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Urinary CD80 and Serum Soluble Urokinase Plasminogen Activator Receptor (SuPAR) as Novel Diagnostic Biomarkers in Pediatric Patients with Nephrotic Syndrome

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: This study aimed to evaluate urinary CD80 and serum SuPAR in patients with primary nephrotic syndrome as a non-invasive diagnostic biomarker to predict steroid responsiveness in those patients.
Methods: This prospective cohort study was carried out on total 60 children and adolescents with idiopathic nephrotic syndrome (INS) at initial presentation and 30 healthy matched controls. Urinary CD80 and serum SuPAR were measured for all subjects. Patients were divided on follow up into two groups: group A: patients proved to be steroid sensitive nephrotic syndrome (n=30), group B: patients proved to be steroid resistant nephrotic syndrome or proved by biopsy to be focal segmental glomerulosclerosis (n=30).
Results: Urinary CD80 levels were significantly higher in group A than group B and C (P <0.001). SuPAR was significantly higher in group B than group A and C (P <0.001). Both urinary CD80 and serum SuPAR were positively correlated to 24h urinary protein, protein/ creatinine ratio and serum cholesterol (P = 0.001, 0.003, <0.001, <0.001 and <0.001 respectively). Also both urinary CD80 and SuPAR were negatively correlated to albumin (P <0.001 and <0.001 respectively). By ROC

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curve, urinary CD80 can predict steroid sensitivity with 80% sensitivity, 96.67% specificity and accuracy 95% and serum SuPAR can predict steroid resistance with 76.67% sensitivity, 88.33% specificity and accuracy 86%.
Conclusions: Urinary CD80 and serum SuPAR can be useful in predicting renal pathology or steroid responsiveness in patients with idiopathic nephrotic syndrome especially if renal biopsy is contraindicated.

Keywords: Urinary CD80; SuPAR; pediatric; nephrotic syndrome.

1. INTRODUCTION

Nephrotic syndrome is the most common glomerular disease encountered during childhood [1]. It is characterized by heavy proteinuria (proteinuria exceeding 40mg/m^2/h or spot urinary protein creatinine ratio exceeding 2 mg/mg), hypoalbuminemia (<2.5 g/dl), edema and hyperlipidemia (serum cholesterol >200 mg/dl) [2,3]. Idiopathic nephrotic syndrome is defined as the association of nephrotic syndrome with nonspecific glomerular abnormalities, including minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and mesangial proliferative glomerulonephritis [4].

Renal biopsy is the only available method of diagnosis of the underlying pathology of nephrotic syndrome, especially in SRNS, but it is invasive and has many complications and therapeutic response predicts long-term outcomes better than histology in the pediatric population [5].

Finding a urinary or blood marker that can predict renal pathology or steroid responsiveness will be of great value in determining disease prognosis without the need for renal biopsy. Several serum and urinary biomarkers were studied to achieve this goal [6].

Cluster of differentiation 80 (CD80) also called B7.1, is a trans-membrane protein normally expressed on the surface of B cells and other antigen presenting cells (APCs) [5]. On APCs, B7-1 acts as a costimulatory molecule through binding to its cognate receptors CD28. It also inhibits T cells activation by binding to CTLA-4 [7]. CD80 expression on podocytes cause actin reorganization and proteinuria [8]. CD80 expression in podocytes or its urinary concentration was studied as a marker of minimal change disease in previous researches [9,10,11,12,13,14].

Serum soluble urokinase-type plasminogen activator receptor (SuPAR) is a glycosylphosphatidylinositol (GPI)-anchored protein on the cell membrane secreted during infections and inflammation [15]. SuPAR is expressed in various cell types such as machrophages, monocytes, endothelial cells, neutrophil, certain cancer cells and kidney podocytes [16].

Few studies were performed on marker that can predict steroid response or renal pathology specially in children, in addition the difference in genetic background in different ethnic groups that can affects clinical presentation of nephrotic syndrome and response to therapy may affect also the reliability of these markers in different populations [6].

The aim of this study was to evaluate urinary CD80 and serum SuPAR in patients with primary nephrotic syndrome and use them as non-invasive diagnostic biomarkers to differentiate the different clinical phenotypes of primary nephrotic syndrome.

2. PATIENTS AND METHODS

This prospective cohort study was carried out on total 60 children and adolescents with INS and 30 healthy matched controls.

Patients with congenital nephrotic syndrome and secondary causes of nephrotic syndrome were excluded from this study.

The diagnosis of INS was based on the presence of nephrotic range proteinuria >40 mg/m^2/h or urinary protein/creatinine ratio > 2 g/g, hypoalbuminemia <2.5 g/dl, generalized edema and hypercholesterolemia >200 mg/dl [2,3]. All children with INS received the standard steroid therapy and were classified into two categories on follow up, SSNS and SRNS, on the basis of their clinical responses toward steroids. The SSNS group (group A=30) included patients who respond (negative urine dipstick to protein for 3 consecutive days) to steroid therapy (60 mg/m^2/d) within 4 weeks of starting therapy. The

SRNS group (group B =30) included patients who showed persistence of proteinuria despite of full dose steroid daily therapy for 6 weeks or proved by biopsy to be FSGS.

All the subjects included in the study were subjected to detailed history, clinical examination with particular emphasis on general examination, anthropometric data and blood pressure were measured.

Regarding laboratory investigations: samples were collected before starting treatment then routine investigations were performed as complete blood picture, ESR, CRP and serum albumin. Specific investigations were performed as urinary CD80 and serum SuPAR by ELISA kits (Shanghai SunRed biological technology company, China); results of urinary CD80 were adjusted for urinary creatinine excretion.

2.1 Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 25 (IBM Inc., Chicago, IL, USA). Shapiro-Wilks normality test and histograms were used to test the distribution of quantitative variables. Parametric variables were expressed as mean and standard deviation (SD) and were compared using ANOVA (F) test among the three groups with post hoc (Tuckey) test to compare each two groups. Non- parametric variables were expressed as median and interquartile range (IQR) and were analyzed using Kruskal-Wallis test; further analysis was performed by Mann–Whitney (U) test to compare each two groups. Categorical variables were expressed as frequency and percentage and were statistically analyzed by Chi-square test. Correlation coefficient (r) was performed. Evaluation of diagnostic performance was performed by ROC curve. P value ≤ 0.05 was considered statistically significant.

3. RESULTS

Weight and BMI Z-score were significantly higher in patient groups (A and B) than controls (P <0.001) (Table 1).

Serum creatinine and blood urea levels were mildly elevated in Group B compared to group A and C (Table 2).

Serum cholesterol and urinary protein/creatinine ratio were higher in group B compared to group A and C while triglyceride levels and 24-hour urinary protein levels were higher in group A and B compared to group C (Table 3).

Urinary CD80 levels were significantly higher in Group A compared to group B and C and higher in group B compared to group C. Serum SuPAR levels were significantly higher in group B compared to group C and A and higher in group A compared to group C (Table 3).

Table 1. Demographic data of the studied groups

		Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P value		
Age (years)		6	8.5	7.5	0.831		
Sex	Male	19(63.3%)	20(66.7%)	17(56.7%)	0.718		
	Female	11(36.7%)	10(36.3%)	13(43.3%)			
Weight Z-score		2.49 ± 0.77	2.41 ± 0.78	1.03 ± 1.47	<0.001*	P1	0.780
						P2	<0.001*
						P3	<0.001*
Height Z-score		0.85 ± 1.24	1.04 ± 1.41	1.15 ± 1.48		0.702	
BMI Z-score		2.17 ± 0.77	2.14 ± 0.83	0.74 ± 1.47	<0.001*	P1	0.923
						P2	<0.001*
						P3	<0.001*
SBP (percentile)		64.70 ± 27.80	69.83 ± 23.20	66.57 ± 20.19	0.703		
DBP (percentile)		74.67 ± 20.50	72.03 ± 18.32	64.47 ± 15.09	0.083		

Data are presented as mean ± SD, median or frequency (%): Statistically significant as p ≤ 0.05, P1: P value between group A and group B, P2: P value between group A than group C, P3: P value between group B and group C, BMI: body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure*

Table 2. Routine laboratory investigations and estimated glomerular filtration rate (eGFR) of the studied groups

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P value	
Hb (g/dL)	**11.72 ± 1.43**	**11.11 ± 1.94**	**11.86 ± 0.78**	**0.110**	
Platelet count (*10^3/mm^3)	411.20 ± 112.64	436.70 ± 126.72	267.83 ± 63.22	<0.001*	P1 0.347 P2 <0.001* P3 <0.001*
TLC (cell/mm^3)	9663.33 ± 4743.45	10003.33-4341.10	6606.80±1879.87	0.001*	P1 0.734 P2 0.003* P3 0.001*
ESR 1st hour (mm)	75.83 ± 15.09	78.17 ± 17.79	8.80 ± 4.37	<0.001	**P1** 0.511 **P2 <0.001*** **P3 <0.001***
ESR 2nd hour (mm)	113.67 ± 18.61	118.50 ± 20.43	21.17 ± 5.78	<0.001*	P1 0.293 P2 <0.001* P3 <0.001*
CRP (mg/l)	9	10	1.5	<0.001*	P1 0.991 P2 <0.001* P3 <0.001*
Creatinine (mg/dL)	0.54 ± 0.19	0.90 ± 0.33	0.56 ± 0.11	<0.001*	P1 <0.001* P2 0.688 P3 <0.001*
Urea (mg/dL)	37	64.5	23	<0.001*	P1 0.007* P2 0.001* P3 <0.001*
Albumin (g/dL)	1.69± 0.28	1.55 ± 0.22	4.78 ± 0.55	<0.001*	P1 0.154 P2 <0.001* P3 <0.001*
eGFR (mg/l)	136.42 ± 48.16	98.09 ± 32.61	113.50 ± 10.48	<0.001*	P1 <0.001* P2 0.029* P3 0.193

*Data are presented as mean ± SD or median *: Statistically significant as p ≤ 0.05, P1: P value between group A and group B, P2: P value between group A than group C, P3: P value between group B and group C, BMI: body mass index, SBP: Systolic blood pressure, DBP*: *Diastolic blood pressure*

Table 3. Lipid profile, urinary investigations and Biomarkers of the studied groups

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P value		
Cholesterol (mg/dL)	465.10 ± 117.38	537.10 ± 147.60	132.87 ± 18.64	**<0.001***	P1 P2 P3	**0.013*** **<0.001*** **<0.001***
Triglycerides (mg/dL)	272.23 ± 132.5	294.53 ± 101.2	97.87 ± 20.38	**<0.001***	P1 P2 P3	0.376 **<0.001*** **<0.001***
24 urinary proteins (mg/day)	6050	7988	67	**<0.001***	P1 P2 P3	0.109 **<0.001*** **<0.001***
Protein/creatinine ratio (mg/mg)	5.7	8.2	0.105	**<0.001***	P1 P2 P3	**0.018*** **<0.001*** **<0.001***
Urinary CD80 (ng/gm creatinine)	643.685	71.57	1.57	**<0.001***	P1 P2 P3	**<0.001*** **<0.001*** **<0.001***

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P value		
SuPAR (pg/mL)	194.845	348.835	58.36	**<0.001***	P1	**<0.001***
					P2	**<0.001***
					P3	**<0.001***

*Data are presented as mean ± SD or median *: Statistically significant as p ≤ 0.05, P1: P value between group A and group B, P2: P value between group A than group C, P3: P value between group B and group C. KW: Kruskal-Wallis, F: ANOVA. Data are represented by mean± SD or median*

Table 4. Renal biopsy in the studied patients

	Group A (n = 30)	Group B (n = 30)	P value
Not performed	21 (70%)	0 (0%)	**<0.001***
MCNS	9 (30%)	5 (16.67%)	
FSGS	0 (0%)	23 (76.67%)	
Focal global, segmental glomerulosclerosis	0 (0%)	1 (3.33%)	
Diffuse mesangial proliferative GN	0 (0%)	1 (3.33%)	

*Data are presented as frequency (%) *: Statistically significant as p ≤ 0.05; MCNS: Minimal Change Nephrotic Syndrome; FSGS: Focal segmental glomerulosclerosis*

Renal biopsies were performed in 30% of group A and the pathology of all were MCNS and performed in all cases of group B and FSGS was the most prevalent pathology in 76.67% (Table).

Both urinary CD80 and serum SuPAR showed positive correlation with age,24h urinary protein, protein/ creatinine ratio and cholesterol (P = 0.584, 0.001, 0.003, <0.001 and 0. 0.712, <0.001, <0.001, <0.001respectively). Both urinary CD80 and serum SuPAR showed no significant correlation with sex, CRP and eGFR (P = 0.997, 0.128, 0.008 and 0.784, 0.089, 0.102 respectively). Both urinary CD80 and serum SuPAR showed negative correlation with serum albumin (P <0.001and<0.001) (**Error! Reference source not found.**).

Urinary CD80 can predict steroid sensitivity significantly with 80% sensitivity, 96.67% specificity, 92.3% PPV, 90.6% NPV, 0.958 AUC and P value <0.001 (**Error! Reference source not found.**A).

SuPAR can predict steroid resistance significantly with 76.67% sensitivity, 88.33% specificity, 76.7% PPV, 88.3% NPV, 0.860 AUC and P value <0.001 (**Error! Reference source not found.**B).

Table 4. Correlation between each of urinary CD80 and SuPAR with some laboratory findings

		Urinary CD80 (ng/gm creatinine)	SuPAR (pg/mL)
Age	R	0.058	-0.039
	P value	0.584	0.712
Sex	R	0.003	-0.029
	P value	0.997	0.784
24h urinary protein	R	0.337	-0.535
(mg/day)	P value	**0.001***	**<0.001***
Protein/ creatinine ratio	R	0.312	0.399
	P value	**0.003***	**<0.001***
Albumin	R	-0.608	-0.666
(g/dL)	P value	**<0.001***	**<0.001***
Cholesterol	R	0.537	0.698
(mg/dL)	P value	**<0.001***	**<0.001***
CRP (mg/l)	R	0.162	0.180
	P value	0.128	0.089
eGFR (mg/l)	R	0.279	-0.0173
	P value	**0.008***	0.102

**: Statistically significant as p ≤ 0.05. r: coefficient of correlation, CRP: C reactive protein, eGFR: estimated glomerular filtration rate*

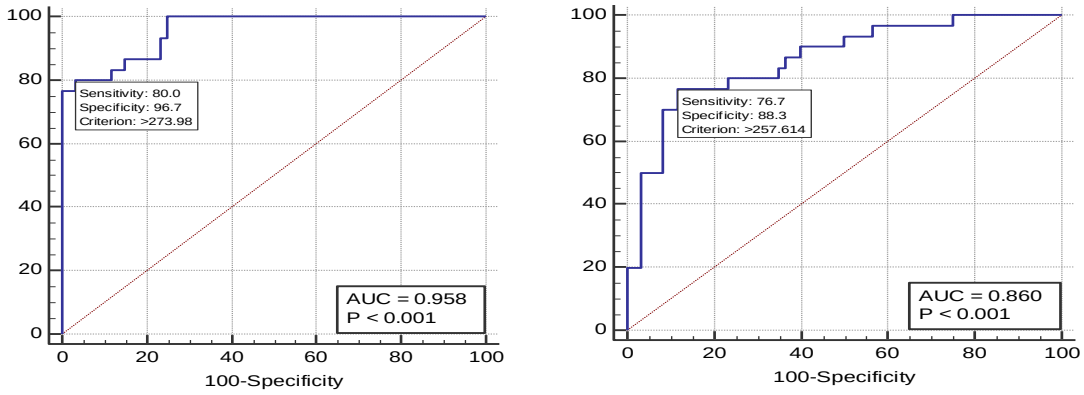

Fig. 1. ROC curves of (A) urinary CD80 to predict steroid sensitivity and(B) SuPAR to predict steroid resistance

4. DISCUSSION

Finding a biomarker that can predict steroid responsiveness in children with INS are of great importance. This study demonstrated high urinary CD80 in children with steroid responsiveness and high serum SuPAR in children with steroid resistance NS. Recent studies have found that the podocyte cells can acquire the phenotype, the function of dendritic cells and can express CD80 [17]. This expression in podocytes leads to actin cytoskeleton reorganization and alter the glomerular filtration barrier permeability causing proteinuria [18]. The soluble part of CD80 (s-CD80) can be sheded in urine [18]. CD80 was observed primarily expressed on the surface of podocytes, based on the observation, since FSGS caused severe damage to the podocyte. Thus, the expression of CD80 was declined, which leads to presence of CD80 in urine [19]. As most of MCD are SSNS and most of FSGS are SRNS so the same results can be applied [20].

Several experimental models have shown the role of podocyte CD80 in proteinuria development. The injection of lipopolysaccharide (LPS) to mice results in proteinuria and podocyte CD80 expression, but proteinuria fails to develop if LPS is injected into CD80 knockout mice [10].

Our results are consistent with Garin *et al;* who reported using of urinary CD80 as a biomarker for differentiation between the relapse phase of MCD and other renal diseases. In their studies, it was speculated that CD80 is derived from podocytes because (1) in the recurrent and remission phase of MCD the blood CD80 is normal, and therefore the urine CD80 does not come from the APCs in the blood; (2) immunofluorescence assay verified that CD80 was expressed by podocytes; (3) the molecular weight of CD80 is 53 kDa, which is the same as that of CD80 on the membrane, rather than the soluble CD80 which is of 23 kDa [11,12].

Also Zeybek et al, Chen et al and Ahmed et al ; reported that there were raised urinary CD80 in patients with MCD [21,22,23].

Also our results in agreement with Ling et al, Cara-Fuentes et al and Guerrico et al; concluded that urinary CD80 levels were significantly higher in patients with MCD than in patients with FSGS or in healthy controls [14,16,17]. Also the follow up study of Ling et al; demonstrated that patients with high uCD80 excretion during the acute stage are more sensitive to steroid treatment, more easily enter remission and experience renal function decline less frequently compared with patients with relatively lower uCD80 excretion [24].

Also in agreement with our results, Mishra et al and Liao et al; found that the level of urinary CD80 in patients with SSNS was high and could be used as a useful marker to differentiate patients of SSNS in relapse from those with SRNS [25,26]. Also Mishra et al, found that there was significant positive correlation between urinary CD80 with the urinary protein/creatinine ratio and serum cholesterol and negative correlation with serum albumin [25].

In contrast to our results, Garin et al, Zeybek et al, Chen et al and Ahmed et al didn't find

correlation between urinary CD80 and proteinuria [11,12,21,22,23].

In contrast to our results, Minamikawa et al**;** found that urinary CD80 is not a reliable marker for MCD in relapse, but The number of patients with FSGS or inherited NS included in this study was only 4 patients (small number) [27].

Serum SuPAR, was suggested as a permeability factor in few studies related to SRNS and FSGS. It can bind to podocyte a5b3 integrin, causing podocyte activation and changes in its structure and function, resulting in proteinuria [28]. Based on the higher the serum SuPAR concentration, the more severe the podocyte injury, so high SuPAR level might be associated with steroid resistance [29].

The absence of correlation between CRP and serum SuPAR in our results indicate that inflammation is not the cause of elevated level of SuPAR and SuPAR may work as a permeability factor rather than an inflammatory marker. High CRP was due to infection in these patients that was the predisposing factor for nephrotic syndrome. Also there was no correlation with eGFR and this support that the decrease of eGFR wasn't the cause of increase level of SuPAR due to decrese in its execretion.

Our results regarding SuPAR were in agreement with Wei et al, Huang et al, Li et al and Segarra et al; who found that the levels of serum SuPAR were higher in patients with FSGS than patients with MCD, different glomerulopathies and normal controls [30,31,32,33].

Peng et al and Mousa et al; found that serum SuPAR levels were higher in SRNS group than SSNS group and control group [15,29].

In contrast to our results, Maas et al, Bock et al, Sinha et al and Wada et al; found that serum SuPAR concentration is not a specific marker for idiopathic FSGS and it can't predict response to steroid treatment [34,35,36,37]. It is not clear whether the low SuPAR levels in these FSGS patients is due to genetic mutations, where the defect is at the level of other podocyte genes and not associated with a circulating factor, or to SuPAR with different biochemical properties that are not readily detected by commercial ELISA tests. It is also possible that pathologically processed SuPAR is podocyte pathogenic, even though the total measured SuPAR levels are low or normal in these FSGS patients.

In agreement with our results, Mousa et al and Mass et al; found significant positive correlations between serum SuPAR and proteinuria and negative correlation with serum albumin [15,34].

In contrast to our study Wei et al, Maas et al and Segarra et al; found negative correlation between serum SuPAR and eGFR but Huang et al, found no significant correlation between serum SuPAR and eGFR [30,32,34]. Also in contrast to our results, Segarra et al and Sinha et al; found that there were no significant correlations between serum SuPAR levels and proteinuria [32,35]. Mousa et al and Sinha et al found a significant positive correlation between serum SuPAR and CRP suggesting that inflammation-induced synthesis might contribute to elevated levels of SuPAR [15,35].

Study limitations: Urinary CD80 and serum SuPAR levels were measured once before starting treatment however follow up serial measurements during relapse and remission may give more dynamic results and explore more clinical values. Being single center study may affect results generalization and reproducibility.

5. CONCLUSIONS

Urinary CD80 and serum SuPAR can be useful in predicting renal pathology or steroid responsiveness in patients with idiopathic nephrotic syndrome specially if renal biopsy is contraindicated

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard, parental written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The study was performed after approval from the Ethical Committee, Faculty of Medicine, Tanta University, Egypt.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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