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Research Article

Lupus Nephritis: Role of Serum Complement Levels as Prognostic Marker

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Abstract

Background: Lupus Nephritis (LN) is one of the most common and serious manifestations in Systemic Lupus Erythematosus (SLE) patients that causes significant morbidity and mortality. Certain biomarkers for LN are sometimes able to assess treatment response of lupus nephritis.

Objective: To compare serum complement levels (C3 & 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 lupus nephritis after kidney biopsy were included in this study. Serum complement levels (C3 & 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. These biomarker values before and after treatment were compared between the treatment response and non response groups.

Results: Serum C3 levels were significantly different in patients of proliferative lupus nephritis (Class III & Class IV) than non proliferative lupus nephritis (Class V) at baseline (0.47 ± 0.32 vs0.89 ± 0.43g/l, $p = 0.009$) and levels changed significantly 6 months after treatment ($p < 0.001$) and likewise for Serum C4 levels (0.10 ± 0.06 vs0.24 ± 0.26g/l, $p = 0.040$). Serum C3 levels were also found to correlate significantly with SLEDAI and renal SLEDAI. No significant difference was observed for 24-hr UTP levels at baseline between remission and non-remission groups.

Conclusion: Serum C3 & C4 levels may be utilized as serological biomarkers to predict and monitor the treatment response of lupus nephritis.

Key words: lupus nephritis (LN); serum complements; systemic lupus erythematosus (SLE)

1. 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 lupus nephritis (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 and it is a serious complication in SLE since it is the major forecaster of poor prognosis [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 10 years after the onset of renal damage and the 5-year survival of nephritis patients is stalled at 82%, whereas 5-year survival for those without nephritis is 92% [10, 12, and 13].

Despite the fact that several efficacious therapies have been used to treat lupus nephritis, the incidence of end-stage renal disease (ESRD) from lupus nephritis 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 lupus nephritis; and it has been shown that late diagnosis of lupus nephritis 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 lupus nephritis are proteinuria, urine protein creatinine ratio, 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 lupus nephritis 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 conflicting 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 have also not correlated well with renal functional recovery. This study aims to evaluate such biomarkers with renal SLEDAI scores [21] to see whether any biomarker can be used satisfactorily to indicate severity and prognosis of lupus nephritis.

2. Materials and 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 twenty seven patients (27) who were diagnosed with lupus nephritis after kidney biopsy. The study was approved by the Ethical Review Committee, BSMMU, and Dhaka, Bangladesh.

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 end stage renal disease (ESRD) or dialysis dependent CKD patients were excluded from the study.

Informed written consents to participate in this study and undergo renal biopsy were recorded before undertaking the procedure. 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. Renal SLEDAI (rSLEDAI) [21] was used to assess kidney disease activity.

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), Urinary total protein (UTP), Serum Creatinine, Serum Electrolytes, Serum alanine aminotransferase (ALT), Antinuclear antibody (ANA), Anti-double-stranded DNA (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, UTP, Serum Creatinine, Anti-dsDNA and serum levels of C3 & C4 were again measured at 3rd and 6th months. Each study patients received either intravenous Cyclophosphamide (NIH protocol) [23] or Mycophenolate mofitel (MMF -2 gm/day) [24] as induction therapy for 6 months.

2.1. Statistical analysis:

Statistical analyses were performed by using windows based computer software with Statistical Packages for Social Sciences (SPSS-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.

3. Results and Observations

A total number of 27 patients were evaluated over the study period. Table I shows maximum 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%)].

	Frequency (n)	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 I: Baseline characteristics of the study subjects

Table II shows urine Routine microscopic examination (RME) findings of 27 lupus nephritis patients at baseline, after 3 months and after 6 months.

	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, n (%), amount of proteinuria	16 (59.3%), 3+ 11 (40.7%), 2+	15 (55.5%), 2+ 12 (44.5%), 1+	11 (40.7 %), 1+ 16 (59.3%), trace

SD: Standard deviation, RME: Routine microscopic examination, HPF: High power field.

Table II: Urine- R/M/E of the study subjects at baseline, after 3 months and 6 months of treatment (n=27)

Table III shows Urine abnormalities at baseline according to different 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 III: Urine abnormalities at baseline according to classes of lupus nephritis (n=27)

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

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**
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 IV: Laboratory parameters of the study subjects at baseline (n=27)

Table-V show pre-treatment (at baseline) and post treatment (after 6 month) 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 treatment with p value <0.05 in both groups but C3 and rSLEDAI were only significant in the proliferative group. C4 was not significant in both groups.

	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 V: Biomarkers at baseline and after 6 months in proliferative and non-proliferative patients (n=27)

4. Discussion

Lupus nephritis (LN) is an immune-mediated glomerulonephritis that is a common consequence in patients with SLE. In this prospective observational study, a total of 27 patients with lupus nephritis were recruited. Most of the study subjects were females 24 (88.9%). Maximum were in the age group of 21 – 30 (44.4%) years. This finding was consistent with previous studies [24] [25] [26]. This can be explained by the fact that lupus nephritis is more common in females.

Renal biopsy was done in all 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., (2019) [27] 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., (2015) [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 lupus nephritis patient is less than class III probably due to two factors. Firstly, in both study all class of LN patients were included and secondly, combined class (III + V) and class (IV + V) lupus nephritis patient was more in both groups.

In our study serum complement components (C3 and C4) levels were found to have improved (become higher) in both proliferative and non-proliferative lupus nephritis 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., (1999) [28] where 19 patients from lupus nephritis group were assessed at presentation and 6 months after treatment. Another study done by Gupta et al., (2015) [5], they recruited 45 patients who all had renal biopsy and similar results were observed. The same results were found for 24 hrs UTP, anti-dsDNA in both group but C3 and rSLEDAI decreased significantly in only proliferative group. No difference was found for C4 levels in both groups. Similar findings were observed in a study done by Davas et al., (1999) [28].

Several published studies have evaluated several serologic markers for lupus nephritis. 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 [24-28]. From the above results it seems clear that C3 and C4 are reliable markers of disease activity in patients with lupus nephritis.

Conclusion

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

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 lupus nephritis (LN) and their relation to the LN classes.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

References

1. Gurevitz S, Snyder J, Wessel E, Frey J, Williamson B. Systemic lupus erythematosus: a review of the disease and treatment options. The Consultant Pharmacist®. 2013 Feb 1; 28(2):110-21.
2. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. Systemic Lupus Erythematosus. Harrison's Principles of Internal Medicine (18th ed), New York: McGraw-Hill 2012; 319
3. Dall'Era M, Yazdany J. Classification of lupus and lupus-related disorders. Dubois' Lupus Erythematosus and Related Syndromes. 2012:1-3.
4. Reyes-Thomas J, Blanco I, Putterman C. Urinary biomarkers in lupus nephritis. Clinical reviews in allergy & immunology. 2011 Jun 1; 40(3):138-50.
5. Gupta R, Yadav A, Misra R, Aggarwal A. Urinary sCD25 as a biomarker of lupus nephritis disease activity. Lupus. 2015 Mar; 24(3):273-9.
6. Mavragani CP, Fragoulis GE, Somarakis G, Drosos A, Tzioufas AG, Moutsopoulos HM. Clinical and laboratory predictors of distinct histopathogical features of lupus nephritis. Medicine. 2015 May; 94(21).
7. Wu M, Yang J, Li X, Chen J. The role of γδ T cells in systemic lupus erythematosus. Journal of immunology research. 2016 Jan 1; 2016.
8. Bomback AS, Appel GB. Updates on the treatment of lupus nephritis. Journal of the American Society of Nephrology. 2010 Dec 1; 21(12):2028-35.
9. Iwata Y, Furuichi K, Kaneko S, Wada T. The role of cytokine in the lupus nephritis. Journal of Biomedicine and Biotechnology. 2011 Jan 1; 2011.
10. Mok CC. Biomarkers for lupus nephritis: a critical appraisal. Journal of Biomedicine and Biotechnology. 2010 Oct; 2010.
11. Anaya JM, Cañas C, Mantilla RD, Pineda-Tamayo R, Tobón GJ, Herrera-Diaz C, Rendón DM, Rojas-Villarraga A, Uribe M. Lupus nephritis in Colombians: contrasts and comparisons with other populations. Clinical reviews in allergy & immunology. 2011 Jun 1; 40(3):199-207.
12. Cameron JS. Lupus nephritis. Journal of the American Society of Nephrology. 1999 Feb 1; 10(2):413-24.
13. de Zubiria Salgado A, Herrera-Diaz C. Lupus nephritis: an overview of recent findings. Autoimmune diseases. 2012 Oct; 2012.
14. Ward MM. Prevalence of physician-diagnosed systemic lupus erythematosus in the United States: results from the third national health and nutrition examination survey. Journal of Women's Health. 2004 Jul 1; 13(6):713-8.
15. Faurschou M, Starklint H, Halberg P, Jacobsen S. Prognostic factors in lupus nephritis: diagnostic and therapeutic delay increases the risk of terminal renal failure. The Journal of rheumatology. 2006 Aug 1; 33(8):1563-9.
16. Bertsias GK, Tektonidou M, Amoura Z, Aringer M, Bajema I, Berden JH, Boletis J, Cervera R, Dörner T, Doria A, Ferrario F. Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Annals of the rheumatic diseases. 2012 Nov 1; 71(11):1771-82.
17. Rovin BH, Zhang X. Biomarkers for lupus nephritis: the quest continues. Clinical Journal of the American Society of Nephrology. 2009 Nov 1; 4(11):1858-65.
18. Živković V, Stanković A, Cvetković T, Mitić B, Kostić S, Nedović J, Stamenković B. Anti-dsDNA, anti-nucleosome and

anti-C1q antibodies as disease activity markers in patients with systemic lupus erythematosus. Srpski arhiv za celokupno lekarstvo. 2014; 142(7-8):431-6.
19. Gladman DD, Urowitz MB, Keystone EC. Serologically active clinically quiescent systemic lupus erythematosus: a discordance between clinical and serologic features. The American journal of medicine. 1979 Feb 1; 66(2):210-5.
20. EL SHAFEY EM, EL NAGAR GF, EL BENDARY AS, Sabry AA, Selim AG. Serum soluble interleukin-2 receptor alpha in systemic lupus erythematosus. Iranian journal of kidney diseases (IJKD). 2008 April 2(2): 80-85.
21. Pitashny M, Schwartz N, Qing X, Hojaili B, Aranow C, Mackay M, Putterman C. Urinary lipocalin-2 is associated with renal disease activity in human lupus nephritis. Arthritis & Rheumatism. 2007 Jun; 56(6):1894-903.
22. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, Balow JE, Bruijn JA, Cook T, Ferrario F, Fogo AB. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Journal of the American Society of Nephrology. 2004 Feb 1; 15(2):241-50.
23. Castro-Santana LE, Colón M, Molina MJ, Rodríguez VE, Mayor AM, Vilá LM. Efficacy of two cyclophosphamide regimens for the treatment of lupus nephritis in Puerto Ricans: low versus standard dose. Ethnicity & disease. 2010; 20(10 1):S1.
24. El-Shafey EM, Abdou SH, Shareef MM. Is mycophenolate mofetil superior to pulse intravenous cyclophosphamide for induction therapy of proliferative lupus nephritis in Egyptian patients? Clinical and experimental nephrology. 2010 Jun 1; 14(3):214-21.
25. Rabrenović V, Poskurica M, Kovačević Z, Nešić V, Savin M, Mitić B, Dimković N, Čučković Č, Vujić D, Plješa S, Peruničić-Peković G. Treatment of lupus nephritis by mycophenolate mofetil. Kidney and Blood Pressure Research. 2010; 33(4):297-303.
26. Gunes C, Keles M, Uyanik A, Cetinkaya R, Sari RA. Treatment Results of Patients With Lupus Nephritis: A Single Center's Experience. The Eurasian journal of medicine. 2010 Dec; 42(3):132.
27. Sharma M, Das HJ, Doley PK, Mahanta PJ. Clinical and histopathological profile of lupus nephritis and response to treatment with cyclophosphamide: A single center study. Saudi Journal of Kidney Diseases and Transplantation. 2019 Mar 1; 30(2):501.
28. Davas EM, Tsirogianni A, Kappou I, Karamitsos D, Economidou I, Dantis PC. Serum IL-6, TNFα, p55 srTNFα, p75 srTNFα, srIL-2α levels and disease acitivity in systemic lupus erythematosus. Clinical rheumatology. 1999 Jan 1; 18(1):17-22.

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