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Serum cystatin C: A prognostic marker in lupus nephritis

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Abstract
Background: Systemic Lupus Erythematosus, commonly known as "Lupus or SLE", is an inflammatory disease of connective tissue and immune system, where we find organs and cells undergo damage initially mediated by tissue-restricting auto antibodies and immune complexes. Our aim was to evaluate the association of Serum Cystatin C in lupus nephritis patients and validate its use as a prognostic marker.
Material and Methods: We studied the level of Serum Urea, Creatinine, Urinary Albumin-Creatinine Ratio (ACR), 24 hours Urine Protein and Serum Cystain C) in SLE without nephritis and Lupus Nephritis patients. Any change after 6 months was noted and correlation of Serum Cystatin C with disease activity scores (SLEDAI) was done.
Results: Comparison of Serum Cystatin C level in the cases showed higher value at the first visit (2.50 ± 1.21) judge against the follow up visit at 6 months (1.03 ± 0.47). This variation was found statistically significant (P value < 0.001). Comparison of Serum Cystatin C level at first visit showed higher value in cases group (2.50 ± 1.21) compared to control (0.70 ±0.26) group. This difference was highly statistically significant (P value <0.001). Mean age of the study participant in the cases group was found 30.43 ± 7.29 years (ranging from 18 to 52 years) where as it was 29.85 ± 9.22 years (ranging from 18 to 58 years) in the control group.
Conclusion: Serum level of Cystatin C among adult Lupus Nephritis patients were higher than adult Non-renal SLE patients and can be used as a prognostic marker and may guide the treatment.

Keywords: Lupus nephritis, serum cystatin C, prognostic marker, SLE

Introduction
Systemic Lupus Erythematosus, commonly known as "Lupus or SLE", is an inflammatory disease of connective tissue and immune system. It is an immune system ailment wherein organs and cells experience harm at first interceded by tissue-restricting auto antibodies and immune complexes [1]. This is an chronic, multisystem, immune system condition which is portrayed by the nearness of auto antibodies to atomic material and immune system deposition in included tissues. While various methodologies have been made in unwinding the anticipation of this type of infection, it remains incompletely comprehended [2].
Renal involvement is one of the important prognostic factors for SLE. Lupus nephritis (LN) is present in 20-75% of patients depending on ethnicity and age. It is more common in younger individuals and individuals of African or Asian ancestry. End stage renal disease is observed among 10 to 15% of the LN patients. [1-4]. Over the last few years there has been a growing interest in searching novel biomarkers which could predict future renal involvement or monitor renal function for early clinical identification, risk stratification and therapy adjustment [5].
Cystatin C has been studied as an alternative Glomerular Filtration Rate (GFR) marker. It is a non-glycosylated low molecular weight protein from the cysteine proteinase inhibitors family, produced at a constant rate by every nucleated cell, freely filtered in the glomerulus and finally reabsorbed and metabolized in the proximal tubule [6]. As there is no significant tubular secretion or extra-renal elimination, its peripheral concentration solely depends on glomerular filtration rate, which makes it a promising marker of renal function. Its production has been shown to be more uniform, as it does not depend on the muscle mass or on diet. [7]. Therefore, cystatin C in serum levels have consistently shown a higher

correlation with the GFR than creatinine [7-9]. Studies on the above parameter had been done in many countries but very few in India. So a study might be essential to clinically establish the correlation of LN and SLE with the novel biomarker. It can also be helpful to compare the efficacy between the classical and the newer parameter. So taking these factor into account here we evaluated the association of Serum Cystatin C in lupus nephritis patients to find a biomarkers (Serum Cystatin C) in SLE and Lupus Nephritis patients.

Material and Methods

30 patients who are known cases of Systemic Lupus Erythematosus with kidney biopsy proven renal involvement obliging the below mentioned inclusion criteria and presented to the Department of Immunology & Rheumatology at Institute of Medical Sciences and SUM Hospital was included as cases in our study. 35 SLE patients, who did not show renal involvement as per the conventional renal parameters which include tests like Serum Urea, Serum creatinine, 24 hour urinary protein, are taken as controls.

The inclusion criteria's were age more than18 years & less than60 years, SLE patients who are diagnosed as per 2012 classification criteria of American College of Rheumatology, Kidney Biopsy Proven Renal involvement, Likewise the exclusion criteria for this observational study was pregnant Women, H/O Diabetes Mellitus, recent H/O Tuberculosis, smokers, alcoholics, hepatitis B, Hepatitis C, HIV positive cases

Method to assess serum cystatin C

It was done by Immunoturbidimetric Assay with the help of commercially available kits from Agappe Diagnostic Limited in Turbochem100 autoanalyzar.

Results

A total of 65 participants were included in the study. All the participants were diagnosed with Systemic Lupus Erythematosus (SLE). These participants were divided, based on the renal involvement into two groups namely SLE without renal involvement group (hence forth called as Control group) and Lupus Nephritis group (henceforth called as case group).

The distribution of the study participants in both the cases and control group was found like 35 patients (53.8%) belonged to control group while 30 patients (46.2%) belonged to cases group.

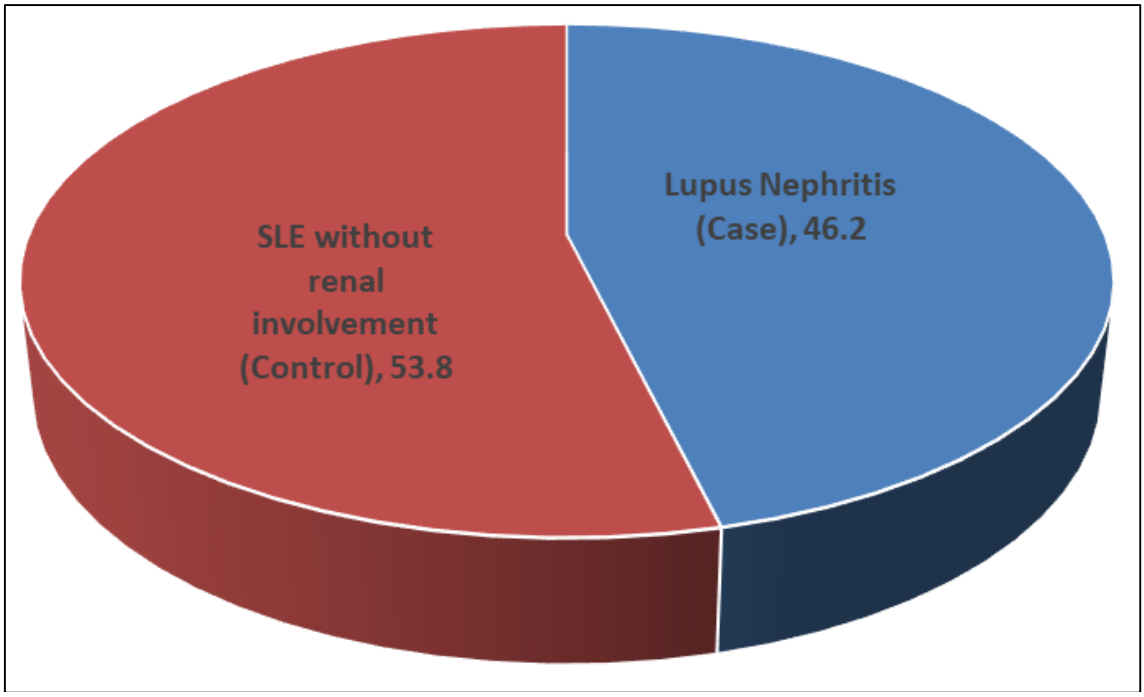

Fig 1: Distribution of study participants in cases and control group

Mean age of the study participant in the cases group was 30.43 ± 7.29 years where as it was 29.85 ± 9.22 years in the control group. Age group wise distribution showed that majority of the study participants were from less than 30 years of age in cases (50.0%) and control (60.0%) group followed by age group between 30 to 40 years (46.7% Vs 28.6%) and age group more than 50 years (3.3% Vs 11.4%).

Comparison of Serum Cystatin C level in lupus nephritis patients showed higher value at the first visit (2.50 ± 1.21) compared to the follow up visit at 6 months after treatment (1.03 ± 0.47). This difference was statistically significant (P value < 0.001). There was no difference in SLE patients with our renal involvement between baseline (0.70 ±0.26) and after treatment at 6 months (0.72 ± 0.22).

Table 1: Serum Cystatin C levels at the first and at 6 months with in the groups

Group	Serum Cystatin C level		P values
	At first visit Mean ± SD	After 6 months Mean ± SD	
SLE with Renal Involvement	2.50 ± 1.21	1.03 ± 0.47	< 0.001
SLE without Renal Involvement	0.70 ±0.26	0.72 ± 0.22	0.396

Comparison of Serum Cystatin C level at first visit showed higher value in SLE patients with renal involvement (2.50 ± 1.21) compared to patients with our renal involvement (0.70 ±0.26). This difference was highly statistically significant (P value <0.001). Similarly, the values at follow up visit had a significantly higher mean value (P = 0.001) for cases group (1.03 ± 0.47) compared to control (0.72 ± 0.22) group.

Table 2: Comparison of Serum Cystatin C level at baseline and after 6 months between the groups

Serum Cystatin C level	SLE with Renal Involvement Mean ± SD	SLE without Renal Involvement Mean ± SD	P values
At first visit	2.50 ± 1.21	0.70 ±0.26	< 0.001
After 6 months	1.03 ± 0.47	0.72 ± 0.22	0.001

Table 3: Comparison of different laboratory parameter at first and after 6months within the groups

Laboratory parameters	SLE with Renal Involvement		P value	SLE without Renal Involvement		P value
	At first visit	After 6 months		At first visit	After 6 months	
Urea	54.0 ± 18.1	28.7 ± 8.2	<0.001	27.3 ± 5.75	26.28±4.79	.040
Creatinine	1.79 ± 0.44	0.76 ± 0.11	<0.001	0.61 ± 0.20	0.64 ± 0.17	.463
Urinary A/C ratio	0.40 ± 0.05	0.15 ± 0.05	<0.001	0.12 ± 0.15	0.05 ± 0.03	.009

Comparison of other laboratory parameters like urea, creatinine, urinary albumin to creatinine ratio was significantly decreased at the follow up visit after treatment at 6 months compared with the baseline. In the control group only serum urea and urinary albumin to creatinine ratio showed significant reduction (Table 3).

Comparison of all the laboratory parameters like urea, creatinine, and and urinary albumin to creatinine ratio at base line level and at 6month follow up were significantly different in cases and control group. (Table 4).

Table 4: Comparison of different laboratory parameter between the groups

Laboratory parameters	At first visit		P value	After 6 months		P value
	Cases	Control		Cases	Control	
Urea	54.0 ± 18.1	27.3 ± 5.75	<0.001	28.7 ± 8.2	26.28±4.79	0.142
Creatinine	1.79 ± 0.44	0.61 ± 0.20	<0.001	0.76 ± 0.11	0.64 ± 0.17	0.001
Urinary A/C ratio	0.40 ± 0.05	0.12 ± 0.15	<0.001	0.15 ± 0.05	0.05 ± 0.03	<0.001

Predictive accuracy of Serum Cystatin C in predicting renal involvement in the SLE patients showed an area under the curve of 0.835. At the value 1.15 mg/l, the sensitivity was 80% and the specificity was 98% (Figure 2).

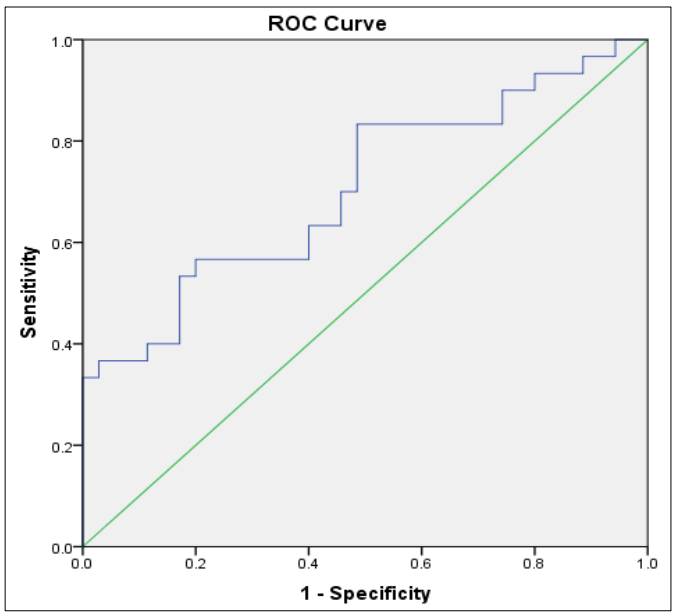

Fig 2: Receiver operating curve showing predictive value of Serum Cystatin C

Discussion

Lupus nephritis (LN) may influence the disease prognosis. A successful treatment of LN requires correct diagnosis, timely intervention and early treatment of any disease complication. Biomarkers which are able to mark disease prognosis at the earliest are still lacking. The aim of the study was to evaluate if Serum Cystatin C can be more useful than the conventional parameters (like Serum Urea, Creatinine, urine routine and microscopy examination, 24 hour urinary protein and urine albumin/creatinine ratio) in monitoring lupus nephritis and in predicting the degree of renal involvement in SLE at baseline and after 6 months of treatment [10, 11] according to the guidelines of American College of Rheumatology. A total number of 65 SLE patients were selected for this study. Among them, newly detected 30 cases of lupus nephritis (46.2%) were selected as cases on the basis of deranged conventional kidney function parameters (like Serum Urea, Creatinine, urine routine and microscopy examination, 24 hour urinary protein and urine albumin/creatinine ratio) and renal involvement was confirmed by kidney biopsy. Control group comprised of 35 non renal SLE patients (53.8%) having normal range conventional parameters for kidney function.

Comparison of Serum Cystatin C level in the patients with renal involvement showed higher value at the first visit (2.50 ± 1.21) compared to the follow up visit at 6 months after treatment (1.03 ± 0.47). This difference was statistically significant (P value < 0.001). Almost same levels of Serum Cystatin C were found in control at the first visit (0.70 ±0.26) compared to the follow up visit at 6 months (0.72 ± 0.22). Comparison of Serum Cystatin C level at first visit showed significantly higher value (P value <0.001) in cases group (2.50 ± 1.21) compared to control (0.70 ±0.26) group. Similarly, the values at follow up visit had a higher mean value for cases group (1.03 ± 0.47) compared to control (0.72 ± 0.22) group. This difference in mean also highly statistically significant (P value = 0.001).

Predictive accuracy of Serum Cystatin C in predicting renal involvement in the SLE patients showed an area under the curve of 0.835. At the value 1.15 mg/l the sensitivity was 80% and the specificity was 98%.In the present study, we have found a significant association of higher level of Serum Cystatin C with degree of renal involvement in Lupus Nephritis patients, which suggest it may be used as a diagnostic as well as prognostic tool to detect the renal function in SLE patients. There were few limitations in this study; first, the duration of the disease was not taken into consideration. Second, serial kidney biopsies could not done in consecutive patients as there were many contraindications for the same. So the degree of kidney involvement could not be assessed or compared with the newer and conventional parameters. Hence, the above factors may have played a role in difference of the results in the present study.

Conclusion

The serum level of Cystatin C is significantly higher in patients with SLE nephritis in comparision to SLE patients without renal involvement. With treatment the level of serum cystatin C significantly decreased at 6 months and correlated with disease activity. Serum Cystin C level has shown significant predictive value for detecting renal involvement. At serum level of 1.15 mg/l, the sensitivity is 80% and the specificity is 98% making a good prognostic tool for Montoring renal involvement in SLE patients.

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