, number of class V LN patient was less than class III probably due to two factors. Firstly, in both studies all classes of LN patients were included and secondly, combined class (III + V) and class (IV + V) LN patient was more in both groups.

In our study serum complement (C3 and C4) levels were found to have improved (become higher) in both proliferative and non-proliferative LN groups from baseline to 6 months post treatment initiation, although not significantly always. Similar findings were observed in a study done by Davas et al.[29] where 19 patients from LN group were assessed at presentation and 6 months after treatment. Another study done by Gupta et al.,[5] they recruited 45 LN patients and 6 months after treatment similar results were observed. The same results we found for 24-hr UTP, anti-dsDNA in both group but C3 and rSLEDAI decreased significantly in only proliferative group, while no significant difference was found for C4 levels in both groups. The findings of this current study were consistent with similar previous studies.[5,29]

Several published studies have evaluated several serologic markers for LN. Decreased levels of C3 and C4, elevated anti-ds DNA and increased proteinuria have been found to correlate with worsening disease activity. Our study produced similar findings in concert with these previous studies.[24,26-29] From the above results it seems clear that serum complement (C3 and C4) levels are reliable markers of disease activity in patients with LN. Further studies will be warranted to elucidate this issue.

Conclusion

This study permits to conclude that serum complement (C3 and C4) levels in patients with LN correlate with disease activity. After 6 months of treatment serum complement levels increased towards normal in both proliferative and non-proliferative lupus nephritis groups. Serum C3 and C4 may be used as tools to detect disease severity and to monitor treatment response in LN.

Limitation

It was a single centre study with a relatively small sample size.

Recommendation

A multi-center prospective study with large sample size should be done to compare other biomarkers as a marker of treatment response of LN and their relation to the LN classes.

Authors' contribution: Khan SB studied the design. Khan SB,Islam RN and Mizan MSB analyzed and interpreted the patient data. Hossain SMZ,Mullah S, Ershad SM, Rahman T, Rahman MM, Feroz S and Kaiser AM screened subjects and collected patient data. Khan SB, Islam RN and Rahman AKMS were the major contributor in writing the manuscript. Khan SB and Islam RN designed the study and helped to revise the manuscript. All authors read and approved the final manuscript.

Conflicts of interest: Nothing to declare.

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