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Original Article

Urinary CD25 as a Biomarker of Lupus Nephritis Activity in Pediatrics

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Abstract

Background
Lupus nephritis is one of the most serious manifestations of Systemic lupus erythematosus. Proteinuria, complement level, anti-dsDNA and creatinine are the most widely used to assess activity.

Aim of Work
The aim of this study was to assess the relationship of urinary s CD25 with lupus nephritis activity as a noninvasive biomarker in children.

Patients and Methods
The study was conducted on 30 patients divided into 2 groups; Group I: 20 patients of SLE, subdivided into 2 subgroups according to presence of lupus nephritis and Group II: 10 healthy subjects as a control group. Urinary sCD25 was measured in both groups.

Results
Urinary sCD25 was significantly higher in active LN in comparison to inactive and controls. Urinary s CD25 level was correlated with SLE activity, proteinuria and blood urea.

Conclusion Urinary sCD25 is a useful noninvasive technique for assessment of lupus nephritis as it shows a good correlation with some clinical and laboratory parameters of disease relapse.

Keywords: SLE, CD25, Nephritis, Children

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Introduction

Systemic lupus erythematosus (SLE) is life long, life-limiting, multi-systemic autoimmune disease [1], whose etiology and pathogenesis are incompletely understood [2].

Glomerulonephritis is one of the most serious manifestations of SLE. Despite the improvement in the medical care of the SLE in the past two decades, the prognosis of lupus nephritis (LN) remains unsatisfactory [3].

The current most widely used biomarkers for the early detection of chronic kidney disease or acute kidney injury are proteinuria, serum creatinine, and blood urea nitrogen. All of these are less than optimal and tend to focus attention on later stages of injury when therapies may be less effective [4].

Renal biopsy is the gold standard for providing information on the histological classes of LN and relative degree of activity and chronicity in the glomeruli. However, it is invasive and serial biopsies are required which is impractical in monitoring LN [3].

Increased sCD25 receptor expression is associated with increased T-cell and B-cell activation and correlate with autoimmune disease. Patients with LN shed sCD25 in the urine, and this may act as a surrogate marker of T-cell activation in the kidney [5].

Urine is an excellent noninvasive resource to be utilized in investigating local immunopathogenesis of LN. Urinary CD25 was shown to be a sensitive and specific biomarker of renal SLE flare [5].

Aim of work

The purpose of this study was to assess the relationship of urinary CD25 with disease activity in children with lupus nephritis as a noninvasive biomarker.

Patients and methods

This cross sectional study was conducted at Pediatric Nephrology Unit, Zagazig University Hospitals during 8 months from September 2015 till April 2016. This study passed the Ethical Committee issue and consents for subject were taken.

Subjects:This study was carried out on 30 patients and divided into two groups:

Group I (patient group): This group was subdivided into:

Subgroup A: This subgroup included 10 patients with SLE without clinical and laboratory picture of renal disease not in activity. There were 5 (50%) males and 5 (50%) females; their ages range from 8 to 14 years.

Subgroup B: This subgroup included 10 patients with SLE with clinically, laboratory and biopsy diagnosed renal diseased in activity and after remission. There were 2 (20%) males and 8 (80%) females, their ages range from 8 to 14 years.

All patients fulfilled at least four of the American College of Rheumatology preliminary criteria for diagnosis of SLE [6]

Group II: This group included 10 children age- and sex-matched healthy subjects as a control group. There were 5 (50%) males and 5 (50%) females.

Inclusion criteria:

- Age from 8 to 14 years old.
- Cases of active lupus nephritis.

Exclusion criteria:

- Patients with End-Stage Renal Disease (ESRD) or had undergone renal transplantation.
- Patients in whom a renal biopsy could not be performed.
- Known cases of lupus nephritis not in active disease.

Methods: All groups were subjected to:

1. Full history taking with special emphasis on disease activity in SLE patients measured by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and laying stress on age, duration of the disease, urinary symptoms, SLE manifestations (e.g. joint pains, rash, cutaneous photosensitivity and CNS symptoms including seizures), symptoms of hypertension as vomiting, headache, blurred vision and type of therapy received by patient.
2. Thorough clinical examination, including vital signs and anthropometric measurements (weight and height), skin rash distribution, joint affection, chest and heart examination, abdominal examination and CNS examination.
3. Data about lupus nephritis:
   a. Presence or absence.
   b. Clinical presentation.
   c. Laboratory evidence.
   d. Renal biopsy.
4. Laboratory testing:
   a. Serum creatinine and blood urea nitrogen (BUN).
   b. Urine analysis, urinary protein to creatinine ratio.
   c. Complete blood count.
   d. Erythrocyte sedimentation rate (ESR).
   e. Anti-DNA (deoxyribonucleic acid) employing indirect immunofluorescent test.
   f. Complement 3 and 4 levels by radio immunodiffusion.
5. sCD25 in urine was determined using Enzyme-Linked Immunosorbent Assay (ELISA).

Aseptically urine was collected and stored at -20°C. The microtiter plate provided in this kit has been precoated with an antibody specific to IL-2 receptor. Samples are then added to microtiter plate wells with conjugated polyclonal antibody preparation. The color change is measured spectrophotometrically at a wave length of 450 ± 2 nm [7].

Statistical analysis

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) and MedCalc 13 for Windows (MedCalc Software bvba, Ostend, Belgium).

Results

This study included 20 patients with SLE; 7 males and 13 females. As regard sex distribution between 30 patients, 40% were male and 60% were female. There was no significant difference regarding age and sex between groups. There is a significant increase in weight in cases than control group (table 1).

The most common presenting symptom in our SLE cases is joint pain (85%), followed with urinary symptoms and skin rash (50%) (table 2).

30% of SLE cases were treated with steroids alone, while 25% of cases were treated with steroids and cyclophosamide (table 3).

There is a significant increase in urinary CD25 in SLE cases with active nephritis in comparison to healthy control and SLE cases without nephritis (figure 1).

There is a significant difference between SLE without nephritis, SLE with inactive nephritis and SLE with active nephritis regarding to UPR/UCR ratio, USCD25, C3, C4, and anti-dsDNA (table 4).

There is no correlation between USCD25 and (C3, C4), but there is a positive significant correlation with anti-dsDNA and SLEDAI (table 5).

Urinary CD25 is the most sensitive and specific in discriminating between active lupus nephritis from inactive lupus nephritis at cutoff value of > 470 pg/mg by ROC curve (table 6).

Table 1: Comparison between SLE cases and control as regard demographic data, anthropometric measurements and laboratory data.

Demographic data	Group I (SLE cases) (n = 20)		Group II (control) (n = 10)		Test	p-value (significance)
	No	%	No	%		
Gender						
Male	7	35	5	50	0.625	0.461 (NS)
Female	13	65	5	50		
Age (years)						
Mean ± SD	11.5 ± 1.73		10.3 ± 2.75		1.26*	0.23 (NS)
Median (range)	12 (8-14)		10.5 (6-14)			
Weight(kg)						
Mean ± SD	37.15 ± 7.48		27.9 ± 6		3.39	0.002 (S)
Median (range)	37 (25-52)		28.5 (18-35)			
Height(cm)						
Mean ± SD	138.8 ± 15.23		142.2 ± 9.48		0.646	0.53 (NS)
Median (range)	139 (117-160)		145 (126-155)			
Hemoglobin (g/dl)						
Mean ± SD	11.24 ± 0.86		11.83 ± 0.91		-1.719	0.097 (NS)
Median (range)	11.25 (9.8-13)		11.85 (10.5-13)			
Urea (mg/dl)						
Mean ± SD	21.45 ± 5.2		17.2 ± 3.7		-2.4	0.015 (S)
Median (range)	20 (14-35)		11.5 (13-23)			
Creatinine (mg/dl)						
Mean ± SD	0.95 ± 0.18		0.76 ± 0.25		2.851	0.008 (S)
Median (range)	1 (0.6-1.2)		0.75 (0.5-1)			

*Independent samples Student's t-test - Chi-square test -p-value < 0.05 is significant

Table 2: Clinical picture of SLE (n = 20**)**.

Symptoms	SLE cases (n = 20)	
	No	%
Urinary symptoms	10	50
Joint pain	17	85
Rash	10	50
Skin rash distribution(face)	10	50
Cutaneous photosensitivity	0	0
CNS symptoms	0	0
Convulsion	0	0
Hypertension	5	25
Chest examination Pleurisy	3	15
Heart examination Pericarditis	2	10
Abdominal examination	0	0
CNS examination Seizure/psychosis	0	0

Table 3: Treatment of SLE cases (n = 20).

Treatment	SLE cases (n = 20)	
	No	%
Steroid	6	30
Steroids + cyclophosphamide	5	25
Steroids + Azathioprine	4	20
Steroids + Hydroxychloroquine	5	25

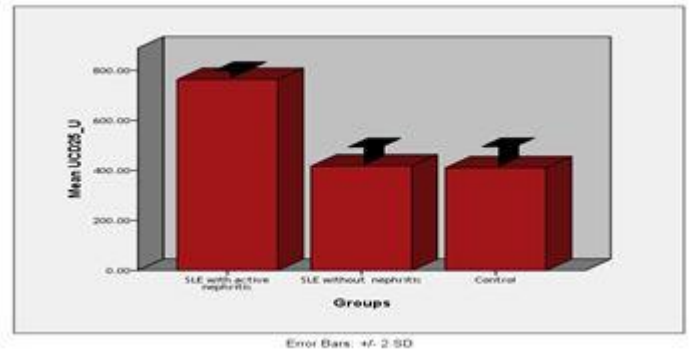

Figure 1: Comparison between healthy control, SLE with active nephritis and SLE without nephritis as regard UCD25

Table 4: Comparison between SLE without nephritis, SLE with inactive nephritis and SLE with active nephritis as regard markers of SLE.

Markers	Subgroup A	Subgroup B		Test	p-value
	SLE without nephritis	SLE with inactive nephritis	SLE with active nephritis		
UP/creatinine ratio					
Mean ± SD	0.14 ± 0.03	0.16 ± 0.03	3.09 ± 1.54	9.8	< 0.001**
Median (range)	0.14 (0.1-0.2)	0.16(0.1-0.2)	3.75(0.18-4.1)		
Anti-dsDNA					
Mean ± SD	94.2 ± 22.07	77.8 ± 10.07	129.8 ± 26.7	7.3	< 0.001**
Median (range)	92.5 (66-130)	75 (65-93)	130.5(85-165)		
ESR 1st h					
Mean ± SD	19.6 ± 15.44	17.5 ± 15.27	23 ± 15.45	0.34	0.71
Median (range)	15 (5-45)	7 (4-40)	30 (4-42)		
ESR 2nd h					
Mean ± SD	31.7 ± 23.1	32.3 ± 24.67	46.9 ± 29.58	1.17	0.28
Median (range)	23.5 (11-70)	14.5 (12-65)	58 (13-80)		
C3 (ng/dl)					
Mean ± SD	68.3 ± 35.8	123.4 ±27.52	37.6 ± 5.73	11.4	< 0.001**
Median (range)	63 (28-113)	125 (80-170)	35.5 (31-47)		
C4 (ng/dl)					
Mean ± SD	23.4 ± 12.5	28.6 ± 5.52	10.7 ± 3.23	8.3	0.0006**
Median (range)	21.5 (10-40)	27.5 (20-35)	11 (6-16)		
US CD25					
Mean ± SD	417.2 ± 35	414.5 ±43.55	763.2 ± 14.93	89.7	< 0.001**
Median (range)	412 (372-473)	420(347-470)	762.5(743-785)		
SLE DAI					
Mean ± SD	1.4 ± 0.3	2.5 ± 0.8	15.8 ± 0.4*	8.8	< 0.001**
Median (range)	1 (0-2) q q	2.4 (2-4)	16 (10-20)		

UsCD25: urinary soluble CD25, Up/creatinine ratio: protein/urine creatinine ratio.
SLE DAI: SLE disease activity index

Table 5: Correlation between study variables in SLE cases (n = 20)**.**

Variables	Upr/Ucr ratio		UsCD25	
	r	p-value (Sig.)	r	p-value (Sig.)
Age (years)	-0.029	0.904 (NS)	+0.196	0.408 (NS)
Weight (kg)	+0.001	0.996 (NS)	+0.389	0.046 (S)*
Height (cm)	+0.016	0.945 (NS)	+0.229	0.156 (NS)
Duration (years)	-0.073	0.760 (NS)	+0.262	0.265 (NS)
SLE DAI	0.421	0.002 (S)*	0.434	0.001 (HS)*
Hemoglobin (g/dl)	+0.046	0.849 (NS)	+0.027	0.910 (NS)
Urea (mg/dl)	-0.036	0.880 (NS)	+0.476	0.0005 (HS)*
Creatinine (mg/dl)	+0.277	0.101 (NS)	-0.107	0.654 (NS)
ESR 1st (mm/hr)	+0.209	0.100 (NS)	-0.177	0.456 (NS)
ESR 2nd (mm/hr)	+0.155	0.149 (NS)	-0.037	0.876 (NS)
Anti-dsDNA (IU/ml)	+0.396	0.042 (S)*	+0.402	0.009 (S)*
C3 (ng/dl)	-0.092	0.698 (NS)	-0.023	0.925 (NS)
C4 (ng/dl)	-0.284	0.224 (NS)	+0.064	0.788 (NS)
Upr/Ucr ratio			+0.415	0.003 (S)*

r Spearman\'s rank correlation coefficient
$p < 0.05$ is significant SLE DAI: SLE disease activity index

Table 6: Diagnostic performance of Upr/Ucr ratio, anti-dsDNA, C3, C4 and UsCD25 in discriminating between active lupus nephritis from inactive lupus nephritis (ROC curve analysis).

Cutoff values	SN% (95% CI)	SP% (95% CI)	PPV% (95%)	NPV% (95% CI)	Accuracy (95% CI)	AUROC (95% CI)
Upr/Ucr ratio > 0.2	80% (44.4-97.5)	100% (69.2-100)	100% (63.1-100)	83.3% (49.9-98.2)	90% (56.8-98.8)	0.94* (0.737-0.997)
Anti-dsDNA > 93 IU/ml	80% (44.4-97.5)	100% (69.2-100)	100% (63.1-100)	83.3% (49.9-98.2)	90% (56.8-98.8)	0.95^{++} (0.751-0.999)
C3 ≤ 47 ng/dl	100% (69.2-100)	100% (69.2-100)	100% (69.2-100)	100% (69.2-100)	100% (69.2-100)	1^{*} (0.832-1)
C4 ≤ 16 ng/dl	100% (69.2-100)	100% (69.2-100)	100% (69.2-100)	100% (69.2-100)	100% (69.2-100)	1^{+} (0.832-1)
UsCD25 > 470 pg/mg	100% (69.2-100)	100 (69.2-100)	100 (69.2-100)	100 (69.2-100)	100 (69.2-100)	1^{+++} (0.832-1)

*$p < 0.001$ (HS); $^{++}p < 0.001$ (HS); $^{+}p < 0.001$ (HS); $^{+++}p < 0.001$ (HS) $p < 0.05$ is significant
ROC curve: Receiver Operating Characteristic curve; SN: Sensitivity; SP: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value; AUROC: Area Under Receiver Operating Characteristic curve; 95% CI: 95% Confidence Interval.

Discussion

Systemic lupus erythematosus (SLE) is a prototypical, autoimmune, multisystem disease characterized by chronic inflammation in multiple organs **[8].**

SLE has a negative impact on quality of life and is associated with high health-care costs and significant productivity loss **[9]**. In consequence, SLE incurs a great burden on both the patient and society **[10].**

Juvenile-onset systemic lupus erythematosus (JSLE) is a typically has a more active disease course and in particular more renal involvement than disease presenting in adulthood. The renal biopsy is the gold standard in confirming the diagnosis and class of lupus nephritis (LN) [11].

Current laboratory markers for lupus nephritis such as proteinuria, urine protein-to-creatinine ratio, creatinine clearance, anti-dsDNA, and complement levels are unsatisfactory. They lack sensitivity and specificity for differentiating renal activity and damage in lupus nephritis. Significant kidney damage can occur before renal function is impaired and first detection by laboratory parameters. Flares of nephritis can occur without any observable and recent increase in the degree of proteinuria **[3]**.

This study was conducted at Pediatric Nephrology Unit, Zagazig University Hospitals to investigate urinary level of sCD25 as a biomarker of disease activity of pediatric lupus nephritis using ELISA test. We aimed to determine whether urinary concentrations of sCD25 are biomarker of active renal disease in JSLE.

In our study, serum creatinine and hemoglobin data emerged as independent predictors of renal insufficiency, these results match with **Howard and Austin [12]** and do not match with **Gaberella et al [13].**who stated that the occurrence of flares characterized by rapid increases in plasma creatinine was the strongest predictor of the eventual development of irreversible deterioration renal function.

In our study, urinary symptoms increased in SLE patients with active nephritis and decrease with patients without nephritis and these results match with **Cameron [14]** who stated that patients with lupus nephritis have abnormalities of urine or renal function early in their course, although up to 60% of adults and 80% of children may develop overt renal abnormalities later.

In our study, hypertension was found in nearly 50% of patients with nephritis and was not common, this matched with **Cameron [14]** who stated that hypertension is not overall more common in those with nephritis than in those without but as expected; those with more severe nephritis are more commonly hypertensive.

Our study showed that UsCD25 achieved a mean ± SD of 763.2 ± 14.93 in SLE with active nephritis patients and a mean ± SD of 414.5 ± 43.55 in SLE without lupus nephritis in comparison to healthy control (410.3 ± 39.6), p-value was < 0.001, which indicates a high sensitivity of UsCD25 in detecting activity and remissions.

This matches with **Chan et al.**[15] who stated that urinary sCD25 levels decreased in the AN group over one year with immunosuppressive treatment and reached the levels seen in inactive disease patients at one year, suggesting that this can be used to follow-up patients.

Higher urinary sCD25 in patients with active nephritis as compared with patients without nephritis suggest that there may be local activation of T cells in kidney **[16]**.

Urinary sCD25 is a good marker of LN for follow up as it falls in patients with good response and stays raised or rises more when there is poor response or relapse **[17].**

Studies have indicated that Neutrophil Gelatinase-Associated Lipocalin (NGAL) might be a useful screening marker and is more predictive than complement or proteinuria. NGAL can detect impending renal or global flares but cannot discriminate against renal severity **[18]**.

In our study, urinary CD25 level correlated well with SLE disease activity as measured by SLEDAI. In addition, urinary CD25 correlates positively with proteinuria, blood urea nitrogen level, so that urinary CD25 correlates with severity of nephritis, we concluded that the measurement of CD25 in urine may be useful for monitoring the severity of renal affection in SLE, and this matches **with El-Shafey et al [18]**.

In our results, patients with active lupus nephritis had lower C3 and C4 than those with inactive LN, also significant higher level of urea levels, these results match with **Terborg et al [19]**.

In our study, we observed significant correlation between UsCD25 with levels of anti-dsDNA antibodies and SLEDAI. In line with our data, **Lin et al [20]** reported a significant increase of UsCD25 in patients with active SLE, determined by the SLEDAI score, as compared to patients with inactive SLE. In contrast, **Bonelli et al [21] and Zhang et al [22]** observed no correlation between UsCD25 and disease activity, the complement levels.

Study Limitations

Our study is small sample size, longitudinal follow up of patients with active nephritis and measurement of urinary sCD25 levels. The limitations are lack of data on expression of CD25 in the kidney biopsy tissue, lack of other
T-cell biomarkers.

Conclusion and recommendations: Urinary CD25 ≥ 470 pg/mg is a useful noninvasive biomarker and the SLEDAI as a disease activity tool for the assessment of renal disease affection in patients with lupus nephritis, as it shows a good correlation with some clinical and laboratory parameters of disease relapse. Urinary CD25 can be used to follow patients with lupus nephritis beside other markers like C3, C4 and Up/Ucr with high sensitivity and specificity.

Ethics approval and consent to participate

This study protocol and the consents were approved and deemed sufficient by "The Postgraduate Clinical Research and Ethical Committee of Pediatric Department, Faculty of Medicine, Zagazig University." And Informed written consent was obtained in every case from their legal guardians.

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Conflict of interest: No

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Declaration

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