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Research Article

The glomerular GCR expression, MEST score and clinical progression in patients with IgAN

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ABSTRACT

Aim: Glucocorticoids are used as the primary treatment in IgA Nephropathy (IgAN), and they manifest their effects by binding to intracellular glucocorticoid receptors. Studies have shown that Glucocorticoid Receptor Expression (GCR) expression correlates with steroid response in various diseases. Our aim was to evaluate the glomerular GCR expression, MEST score and clinical progression in patients with IgAN.

Materials and methods: This study included 103 patients (58 male) with biopsy proven primary IgAN, who were treated with angiotensin converting enzyme inhibitor/angiotensin receptor blocker and methyl prednisolone and followed-up between 2002-2019. GCR expression determined immunohistochemically, MEST score, clinical and laboratory parameters of the patients were evaluated from the beginning of IgAN diagnosis.

Results: Mean age was 40,79 ± 12. Demographic and laboratory data were similar according to GCR staining rate. In patients with meningeal proliferation (M1) GCR was stained more intensely than those with M0. At baseline Glomerular Filtration (GFR) (↑) and proteinuria (↓) were statistically significant different in patients with T0 or E0 compared to patients with T1 or E1. Systolic Blood Pressure (BP) was significantly higher in E1 patients. At diagnosis increased systolic and diastolic BP, increased counts of White Blood Cell (WBC) and neutrophil, increased levels of parathormone, BUN, creatinine, uric acid, potassium, magnesium, total cholesterol, LDL, elevated sclerosis rate, decreased total protein level, decreased GFR level were found to be poor prognostic factors in our study.

Conclusion: Any correlation was not found between the rate of GCR staining and clinical and biochemical parameters in patients with Ian, M1 was higher in those with high GCR expression. Patients with high proteinuria, low GFR, and high blood pressure at baseline and 6. Month had higher MEST scores. Larger studies are needed to evaluate the effect of GCR expression in the treatment or clinical course of IgAN.

Keywords: IgA nephropathy, Glucocorticoid receptor, MEST score, High blood pressure, Creatinine

INTRODUCTION

IgAN, Berger's disease (described in 1968), is the most common primary glomerulonephritis worldwide [1]. The disease is characterized by episodic hematuria accompanied by IgA deposition in the mesengium on immunofluorescence [2]. Unfavorable prognostic factors for future development of end stage renal disease include impaired renal function at the time of diagnosis [3].

The Oxford classification described 4 lesions with Mesangial proliferation (M0 or M1), absence or presence of any degree of endocapillary hypercellularity (E0 and E1), any glomerulosclerotic lesion (S0 or S1) and tubular atrophy/interstitial fibrosis severity of interstitial fibrosis (T0: 1-25%; T1: 26-50%; T2: >50%) [4,5]. VALIGA has also confirmed the association between renal outcomes with some lesions such as M1, S1, T1/2 and the association of M1 and E1 with subsequent increase in proteinuria [6]. Corticosteroids exert their actions by binding to the intracellula r Glucocorticoid Receptors (GCRs) to form the glucocorticoid-GCR complexes [7]. Previous studies have shown that GCR expression is correlated with the extent of steroid response in several diseases [8,9]. However, few studies have reported on this

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association in patients with IgAN. In this study, we evaluate the glomerular GCR expression, MEST score and clinical progression in patients with IgAN evaluated.

MATERIALS AND METHODS

This study included 103 patients with pathological diagnosis of IgA nephropathy who were also followed up in our nephrology outpatient clinic. Between 2002 and 2019, 200 patients with IgAN were identified from our hospital records. Patients who were followed for less than 3 months or who did not regularly follow-up, patients with recurrence IgAN in the transplant kidney, and patients whose consent could not be obtained for participation in the study were excluded from the study.

In the post-biopsy period, patients receiving Angiotensin Converting Enzyme Inhibitor/ Angiotensin Receptor Blocker (ACEI/ARB) for at least 3 months; according to the KDIGO guidelines, methylprednisolone 0.5-0.7 mg/kg/day, maximum 64 mg/day was given in patients with eGFR>30 ml/min and proteinuria >1 g/day. The steroid dose was reduced according to clinical response and administered as 4 mg/day maintenance. At the beginning of the treatment and at the 3^{rd}, 6^{th}, 12^{th} months; complete blood count, BUN, creatinine, eGFR, albumin, PTH, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, proteinuria values were recorded. The MEST score was calculated by the nephropathologist in kidney biopsy samples of patients diagnosed with IgAN. Kidney biopsy samples were immunohistochemically stained according to the recommendations of the GCR expression commercial kit (rabbit polyclonal antibody anti-glucocorticoid receptor antibody-ChIP Grade ab 3671).

The rate of staining of the glomeruli in the samples, the rate of staining in the glomeruli in which staining was detected and the intensity of staining were evaluated semi quantitatively. The 6^{th} and 12^{th} month progression indexes of the patients were calculated according to the international IgAN prediction tool.

This study approved by Cukurova university faculty of medicine "clinical research ethics committee" on 28 August 2019 (meeting no: 3) and Cukurova university "department of scientific research projects" on 19 November 2019 (Project number: TTU-2019-12465).

Statistical analysis

Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum where appropriate. *Chi-square* test was used to compare categorical variables between the groups. For comparison of continuous variables between two groups, the Student's t-test or Mann-Whitney U test was used depending on whether the statistical hypotheses were fulfilled or not. To evaluate the change in the measurements obtained in the time interval, the repeated measurements analysis was applied. All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

103 patients with IgA nephropathy were included in the study. The demographic characteristics and some biochemical parameters of the patients presented in Tables 1 and 2.

Parameters	**Mean ± SD**	**Parameters**	**Mean ± SD**
Male/female	58/45	Age (years)	40,79 ± 12
BMI	26.8 ± 4.3	Height (cm)	167,3 ± 8,2
Diastolic BP(mmHg)	85,5 ± 11.0	Systolic BP mmHg	135,67 ± 17,5
No smoking	73 (%70,9)	Mean BP (mmHg)	135,67 ± 17.5
Hemoglobin (g/dL)	12,8 ± 2,0	Sodium mEq/L	138,2 ± 2,8
RBC (10^6/ µL)	4,5 ± 0,7	Potassium (mEq/L)	4,4 ± 0,5
MCV (f/L)	83,0 ± 7,1	Magnesium (mg/dL)	1,9 ± 0,2
WBC (10^3/µL)	9,2 ± 3,2	ESR (mm/h)	31,2 ± 18,6
PLT (10^3/µL)	274,5 ± 91,5	PTH (pg/)	84,2 ± 72,3
RDW (%)	13,9 ± 2,0	TSH (mIU/L)	2,2 ± 1,9
CRP (mg/L)	2,7 ± 4,0	Total cholesterol(mg/dL)	215,1 ± 52,0
Glukoz (mg/dl)	99,3 ± 28,0	LDL cholesterol (mg/dL)	133,5 ± 43,0
Total protein (g/L)	6,4 ± 0,8	HDL cholesterol (mg/dL)	42,7 ± 13,5
Calcium (mg/dL)	9,0 ± 0,5	Triglyceride (mg/dL)	197,8 ± 114,8
Phosphorus (mg/dL)	3,9 ± 1,0	25-OH-vitamin D (IU)	14,8 ± 8,3
AST (IU/L)	19,8 ± 8,4	Ferritin (mg/dL)	92,0 ± 1156,6
ALT (IU/L)	21,3 ± 12,5		

Table 1. Demographic characteristics and some laboratory parameters of patients at baseline.

Parameters	Baseline	3 month	6 month	12 month
BUN (mg/dl)	26,32 ± 19,0	29,7 ± 21,4	31,5 ± 28,8	25,7 ± 16,8
Creatinine (mg/dL)	1,7 ± 1,3	1,8 ± 1,6	1,9 ± 2,0	1,7 ± 1,5
Uric acid (mg/dL)	6,7 ± 1,8	6,9 ± 2,0	6,8 ± 2,1	6,5 ± 1,8
Albumin (g/dL)	3,4 ± 0,5	3,6 ± 0,5	3,7 ± 0,5	4,3 ± 3,5
GFR(ml/min/1,73 m²)	64,0 ± 37,3	64,8 ± 38,9	66,7 ± 40,1	69,2 ± 39,9
Proteinuria (mg/day)	3526,73 ± 2801,4	2006,84 ± 2252,1	1421,37 ± 1356,7	1177,75 ± 1261,4
Progression risk score			14,07 ± 20,7 Min-max 0,22/93,0	46,681 ± 32,966 Min-max 2/100

Table 2. Laboratory parameters at baseline, 3 Month, 6 Month and 12 month.

The comparisons glucucorticoid receptor staining intensity with MEST score summarised in Table 3. Statistically significant difference was found only M0 and M1 for GCR staining intensity.

GCR staining rate					
MEST Score		<30 n (%)	50-60 n (%)	>80 n (%)	p value
M	0	4 (57,1)	3 (42,9)	0 (0)	0,025
	1	21 (28,8)	21 (28,8)	31 (42,5)	
E	0	16 (30,2)	17 (32,1)	20 (37,7)	0,851
	1	9 (33,3)	7 (25,9)	11 (40,7)	
S	0	8 (38,1)	4 (19)	9(42,9)	0,430
	1	17 (28,8)	20 (33,9)	22 (37,3)	
T	0	19 (30,2)	21 (33,3)	23 (36,5)	0,575
	1	6 (37,5)	3 (18,8)	7 (43,8)	
	2	0 (0)	0 (0)	1 (100)	
MEST total	0	3 (75)	1 (25)	0 (0)	0,191
	1	5 (26,3)	5 (26,3)	9 (47,4)	
	2	8 (33,3)	9 (37,5)	7 (29,2)	
	3	4 (17,4)	8 (34,8)	11 (47,8)	
	4	5 (55,6)	1 (11,1)	3 (33,3)	
	5	0 (0)	0 (0)	1 (100)	

Table 3. Comparison of Glucocorticoid Receptor (GCR) staining rate and MEST score.

As seen in Table 3, while there were statistical difference in BUN, albumin, uric acid, values, over time, for GCR staining intensity statistically significant difference were found for serum albumin and uric acid over time (Table 4).

	GCR<30	GCR 50-60	GCR >80	P time	p time G
BUN (mg/dl) 0	23,642 ± 17,58	26,19 ± 16,52	22,29 ± 16,64	0,024	0,747
3	32,42 ± 26,86	27,85 ± 18,57	26,26 ± 17,26		
6	28,78 ± 27,78	30,52 ± 25,11	30,01 ± 26,64		
12	24,05 ± 16,94	26,43 ± 15,55	24,04 ± 15,45		
Creatinine (mg/dl) 0	1,751 ± 1,563	1,555 ± 0,664	1,446 ± 1,402	0,372	0,980
3	1,944 ± 2,054	1,812 ± 1,692	1,496 ± 1,347		
6	2,106 ± 2,447	1,900 ± 2,021	1,531 ± 1,352		
12	2,088 ± 2,162	1,798 ± 1,519	1,548 ± 1,492		
Uric acid (mg/dl) 0	6,322 ± 1,497	7,070 ± 1,616	6,300 ± 1,955	0,024	0,055
3	6,330 ± 1,576	7,091 ± 1,666	7,003 ± 2,467		
6	6,359 ± 1,689	7,704 ± 2,136	6,820 ± 2,392		
12	5,537 ± 1,244	6,991 ± 1,758	6,820 ± 2,391		

Albumin (g/dl) 0	3,741 ±0,437	3,465 ± 0,463	3,303 ± 0,673	0,000	0,009
3	3,655 ± 0,547	3,621 ± 0,451	3,646 ± 0,570		
6	3,774 ± 0,477	3,670 ± 0,588	3,733 ± 0,439		
12	3,943 ± 0,544	4,046 ± 0,530	4,041 ± 0,389		
GFR (ml/min/1,73 m²) 0	71,71 ± 41,99	60,17 ± 34,40	76,77 ± 39,96	0,321	0,957
3	69,51 ± 44,55	63,16 ± 36,09	75,10 ± 41,10		
6	74,27 ± 43,65	65,91 ± 38,23	76,89 ± 43,47		
12	73,94 ± 45,66	67,61 ± 39,81	78,76 ± 42,73		
Proteinuria (mg/day) 0	3092 ± 1644	3182 ± 1937	4456 ± 3899	<0,001	0,301
3	1877 ± 2083	1709 ± 1367	2473 ± 3366		
6	1347 ± 1198	1193 ± 1062	1306 ± 1395		
12	1087 ± 11087	1170 ± 1681	1304 ± 1290		

Table 4. Correlation between changes in BUN, creatinine, uric acid, albumin, Glomerular Filtration Rate (GFR), proteinuria values over time and Glucocorticoid Receptor Staining (GCR)

Patients with M0 or M1 lesion were similar for GFR, BP and proteinuria at baseline, 3, 6, 12 Month (Table 5).

The patients classified into 2 groups according to the presence of endocapillary proliferation (E0 and E1) in the glomeruli and tubular injury (T0, T1 and T2). The GFR and daily proteinuria of the patients at 3 months, 6 months with endocapillary proliferation were found to be statistically significant lower and higher than the patients without endocapillary proliferation respectively. Also systolic blood pressure has been found to be statistically significantly higher in patients with endocapillary proliferation. Diastolic blood pressure was nonsignificantly higher in patients with endocapillary proliferation (Table 6).

	M0	**M1**	**p**
GFR 0.	62,49 ± 30,68	65,53 ± 38,59	0,867
GFR 3.month	55,44 ± 30,26	66,48 ± 39,24	0,476
GFR 6. Month	62,59 ± 37,70	67,69 ± 40,37	0,666
GFR 12. month	63,87 ± 37,87	68,64 ± 40,84	0,706
Proteinuria 0. month	2914 ± 1840	3694 ± 2964	0,528
Proteinuria 3.month	1395 ± 854,6	2094 ± 2329	0,688
Proteinuria 6. month	1383 ± 1163	1455 ± 1390	0,951
Proteinuria 12.month	867,1 ± 757,1	1268 ± 1333	0,532
Systolic BP	140,5 ± 19,43	135,7 ± 17,52	0,438
Diastolic BP	87,78 ± 8,333	85,43 ± 10,60	0,522

Table 5. The relationship glomerular meningeal proliferation Glomerular Filtration Rate (GFR) (ml/dk/1,73 m²), proteinuria (mg/day) and Blood Pressure (BP) (mmHg).

	E0	**E1**	**P**	**T0**	**T1**	**P**
GFR 0	71,38 ± 37,43	58,40 ± 38,54	0,116	72,72 ± 37,43	46,34 ± 3392	0,005
GFR 3	73,35 ± 38,02	54,83 ± 39,47	0,031	73,10 ± 38,23	45,98 ± 36,42	0,005
GFR 6	75,97 ± 39,12	56,13 ± 41,23	0,025	75,76 ± 40,15	46,46 ± 34,95	0,003
GFR 12	75,44 ± 39,32	59,49 ± 42,73	0,085	73,66 ± 40,21	56,61 ± 42,10	0,109
Proteinuria 0	3336 ± 2981	3986 ± 2273	0,016	3245 ± 2589	4674 ± 3095	0,040
Proteinuria 3	1654 ± 1648	2907 ± 3202	0,028	1863 ± 2314	2857 ± 2452	0,032
Proteinuria 6	1183 ± 1043	2032 ± 1699	0,024	1363 ± 1242	1868 ± 1681	0,228
Proteinuria 12	1113 ± 1215	1451 ± 1416	0,520	1126 ± 1232	1602 ± 1456	0,272
SBP mmHg	132,7 ± 16,26	139,9 ± 18,11	0,050	134,1 ± 17,44	139,2 ± 16,06	0,230
DBP mmHg	83,77 ± 10,15	86,97 ± 1015	0,148	84,66 ± 10,25	85,71 ± 10,28	0,678

Table 6. Comparison of endocapillary proliferation the glomeruli and tubular injury in with GFR, proteinuria, and Blood Pressure (BP).

Patients were classified into 3 groups according to the rate of tubular lesion. GFR was found to be lower as the degree of tubular atrophy increased statistically at 0, 3, and 6 months, but it was not statistically significant at 12 months. When proteinuria and tubular atrophy were compared, a statistically significant difference was found at month 0 and 3. No statistically significant difference was found between the degree of tubular atrophy and blood pressure.

Demographic data, laboratory and biopsy results of the patients at the time of diagnosis compared between groups of patients who achieved remission at 12 months and those who did not (Table 7). In the remission group, which formed by the sum of the partial remission (proteinuria 300 mg/day-3,5 g/day) and the complete remission group (proteinuria <300 mg/day), 80 people who achieved remission in the 12th month and 4 people who did not achieved remission determined. No significant difference observed between the two groups in terms of age, MEST score and GCR staining. When examined in terms of GFR, proteinuria, systolic blood pressure, and diastolic blood pressure, there was a statistically significant difference between the groups in remission and those who did not.

Parameter	**Remission**	**Non-remission**	**P value**
M0	8 (100)	0 (0)	1
M1	73 (93,6)	5 (6,4)	
E0	54 (96,4)	2 (3,6)	0,337
E1	27 (90)	3 (10)	
S0	24 (100)	0 (0,0)	0,316
S1	57 (91,9)	5 (8,1)	
T0	65 (97)	2 (3)	0,139
T1	15 (83,3)	3 (16,7)	
T2	1 (100)	0 (0,0)	
Age (years)	41,2 ± 12,36	42,2 ± 12,59	0,914
GFR 0	67,20 ± 37,53	34,51 ± 27,04	0,075
GFR 3	67,75 ± 38,95	29,72 ± 23,62	0,028
GFR 6	71,25 ± 39,30	24,12 ± 24,67	0,007
GFR 12	73,39 ± 39,03	14,54 ± 8,072	0,001
Proteinuria 0	3270 ± 2587	6492 ± 2638	0,008
Proteinuria 3	1718 ± 1909	7130 ± 3109	0,017
Proteinuria 6	1237 ± 1108	3353 ± 1286	0,000
Proteinuria 12	961 ± 800	5052 ± 1795	0,007
Systolic BP	134,1 ± 16,71	164,8 ± 5,02	0,001
Diastolic BP	85 ± 11,11	96,00 ± 5,477	0,016
GCR<30	25 (92,6)	2 (7,4)	0,899
GCR 50-60	22 (95,7)	1 (4,3)	
GCR>80	27 (93,1)	2 (6,9)	
0: Baseline; 3: 3 Months; 6: 6 months; 12: 12 months; GFR: Glomerular Filtration Rate ml/min/1,73 m²; Proteinuria: mg/day; BP: Blood Pressure mmHg			

Table 7. Comparison of the demographic data of the patients at the time of diagnosis, laboratory and biopsy results between the patient groups in remission and non-remission at 12 months.

At the time of diagnosis although demographic characteristics, comorbidities, MEST scores and GCR expression were similar, serum total protein (↑), uric acid (↑), PTH (↑), WBC and neutrophyl count (↑), systolic and diastolic blood pressure (↑), GFR (↓) were found significantly different in patients with those with proteinuria ≥1 g/day at 12 months comparing to patient with proteinuria <1 g/day at 12 months ($p<0,05$ for all). Also in patients with those with GFR < 60 mL/min/1,73 m² at 12 months comparing to patient with GFR ≥ 60 mL/min/1,73 m² 12 months at the time of diagnosis although gender, MEST score, GCR expression, levels of trygliseride, HDL and LDL were similar but PTH, total cholestrol (↑), GFR (↓), creatinine (↑), BUN (↑), systolic and diastolic BP (↑) were found significantly different ($p<0,05$ for all).

DISCUSSION

Corticosteroids exert their effects by binding to intracellular Glucocorticoid Receptors (GCRs) to form glucocorticoid-GCR complexes [10]. Previous studies have shown that GCR expression correlates with steroid response in a variety of diseases [11]. However, few studies have been reported on this relationship in the literature. In this study, we evaluated whether the response to steroids in IgAN patients is dependent on GCR expression.

No significant results were obtained in the comparison of demographic and laboratory data according to the GCR staining rate. In comparison of GCR with MEST score, the rate of GCR staining was found to be higher in patients with Mesangial proliferation (M1) than in those without (M0). Although there was a statistically significant difference in BUN, proteinuria over

time but no significant difference has shown between the groups comparing to the rate of GCR staining there was a statistically significant difference in uric acid, albumin over time and according to the GCR staining rate. In a study GCR mRNA expression measured by RT-PCR was compared with steroid response and it was found that GCR mRNA expression was 2.5 fold higher in the group with complete remission compared to the group without complete remission. This finding was confirmed by immunohistochemical studies, which showed that the complete remission group had more cells with positive staining for GCRs. Mean semi-quantitative scores for glomerular GCR were significantly higher in the CR group compared to the non-CR group [12]. In our study, patients with a GCR staining rate >80% had a higher rate of remission, but no statistically significant difference determined. We can explain this situation with the small number of patients.

In our study, eGFR and proteinuria have been shown to be higher in M1 patients with meningeal proliferation according to the Oxford MEST classification than in M0 patients without meningeal proliferation, but no statistically significant difference was found for both. Interestingly, the eGFR level at 3, 6 month has been shown to be statistically significantly higher in patients without endocapillary proliferation (E0) than in patients with endocapillary proliferation (E1). In patients with E1; systolic blood pressure and proteinuria have been shown to be statistically significantly higher. Diastolic blood pressure has also been shown to be higher in patients with E1, but it was not statistically significant. In patients with segmental sclerosis (S1), eGFR values at 3^{th} month and 6^{th} month were lower and proteinuria at 0,3,6 month was found to be higher than those without segmental sclerosis, which were statistically significant. Systolic and diastolic blood pressures were found to be nonsignificantly higher in S1 patients compared to S0 patients. In patients with T0 compared to patients with T1 eGFR values at 0. 3, 6 month were found to be higher and proteinuria at 0. 3 month statisticaly significantly lower and these differences were statistically significant.

Pathological findings are accepted as an important factor for the prognosis of IgAN. According to the Oxford classification, M, E, S, T and C lesions are partially associated with prognosis. Barbour reported that M/T lesions were independently associated with renal outcome. The results of Bellur, et al. support the Oxford classification S-score in non-immunosuppressed patients. Coppo R analyzed 1147 IgAN patients in the VALIGA cohort and suggested that M/S/T independently predicted renal outcome (50% reduction in renal function and/or ESRD) [13,14]. However, in a subgroup of 219 patients with minimal proteinuria, no MEST score predicted renal outcome in multivariate analysis, these findings were similar to our results. Another review conducted by Coppo R failed to confirm a predictive value of MEST scores in a subgroup of 174 children (<18 years) in the VALIGA cohort. These results showed that the evaluation of the Oxford classification should be stratified. In a study by Shu et al., the pathological indicator M1 lesion was found to be an independent factor in predicting ESRD [15]. In our study, the initial pathological values of the patients and the eGFR values at 12 months were compared. Those with S1 lesions in the biopsy at the time of diagnosis were more patients with eGFR <60 Found to be higher in patients with E1 than those with E0, but it was not statistically significant.

Interestingly at the time of diagnosis although demographic characteristics, comorbidities, MEST scores and GCR expession mL/min/1.73 m^2 at 12 months compared to those with eGFR ≥60 mL/min/1.73 m^2 but it was not statistically significant. Again, the number of patients with T_1 on biopsy was higher in patients with eGFR <60 mL/min/1.73 m^2 compared to those with eGFR ≥60 mL/min/1.73 m^2, and it was not significant.

In this retrospective analysis, the patients were evaluated as remission and non-remission groups. In the KDIGO guideline, the criteria for remission in IgA nephropathy have not been clearly defined [16]. It is observed that many different remission criteria have been determined in the literature studies. In a clinical trial; Having 0.3 g/day proteinuria is similar to 0.3 to 1.0 g/day, but for each gram above 1 g/day (reference group) ESRD has worse renal survival, 1 to 2 g/day found a 3.5 fold risk for a day, 5-fold a risk for 2 to 3 g/day, and a 10-fold risk for ESRD above 3 g/day [17]. In our study our criteria for complete remission was proteinuria <0.3 g/day, as studies have shown that the optimal goal in treatment is to keep proteinuria below 0.3 g/day. We determined partial remission between 0.3 g/day and 3.5 g/day. Since the loss of kidney function was approximately 25 times higher in patients with proteinuria >3.5 g/day compared to patients with proteinuria <1 g/day in studies, we determined the criterion for non-remission as proteinuria >3.5 g/day. Eighty five (78.7%) patients at 3 months, 80 (74.1%) at 6 months, and 75 (74.3%) patients at 12 months were considered in partial remission. Patients in complete remission were 77 (6.5%) at the 3^{rd} month, 17 (15.7%) at the 6^{th} month, and 20 (19.8%) at the 12^{th} month. There were 6 (5.9%) patients who did not go into remission at the end of the 12^{th} month. In another study protienuria >1 g/day in IgA nephropathy has been associated with a rapid decline in eGFR and progression to ESRD [18].

Confirmed prognostic markers for IgA nephropathy include eGFR and proteinuria. Low eGFR at diagnosis or at follow-up is an indicator of poor prognosis. In a large scale cohort study of 1155 patients with IgA nephropathy in China, eGFR <60 ml/min/1.73 m^2 at the time of diagnosis 50% reduction in eGFR or ESRD. Also in our study it has been shown to be an independent risk factor for progression. It was found to be statistically significant higher than those with 60 mL/min/1.73 m^2, consistent with another study. Another independent risk factor in patients with IgA nephropathy is proteinuria. Proteinuria >1 g/day was found to be associated with rapid decline in kidney functions and progression to ESRD. In this study, we also identified 57 (60%) patients with proteinuria <1 g/day at the end of the 12^{th} month. those in remission; we considered it as the sum of patients with complete remission and partial remission. Consistent with the literature, we found that proteinuria was lower in patients with remission, both at the time of diagnosis and at 3 month follow-up [19].

Another parameter of the prognostic factor in IgA nephropathy is the levels of blood pressure at the time of diagnosis and follow-up period. High blood pressure; it is associated with increased protein excretion and a faster eGFR decline. In our study, systolic and diastolic blood pressure was found to be statistically significant lower in the remission group comparing to non-remission group [20]. Also systolic blood pressure in patients with endocapillary proliferation (E1) in the glomeruli was significantly higher than in patients with E0. We did not found similar finding earlier study. Diastolic blood pressure was also were similar, significantly higher levels of serum total protein, uric acid, parathormon, systolic and diastolic blood pressure and increased white blood cell and neutrophil count, and lower GFR were in patients with those with proteinuria ≥ 1 g/day at 12

month comparing to patient with proteinuria <1 g/day at 12 Month. Similarly significantly higher levels of PTH, total cholestrol, creatinine, BUN, systolic and diastolic BP were in patients with GFR<60 mL/min/1,73 m² at 12. Month comparing to patient with GFR ≥ 60 mL/min/1,73 m² 12 Month. Similarly our finding in a study conducted in China, it was found that hypercholesterolemia played a role in 50% reduction in eGFR and progression to ESRD in univariate analyses, but lost its significance in multivariate analyses. In the univariate survival analysis of 1151 patients with IgA nephropathy in China, it was found that the count of white blood cell and neutrpohil showed significant associations with IgAN progression.

CONCLUSION

In conclusion, although no correlation was found between the rate of GCR expression showing glucocorticoid receptor activation and steroid response, and progression in patients with IgA nephritis, M1 was higher in those with high GCR staining. However, patients with high proteinuria, low GFR, and high blood pressure at baseline and 6 month, had higher MEST scores for E, S, and T. Larger studies are needed to evaluate the effect of GCR expression in the treatment or clinical course of IgA nephropathy.

REFERENCES

1. Berger J, Hinglais N (1968). Intercapillary deposits of IgA-IgG. J Urol Nephrol. 74:694
2. D'Amico G (2000). Natural history of idiopathic IgA nephropathy: role of clinical and histological prognostic factors. Am J Kidney Dis. 36(2): 227-237.
3. Cattran DC, Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS (2009). Working Group of the International IgA Nephropathy Network and the Renal Pathology Society; The Oxford classification of IgA nephropathy: Rationale, clinicopathological correlations, and classification. Kidney Int. 76(5):534-545.
4. Roberts IS, Roberts IS, Cook HT, Troyanov S, Alpers CE, Amore A (2009). The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney Int. 76(5):546-556.
5. Coppo R, Troyanov S, Bellur S, Cattran D, Cook HT, Feehally J (2014). Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. Kidney Int. 86(4):828-836.
6. Bamberger CM, Schulte HM, Chrousos GP (1996). Molecular determinants of glucocorticoid receptor function and tissue sensitivity to glucocorticoids, Endocr Rev. 17(3):245-261.
7. Schlaghecke R, Kornely E, Wollenhaupt J, Specker C (1992). Glucocorticoid receptors in rheumatoid arthritis. Arthritis Rheum. 35(7):740-744.
8. Han SH, Park SY, Li JJ, Kwak SJ, Jung DS, Choi HY (2008). Glomerular glucocorticoid receptor expression is reduced in late responders to steroids in adult-onset minimal change disease. Nephrol Dial Transplant. 23(1):169-175.
9. Kee YK, Nam BY, Jhee JH, Park JT, Lim BJ, Yoo TH, et al. (2019). The association of glomerular glucocorticoid receptor expression with responsiveness to corticosteroid treatment in IgA nephropathy. Am J Nephrol 50(3):187-195.
10. Boyd JK, Cheung CK, Molyneux K, Feehally J, Barratt J (2012). An update on the pathogenesis and treatment of IgA nephropathy. Kidney Int. 81(9):833-843.
11. Bellur SS, Lepeytre F, Vorobyeva O, Troyanov S, Cook HT, Roberts IS (2017). Evidence from the Oxford Classification cohort supports the clinical value of subclassification of focal segmental glomerulosclerosis in IgA nephropathy. Kidney Int. 91:235-243.
12. Shu D, Xu F, Su Z, Zhang J, Chen C, Zhang J (2017). Risk factors of progressive IgA nephropathy which progress to end stage renal disease within ten years: A case control study. BMC Nephrol. 18(1):1-6.
13. Cattran DC, Feehally J, Cook HT, Liu ZH, Fervenza FC, Mezzano SA (2012). KDIGO clinical practice guideline for glomerulonephritis. Kidney Int Suppl. 2:139-274.
14. Reich HN, Troyanov S, Scholey JW, Cattran DC (2007). Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol. 18(12):3177-3183.
15. Berthoux F, Mohey H, Laurent B, Mariat C, Afiani A, Thibaudin L (2011). Predicting the risk for dialysis or death in IgA nephropathy. J Am Soc Nephrol. 22(4):752-761.
16. de Boer IH, Caramori ML, Chan JC, Heerspink HJ, Hurst C, Khunti K (2020). KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 98(4):1-115.
17. Le W, Liang S, Hu Y (2012). Long term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population. Nephrol Dial Transplant. 27(4):1479-1485.
18. Li Q, Chen P, Shi S, Liu L, Lv J, Zhu L (2020). Neutrophil-to-lymphocyte ratio as an independent inflammatory indicator of poor prognosis in IgA nephropathy. Int Immunopharmacol. 87:106-181.
19. Schena FP, Pesce F (2009). Chapter 2: Epidemiology and ancestral diMerence. In: Kar Neng Lai editor(s). Recent advances in IgA nephropathy. Singapore: World Scientific. 9-19.
20. Bamberger CM, Schulte HM, Chrousos GP (1996). Molecular determinants of glucocorticoid receptor function and tissue sensitivity to glucocorticoids. Endocr Rev. 17(3):245-61.