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The utility of biomarkers to predict steroid response in idiopathic nephrotic syndrome

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ABSTRACT

Objective: The most common form of nephrotic syndrome (NS) is minimal change disease (MCD) in children and focal segmental glomerulosclerosis (FSGS) following it. As, it is important to predict corticosteroid (CS) response at the beginning of the disease, we aimed to evaluate the efficacy of some biomarkers in terms of predicting steroid response in patients with NS.

Patients and Methods: Twenty patients who met the inclusion criteria for the study were divided into 3 groups and 6 healthy control participants were included in the analysis as the 4th group. Group-1 included 10 patients at the first episode of idiopathic NS (INS), group-2 included the same 10 patients in remission, group-3 included 10 patients with steroid resistant NS (SRNS) diagnosed as FSGS by renal biopsy, and group-4 included six healthy children as controls. Urinary and serum cluster of differentiation (CD) CD80, IL-17, IL-23, IL-10, TGF-β, CD86, CD28, CTLA-4 levels were measured for all groups.

Results: Urinary CD80 level in INS-relapse group was significantly higher than the levels of the INS-remission, FSGS and control groups ($p<0.001$). Urinary CD28 and uIL-10 were significantly increased in INS-remission group than INS-relapse ($p<0.05$, $p<0.001$). Serum IL-17 was significantly higher in INS-relapse group than in INS-remission group ($p<0.01$). There was no difference in IL-23,TGF-β,CD86 parameters between groups.

Conclusion: In our study, urinary CD80 levels were significantly higher in the relapse group compared to the other groups. When supported by more comprehensive clinical studies, urinary CD80 level may be a good biomarker to predict CS response and to predict in favor of MCD.

Keywords: Biomarkers, CD80, Nephrotic syndrome, Steroid response

1. INTRODUCTION

The most common form of nephrotic syndrome (NS) is minimal change disease (MCD) in children. It is considered that proteinuria is due to a circulating factor secreted by lymphocytes and suggested that MCD is a disorder of T cell function [1, 2]. The second most common type of NS is focal segmental glomerulosclerosis (FSGS) following MCD. Most nephrotic children with MCD respond to corticosteroid (CS) therapy, whereas, those with FSGS are relatively resistant. There is a risk of progression to end-stage renal disease in FSGS and the treatment and prognosis of MCD and FSGS differ considerably. Currently, the gold standard to differentiate MCD and FSGS is renal biopsy. But, this method is invasive and rarely used especially for patients estimated to be MCD with clinical findings and the patients with first episode of NS whose steroid response is unknown. It is very important to identify biomarkers to predict whether patients are likely to respond CS treatment or not as it can guide the physician.

In idiopathic nephrotic syndrome, although, the use of certain biomarkers to assess treatment response is controversial in the literature, cluster of differentiation 80 (CD80) is the one that has been most emphasized. CD80 is found to be expressed by podoyctes in experimental models of glomerular disease associated with NS [3]. It is reported that CD80 is expressed by the podocytes in patients with MCD and urinary CD80 (uCD80) in MCD relapse is higher than patients in MCD remission and other glomerular diseases like FSGS, membranoproliferative glomerulonephritis, IgA nephropathy and membranous nephropathy [4, 5]. The antigen-specific T-cell receptor binds to CD80/CD86 costimulatory molecules expressed on the surface

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of antigen-presenting cells [6]. It acts as a costimulatory molecule through binding to its receptor CD28 on T cells [3]. CD80 is induced in podocytes by circulating cytokines, microbial products or allergens. Th-17 cell is a member of the CD4 effector T-cell family and is an important mediator in inflammatory and autoimmune diseases by T-cell mediated immunity [7]. In normal settings, the inflammatory immunity and CD80 expression is terminated by regulatory cytokines secreted from T regulatory (Treg) cells, Cytotoxic T-Lymphocyte-Associated 4 (CTLA-4), IL-10, and Transforming Growth Factor-β (TGF-β). Patients with MCD exhibited a significant increase in Th-17 number and related cytokines IL-17 and IL-23, as well as an obvious decrease in Treg number and related cytokines CTLA-4, TGF-β and IL-10 [8]. It is proposed that due to Treg dysfunction and impaired regulatory cytokines, podocyte CD80 expression becomes persistent and induces proteinuria [9].

In this study we aimed to assess the clinical utility of serum and urinary biomarkers to predict CS response. This is a preliminary study evaluating CD80 and other biomarkers in patients at the first episode of idiopathic NS (INS) before CS therapy.

2. PATIENTS and METHODS

This study is a prospective study including twenty six patients who were admitted to the Division of Pediatric Nephrology between March 2018 and March 2020. The study was approved by the Marmara University, School of Medic

ine Clinical Research Ethics Committee (09-2014-0018) and written informed consent was obtained before participation. We divided the participants in 4 groups. Group-1 included 10 patients at the first attack of INS, group-2 included the same 10 patients in remission, group-3 included 10 patients with NS resistant to CS therapy and diagnosed as FSGS by renal biopsy, and group-4 included 6 healthy children as controls. The mean age of the patients with INS, FSGS and controls were 4.8±2.2, 14.8±4.6 and 8.7±3.5 years respectively. Serum albumin and urinary protein levels are shown in Table I. Urinary (u) and serum (s) CD80, CD86, CD28, IL-17, IL-23, IL-10, TGF-β, CTLA-4 were measured in blood and urine using a commercially available ELISA kit (Bender MedSystems, Burlingame, CA) for all groups and urinary concentrations were adjusted with urinary creatinine.

Relapse of the NS was defined as the presence of massive proteinuria confirmed by a urine protein/creatinine ratio (up/uc) ≥2 or 24-hour proteinuria ≥40 mg/m²/hour, and a serum albumin of ≤2.5 g/dl during the course of the episode. Complete remission was defined as no proteinuria confirmed by a up/uc ≤0.2 or 24-hour proteinuria ≤4 mg/m²/hour and a serum albumin of >2.5 g/dl. The mean follow up time was 36.2±3.73 months and the mean relapse rate in patients with INS was 0.7±0.56 per year. All of the patients with INS who had relapses, progressed into remission with CS treatment. These patients were evaluated as steroid sensitive NS (SSNS). Corticosteroid resistance, which means steroid resistant NS (SRNS), was not observed in any patient during follow-up. These findings strongly suggest that these patients with INS are most likely MCDs.

Table I. *Characteristic of Patients with INS, FSGS, Control Subjects*

	Age (years)	Gender	Serum albumin (gr/dl)	24 hour proteinuria (mg/m²/hour)	up/uc ratio
INS in attack					
1	9.9	M	2.3	140	9.8
2	3.4	M	1.6	56	7.4
3	4.6	F	1.32	210	12.6
4	7.1	M	2.3	42	8.7
5	5.6	M	1.5	389	11.8
6	4.1	M	1.4	166	7.5
7	2.8	M	1.45	-	18.7
8	4	M	1.48	62	13.5
9	4.4	M	1.5	243	12.3
10	2	M	1.7	-	9.2
Mean	4.8±2.2		1.65±0.35	163.5±121.25	11.15±3.42
INS in remission					
1	9.9	M	4.6	2.7	0.08
2	3.4	M	3	2.4	0.12
3	4.6	F	4.28	3.6	0.07
4	7.1	M	4.5	1.5	0.13
5	5.6	M	4.39	4.2	0.11
6	4.1	M	3.2	1.84	0.07
7	2.8	M	3.2	-	0.2
8	4	M	4.4	2.5	0.1
9	4.4	M	4	3	0.08
10	2	M	3.5	-	0.02
Mean	4.8±2.2		3.9±0.61	2.71±1.34	0.098±0.04
FSGS					
11	20.2	F	3.4	128	14.3
12	19.5	F	4.1	35	1.6
13	14.8	M	4.2	38	1.4
14	14.8	M	4.6	42	1.5
15	17.4	F	4.6	29	1.1
16	15.8	M	4.4	33	0.2
17	9.2	M	4.6	48	0.18
18	17.1	F	4.6	47	0.17
19	14.3	M	4.4	38	1.7
20	10.9	F	4.8	55	0.15
Mean	14.8±4.6		4.37±0.4	49.3±28.72	4.03±3.69
Control					
21	9.7	F		Neg	
22	13.9	M		Neg	
23	10.1	F		Neg	
24	11.4	M		Neg	
25	5	F		Neg	
26	7.33	M		Neg	
Mean	8.7±3.5				

INS: Idiopathic nephrotic syndrome, up: Urinary protein, uc: Urinary creatinine, FSGS: Focal segmental glomerulosclerosis

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Statistical Analysis

We conducted statistical analysis using SPSS, parametric T test was used for CD80 with homogeneous distribution and non parametric ANOVA (Kruskal-Wallis test) for other parameters because of the non homogeneous distribution and we determined differences between medians using Dunn's comparisons test. A p value < 0.05 was considered significant.

3. RESULTS

Urinary CD80 excretion was significantly elevated in group-1 (INS-relapse) than in group-2 (INS-remission, (p<0.001), group-3 (FSGS, (p<0.001) and group-4 (control, (p<0.001) (Table II and Figure 1). There was no statistically difference in uCD80 excretion between the INS-remission and FSGS groups and also between the control group (Table II). In contrast with the urinary findings, sCD80 concentrations were not different among patients in 4 groups (Table III). Urinary CD28 and uIL-10 were significantly increased in INS-remission group compared to INS-relapse group (p<0.05, p<0.001). There was no difference between groups for other urinary parameters (Table II). Serum IL-17 was significantly higher in INS-relapse than in INS-remission (p<0.01). Serum CTLA-4 was significantly higher in FSGS group than in INS-remission group, but not higher than control group causing a nonsense relation. There was no difference in serum and urinary IL-23, TGF-β, CD86 and urinary CTLA-4 between groups (Table III).

Table II. *Urine Median Levels of Biomarkers in Study Patients*

	INS in attack	INS in remission	FSGS	Control	P
CD80 (ng/gr)	647.25*	92.92*	96.90*	116.62*	0.0001
CD86 (ng/gr)	49.29	25.16	19.35	17.51	0.0857
CD28 (ng/gr)	0*	1970.20*	663.53	12.27	0.0410
IL-17 (pg/gr)	0	0	0	0	0.160
IL-23 (pg/gr)	49378	4515,3	4522.5	0	0.0673
IL-10 (pg/gr)	0*	1084.8*	130.49	0	0.002
TGF-β (pg/gr)	1124650	0	319331	287471	0.114
CTLA-4 (ng/gr)	19.48	9933.9	5052.5	4118.3	0.072

INS: Idiopathic nephrotic syndrome, FSGS: Focal segmental glomerulosclerosis
**groups which the statistical difference is derived from*

Table III. *Serum Median Levels of Biomarkers in Study Patients*

	INS in attack	INS in remission	FSGS	Control	P
CD80 (ng/ml)	0.5050	0.3060	0.3360	0.62	0.05
CD86 (ng/ml)	0.1005	0.68	0.0310	0.058	0.4306
CD28 (ng/ml)	0	0	0.714	0.72	0.2172
IL-17 (pg/ml)	0.2750*	0*	0.042	0.024	0.0093
IL-23 (pg/ml)	32.194	87.939	16.607	38.446	0.2063
IL-10 (pg/ml)	1.718	0.8130	0.4030	0.4020	0.3837
TGF-β (pg/ml)	45273	69462	57116	48156	0.7669
CTLA-4 (ng/ml)	2.64	2.475	8.65	6.37	0.01

INS: Idiopathic nephrotic syndrome, FSGS: Focal segmental glomerulosclerosis
**groups which the statistical difference is derived from*

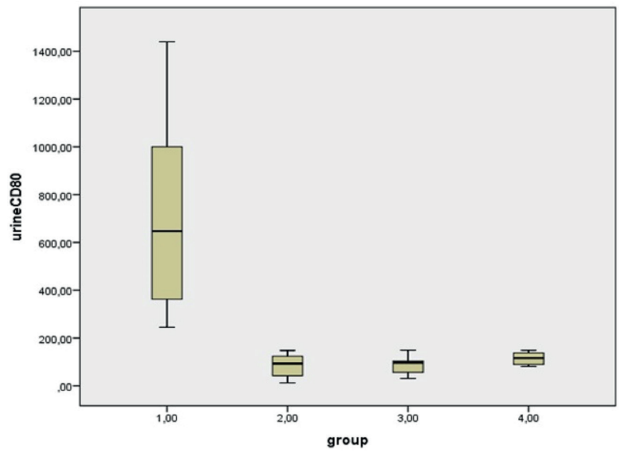

Figure 1*: uCD80 excretion (ng/gr creatinine) in study patients*

4. DISCUSSION

In the current study, CD80 and other biomarkers in patients at the first episode of INS were evaluated in terms of determining the response to steroid treatment. uCD80 levels were found high in patients with SSNS in the first attack, but not in remission and FSGS. This data suggest that uCD80 may be a useful differential marker to distinguish SSNS from SRNS.

Since, steroid response is the most important predictor of prognosis in children with nephrotic syndrome, biomarkers that can be used to predict steroid resistance may be useful in determining prognosis and guiding treatment. A two hit mechanism is accused for T cell disorder: the first hit is CD80 is induced in podocytes by circulating cytokines, microbial products or allergens and the second hit is Treg dysfunction and/or impaired autoregulatory function by the podocyte thus elevated podocyte CD80 expression becomes persistent and induces proteinuria [9]. When human podocytes were incubated with MCD patients' serum in relapse, a significant increase in CD80 expression was found compared to those incubated with MCD patients' serum in remission [10]. But, in another study, no significant upregulation of CD80 was detected in biopsy samples of MCD and FSGS. Also, in the same study, there was no difference in CD80 expression between MCD and FSGS patients in relapse and remission [11]. These conflicting results make it difficult to understand the exact role of CD80 in pathophysiology of NS.

We hypothesize that uCD80 can distinguish MCD from FSGS, as Garin et al., have previously shown. They showed elevated uCD80 levels in pediatric patients with MCD in relapse when compared with MCD in remission, healthy controls and a small number of patients with other glomerular diseases [4,12]. In two other studies, it was also shown that uCD80 was significantly higher in MCD relapse than in FSGS, other glomerulopathies and control groups [5,13]. The increase of uCD80 was found closely associated with relapse of SSNS but was not related to

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the frequency of relapse [14]. When uCD80 was evaluated as a prognostic factor, the patients with high levels of uCD80 showed good response to immunosuppression therapy and decreased rates of chronic kidney disease and then uCD80 expression was thought to be a predictor of good outcome in children with primary NS [15]. However, in another study, uCD80 was elevated in all patients with active kidney disease even in patients with inherited NS and uCD80 was found positively correlated to urinary protein levels. It was stated that uCD80 is unreliable as a differential diagnostic marker between MCD, FSGS and other glomerular diseases [16]. These results are also confusing like the results of studies on CD80 expression in kidney biopsy samples.

In this study, uCD80 levels were found high in patients with SSNS in the first attack, but not in remission and SRNS diagnosed as FSGS. This data suggest that uCD80 may be a useful differential marker to distinguish SSNS from SRNS. However, due to the small number of patients, we could not define a cut-off point for uCD80 level that differentiates SSNS patients from SRNS.

The antigen-specific T-cell receptor binds to CD80/CD86 costimulatory molecules expressed on the surface of antigen-presenting cells [6]. It acts as a costimulatory molecule through binding to its receptors CD28 on T cells [3] . While we expected uCD28 level, like uCD80, to increase at the time of the first attack, urinary CD28 was found to be significantly higher in the remission group than in the relapse group. This was an unexpected result for us. When we searched the literature on this subject, no relevant study was found. To demonstrate the effect of uCD28 if any in the pathogenesis of MCD, prospective well-defined studies are needed.

Treg and Th17 cells are two important subsets of T helper cells. The Th17/Treg balance controls autoimmunity and inflammation and has been found to play an important role in pathogenesis of autoimmune diseases. To assess whether this balance was disturbed in MCD patients, Th-17/Treg balance had been evaluated in 25 new-onset MCD adult patients. Serum Th-17 number, Th-17 related cytokines IL-17 and IL-23 were significantly higher than in the control group and correlated with proteinuria and decreased serum albumin levels [8]. Urinary IL-17 levels were significantly increased in patients with MCD relapse and decreased to baseline with remission [17]. Similarly, in our study sIL-17 levels were significantly higher in relapse group than in remission group confirming the possible relationship of this molecule with physiopathology of SSNS but there was no difference in uIL-17 levels, sIL-23 and uIL-23 levels.

An obvious decrease was observed in serum T-reg number and related cytokines TGF-β and IL-10 in MCD patients in relapse but not in remission [8]. It was shown that the percentages of T-reg cells were similar between patients with MCD in relapse, remission and controls but in relapse group T-reg cells had an impaired ability to suppress T-eff cell proliferation [9,18]. When uTGF-β levels were compared between MCD and FSGS, it was significantly higher in FSGS group than in MCD. Urinary TGF-β was also evaluated according to steroid responsiveness and there was no significant difference between SSNS and SRNS patients. The authors indicated that uTGF-β was able to differentiate between FSGS and MCD but was not a biomarker of steroid responsiveness [19]. In a study with 32 SSNS patients, sIL-10 levels showed no significant difference between relapse and remission phase, but sTGF-β levels of relapse phase were significantly lower than those of remission phase or control group, and returned to normal control levels after steroid therapy [20]. We only found a significant decrease in uIL-10 levels in relapse group compared to remission group, dropping hints that uIL-10 may be an important marker in the physiopathology of MCD. There was no difference between groups for urinary and serum TGF-β levels.

A decrease in Treg number and related cytokines CTLA-4, TGF-β and IL-10 were shown in patients with MCD. It is proposed that due to Treg dysfunction and impaired regulatory cytokines, podocyte CD80 expression becomes persistent and induces proteinuria [8,9]. Garin et al., reported urinary CTLA-4 tends to be low, but not significant, in MCD in relapse [4]. In another study evaluating uCD80, urinary CTLA-4 and their relation, uCD80 was increased significantly in MCD relapse as compared to remission and healthy controls, but urinary CTLA-4 excretion was also higher in MCD patients in relapse than in remission and controls. uCD80 was high as expected but urinary CTLA-4 was not low in MCD patients in relapse and no significant correlation was observed between uCD80 and urinary CTLA-4 [21]. In our study, there was no significant difference in serum and urinary CTLA-4 levels between four groups. According to these results, it is considered that CTLA-4 may not have an important role in pathophysiology of NS.

We have some limitations in this study. Renal biopsy for SSNS patients was not performed because of ethical concerns. But the advantage of our study is to have a relatively long follow-up time for newly diagnosed patients. All ten patients in the study group are still being followed-up as steroid sensitive that is more in favour of MCD. Though, the number of patients are limited, the major advantage of this study is that all the patients included were at the first attack of NS before CS therapy. Patients with SSNS followed up in our department were not included in the study. But the major limitation of our study is that for patients with FSGS, we could not get blood and urine samples during the acute phase of first nephrotic syndrome attack. These patients were already followed in our outpatient clinic. The serum albumin in the FSGS group was actually higher and urinary protein excretion was lower than in the attack group. But, even FSGS patients with hypoalbuminemia and massive proteinuria had lower uCD80 levels than patients with SSNS. For patients with FSGS, it would be much more meaningful to take samples when they emerged as the first episode of NS and have not yet received immunosuppressive treatment. For this reason, prospective studies with a larger number of patients presented with first NS attack who thought to be MCD or FSGS should be planned.

Urinary CD80 is elevated in patients with SSNS. It may be a promising biomarker to predict steroid response and it seems

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to have an important role in the pathogenesis of MCD as the leading cause of SSNS.

The study was approved by the Marmara University, School of Medicine Clinical Research Ethics Committee (09-2014-0018) and written informed consent was obtained before participation.

Compliance with Ethical Standards

Ethical approval: The study was approved by the Marmara University, School of Medicine Clinical Research Ethics Committee (09-2014-0018) and written informed consent was obtained before participation.

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