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RESEARCH ARTICLE

Effect of Proteinuria Degree (Below and Above 1g/day) on Survival in Patients with IgA Nephropathy

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Abstract

Immunglobulin A nefropathy is the most widely encountered primary glomerular disease in the world and ıs one of the maın causes of ESRD. Aim of our study is to identify the effect of proteinurıa level to survey during their diagnosis in the patients who are diagnosed as Ig A nefropathy by renal biopsy.

Fifty two patients, who were diagnosed by renal biopsy and followed in our nefrology clinic between 2002 and 2010 were included in our study.Patients first 1 st,3 rd ,6 th ,12 th ,24 th month and last arterial blood pressure ,urea ,creatinin ,glomerul filtration rate (by short MDRD formula) proteinurıa level for 24 hours and the treatment patients got during their following were all recorded. Patients were divided in two groups those whose proteinurıa was lower and higher than 1 gr/day. While findings from the study were being evaluated NCSS 2007 & PASS 2008 Statistical software programme was used for the statistical analyses.

Starting creatinin level was 1,02±0,32 mg/dl and last creatinin level was 0,90±0,15 mg/dl for those whose proteinürıa level is <1 gr/day. Starting creatinin level was 1,34±0,96 mg/dl and last creatinin level was 1,33±0,82mg/dl ($p<0.05$) for those whose proteinürıa level is > 1gr/day. Starting GFR was 83,58 ±27,17 ml/min and last GFR was 89,35±19,06 ml/min (p=0,80) for cases whose proteinürea level is <1gr/day. Starting GFR was 77,43 ± 30,97 ml/min and last GFR was 71,60±28,30 ml/min (p=0,008) for cases whose proteinürıa level is > 1 gr/day. Starting proteinürıa level was 0,34 ± 0,2 gr/day, last proteinurıa level was 0,28 ± 0,25 gr/day (p=0.06) for cases whose proteinurıa level < 1gr /day. Starting proteinurıa level was found as 2,20 +-1,41 gr/day and last proteinuria level was found as 1,05 ± 1,56 gr/day (p=0,02) for cases whose proteinurıa level > 1gr. Durıng their followıng cases whose proteınurıa < 1gr/day didn't need dialiysis and 3 cases whose proteinurıa level is > 1 gr/day needed dialysis programme.

1st,3rd,6 th,12th,24th, month and last creatinin level of cases whose starting poteinurıa level is 1 gr and above is found to be statıstıcally significantly higher than those cases whose proteinurıa level is under 1gr, Complete remission rate is high in those whose proteinurıa level is under 1 gr. Result of our study have shown that there is a significant relationship between the level (higher and below 1 gr/day) of proteinurıa and survey in Ig A nefropathy.

1. Introductıon

Immunoglobulin A nephropathy (IgAN) is defined as the most common primary glomerular disease worldwide (1). It is among the leading causes of end-stage renal disease (ESRD) (2, 3). The definitive diagnosis of immunoglobulin A nephropathy is

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made histopathologically; it is characterized by widespread IgA deposition in the mesangium, accompanied by varying degrees of focal or diffuse mesangial proliferation. In addition to IgA, other immunoglobulins such as IgG, IgM, C3, and terminal complement components may also accumulate in the mesangium with less frequency and intensity (4).

Although no definitive etiological agent has been identified to date, the association of typical macroscopic attacks of the disease with upper respiratory tract infections has drawn attention to potential microbiological agents. Some food antigens have also been suggested as possible etiological factors. However, none of these antigens have been demonstrated in the deposits accumulated in the glomeruli (5). Clinically, IgA nephropathy is commonly known for presenting with macroscopic hematuria following upper respiratory tract infections (synpharyngitic hematuria), but in reality, it has a broad clinical spectrum, and no clinical finding is pathognomonic. In addition to geographical and genetic variations in prevalence, differing regional approaches to urinary abnormalities and renal biopsy also contribute to variability in diagnosis frequency, as asymptomatic urinary abnormalities are quite common. IgA nephropathy, initially referred to as "benign recurrent hematuria," is now recognized as not so benign, as it can progress over time and is considered a major cause of end-stage renal disease (ESRD) (6).

In studies on IgA nephropathy, serum creatinine levels at diagnosis, arterial blood pressure, and proteinuria have been found to be independent significant risk factors in many studies (7-10). Particularly, patients with nephrotic-range proteinuria at onset have been reported to have shorter renal survival (2). While outcomes vary in patients with daily protein excretion below 1 gram, proteinuria greater than 1 g/day is considered a risk factor for disease progression (11).

This study aims to compare clinical course and survival in patients based on proteinuria levels at the time of diagnosis (proteinuria ≥1 g/day vs. <1 g/day).

2. Materıals And Methods

This study was conducted at the Nephrology Clinic of S.B. Göztepe Training and Research Hospital. A total of 52 patient files diagnosed with IgA nephropathy through renal biopsy between 2002 and 2010 were retrospectively reviewed. Patients aged over 18 years and followed for at least 6 months were included in the study.

The following data were recorded from patient outpatient files: histopathological features of renal biopsies (glomerular sclerosis, interstitial fibrosis, tubular atrophy, presence of crescents), age at pathological diagnosis, systolic blood pressure (SBP), diastolic blood pressure (DBP), hemoglobin, creatinine clearance, serum creatinine, total cholesterol, triglycerides, albumin levels, IgA level, presence of proteinuria and hematuria, 24-hour urine protein levels, and hepatic viral serologies.

During follow-up at 6–12 month intervals and within the last 6 months prior to the end of the study, the following parameters were again recorded from patient files: blood pressure, hemoglobin, creatinine clearance, serum creatinine, total cholesterol, triglycerides, albumin levels, presence of proteinuria and hematuria, and 24-hour urine protein levels. Blood pressure measurements ≥130/80 mmHg were accepted as hypertension. An initial serum creatinine level of ≥1.3 mg/dl was considered renal failure. Protein excretion of ≥3.5 g/day in 24-hour urine was considered nephrotic-range proteinuria.

Proteinuria was considered absent if both at diagnosis and in the last 3 follow-ups the median 24-hour urine protein value was ≤0.5 g/day. Complete remission was defined as an initial 24-hour urine protein value >0.5 g/day with a median of ≤0.5 g/day in the last 3 follow-ups. Partial remission was defined as a decrease to sub-nephrotic levels in those who initially had nephrotic-range proteinuria (>3.5 g/day), or a reduction of more than 50% in proteinuria in those without nephrotic-range levels. Lack of remission was defined as failure to meet either of these criteria.

Post-diagnosis treatments administered to patients (steroids, cyclophosphamide, azathioprine, angiotensin-converting enzyme inhibitors [ACE-I], angiotensin receptor blockers [ARB], calcium channel blockers [CCB], omega-3 fatty acids, statins, and antiplatelet agents) were also recorded from patient files.

The presence of any of the following three parameters was accepted as the study endpoint:

1. Serum creatinine ≥1.3 mg/dl
2. Development of ESRD
3. Doubling of initial creatinine levels and/or development of ESRD

Patients were divided into two groups based on their initial proteinuria levels: Proteinuria ≥1 g/day and Proteinuria <1 g/day. At the end of follow-up, the two groups were compared in terms of various parameters (serum creatinine, 24-hour urine protein, creatinine clearance, systolic and diastolic blood pressure, disease status, renal survival).

For statistical analysis, the NCSS (Number Cruncher Statistical System) 2007 & PASS 2008 Statistical Software (Utah, USA) was used. In addition to descriptive statistical methods (mean, standard deviation), the Student's t-test was used for intergroup comparisons of normally distributed quantitative variables, and the paired sample t-test for intragroup comparisons. The Chi-square test was used for comparing qualitative variables. A p-value of <0.05 was considered statistically significant.

3. Results

A total of 52 patients were included in the study, and the demographic characteristics of the included patients are presented in Table 1.

Table 1. *Distribution of Demographic Characteristics*

		Proteinuria		Total
		<1 gr	≥1 gr	
		Mean±SD (Median)	Mean±SD (Median)	Mean±SD (Median)
Age(years)		36,00±9,43	33,50±1083	34,65±1019
Duration of Follow-up		47,17±22,50 (42)	36,32±25,61 (27)	41,33±24,62 (36)
		n (%)	n (%)	n (%)
Gender	**Male**	17 (%70,8)	20 (%71,4)	37 (%71,1)
	Female	7 (%29,1)	8 (%28,5	15 (%28,8)

The presenting complaints of the patients are presented in Table 2.

Table 2. *Presenting Complaints*

Systemic Inquiry	Proteinuria		Total
	<1 gr	≥1 gr	
	n (%)	n (%)	n (%)
Infection in the Last 1 Month	0 (%0)	1 (%3,6)	1 (%1,9)
Joint Discomfort	0 (%0)	2 (%7,1)	2 (%3,8)
Fever	2 (%8,3)	1 (%3,6)	3 (%5,8)
Nausea-Vomiting	2 (%8,3)	5 (%17,9)	7 (%13,5)
Dispnea	1 (%4,2)	5 (%17,9)	6 (%11,5)
Urine Color Change	9 (%37,5)	13 (%46,4)	22 (%42,3)
Flank Pain	5 (%20,8)	2 (%7,1)	7 (%13,5)
Other	0 (%0)	1 (%3,6)	1 (%1,9)

The clinical status of the patients included in the study according to their baseline proteinuria levels is presented in Table 3.

Table 3. *Clinical Status of the Patients*

Clinical Presentation at Admission	Proteinuria		Total
	<1 gr	≥1 gr	
	n (%)	n (%)	n (%)
Edema	2 (%8,3)	8 (%28,6)	10 (%19,2)
Isolated Macroscopic Hematuria	4 (%16,7)	1 (%3,6)	5 (%9,6)
Hematuria + Proteinuria	6 (%25)	24 (%85,7)	30 (%57,7)
Isolated Microscopic Hematuria	13 (%54,2)	2 (%7,1)	15 (%28,8)
Hypertension	6 (%25)	12 (%42,9)	18 (%34,6)

The distribution of the histopathological features obtained from renal biopsy results of the patients included in the study according to their baseline proteinuria levels is presented in Table 4.

Table 4. *Distribution of Histopathological Features*

Pathology	Proteinuria		Total
	<1 gr	≥1 gr	
	n (%)	n (%)	n (%)
Focal Glomerulosclerosis	10 (%41,7)	11 (%39,3)	21 (%40,4)
Focal Proliferative Glomerulonephritis	13 (%54,2)	6 (%21,4)	19 (%36,5)

Diffuse Proliferative Glomerulonephritis	1 (%4,2)	9 (%23,1)	10 (%19,2)
Advanced Sclerosis	0 (%0)	2 (%7,1)	2 (%3,8)

When the systolic and diastolic blood pressures of patients were compared according to their baseline proteinuria levels, the group with proteinuria ≥1g/day had significantly higher systolic and diastolic blood pressures at baseline ($p<0.05$). When the systolic and diastolic blood pressures of both groups were compared at their last follow-up, no significant difference was observed between the groups ($p>0.05$) (Tables 5, 6).

Table 5. *Evaluation of Systolic Blood Pressure According to Proteinuria Levels*

SBP	**Proteinuria**		***P***
	< 1 gr	**≥ 1 gr**	
	Mean±SD	**Mean±SD**	
Baseline	119,58±17,56	134,82±31,19	***0,039****
Final Follow-up	115,0±12,85	122,86±22,08	***0,132***
⁺ Baseline – Final Follow-up	***0,178***	***0,676***	

*⁺Paired Samples t test *p<0,05*

Table 6. *Evaluation of Diastolic Blood Pressure According to Proteinuria Levels*

DBP	**Proteinuria**		***P***
	< 1 gr	**≥ 1 gr**	
	Mean±SD	**Mean±SD**	
Baseline	75,63±8,76	84,29±15,01	***0,013****
Final Follow-up	74,79±6,83	76,43±11,93	***0,540***
⁺ Baseline – Final Follow-up	***0,021****	***0,008****	

*⁺Paired Samples t test *p<0,05 **p<0,01*

When the patients' 24-hour urinary protein levels (below and above 1 gram) were compared in terms of creatinine levels, both groups were found to be similar at baseline ($p>0.05$). However, at the last follow-up, creatinine levels were significantly higher in the group with proteinuria ≥1g/day ($p<0.05$) (Table 7, Figure 5).

Table 7. *Evaluation of Creatinine According to Proteinuria Levels*

Creatinine	**Proteinuria**		***P***
	< 1 gr	**≥ 1 gr**	
	Mean±SD	**Mean±SD**	
Baseline	1,02±0,32	1,34±0,96	***0,110***
Final Follow-up	0,90±0,15	1,33±0,82	***0,032****

**p<0,05*

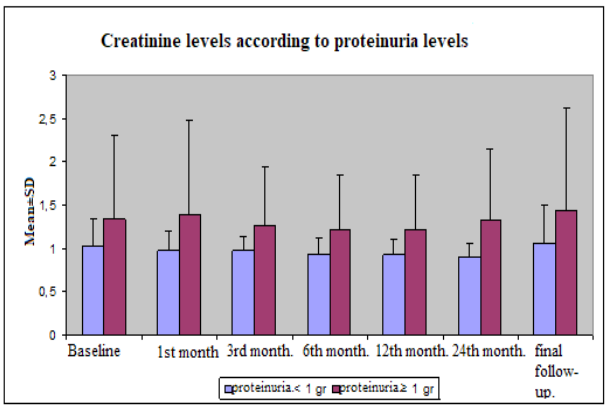

Figure 5. *Creatinine levels according to proteinuria levels*

When comparing the creatinine clearance values calculated using the MDRD formula for both groups, the clearance values were similar at baseline (p>0.05), while at the last follow-up, the creatinine clearance was significantly lower in the group with proteinuria ≥1g/day (p<0.05) (Table 8, Figure 6).

Table 8. *Evaluation of Clearance According to Proteinuria Levels*

MDRD	Proteinuria		*P*
	< 1 gr	≥ 1 gr	
	Mean±SD	Mean±SD	
Baseline	83,58±27,17	77,43±30,97	***0,453***
Final Follow-up	89,35±19,06	71,60±28,30	***0,019****

*Student t test was used *p<0,05*

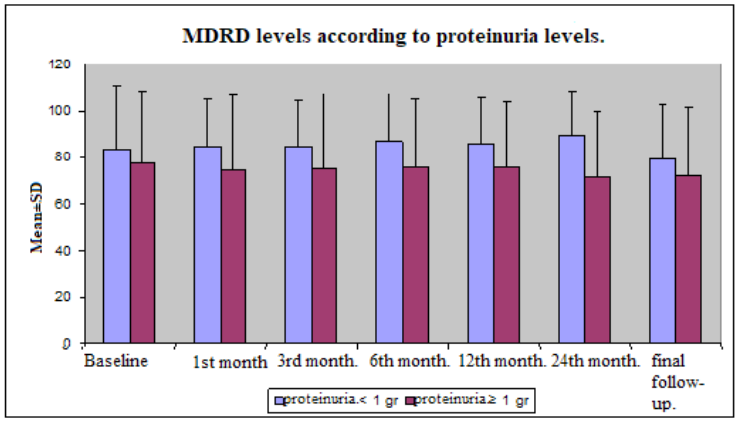

Figure 6. *Creatinine clearance levels according to proteinuria levels.*

When comparing the proteinuria progression between the two groups, the proteinuria level was significantly higher in the group with proteinuria ≥1g/day at both baseline and the last follow-up measurements (p<0.05) (Table 9, Figure 7).

Table 9. *Evaluation of Total Proteinuria According to Proteinuria Levels*

Total Proteinuria (mg/24 hours)	Proteinuria		*P*
	< 1 gr	≥ 1 gr	
	Mean±SD	Mean±SD	
Baseline	0,34±0,27	2,20±1,41	***0,001****
Final Follow-up	0,28±0,25	1,05±1,56	***0,049****

**p<0,05 **p<0,01*

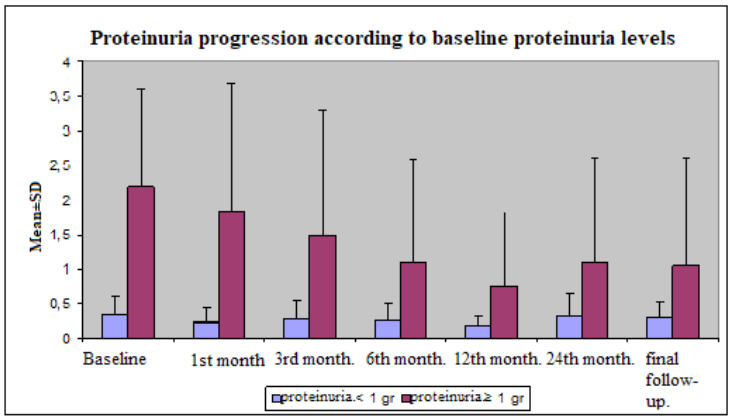

Figure 7. *Proteinuria progression according to baseline proteinuria levels*

When comparing the disease outcomes between the two groups, the remission rates were significantly higher in the group with proteinuria <1g/day (p<0.01) (Figure 8).

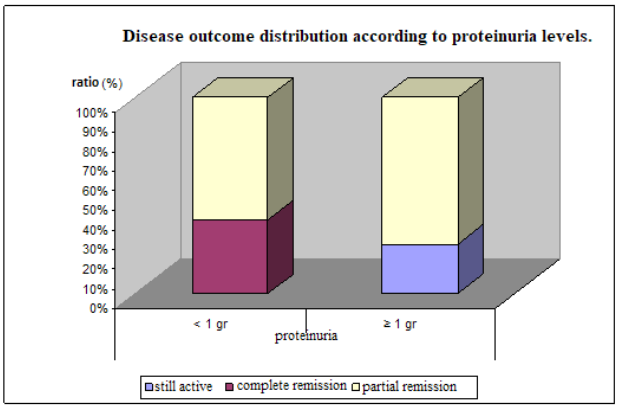

Figure 8. *Disease outcome distribution according to proteinuria levels.*

4. Discussion

The mean age of the patients was 34.65 ± 10.19 years. In previous studies, the reported mean age has ranged between 22 and 40 years, most commonly between 25 and 30 years (12). The male-to-female ratio was 37/15, indicating a higher proportion of female patients compared to the 3:1 ratio commonly reported in the literature (6).

Histopathological findings provide valuable insights into prognosis. Widespread global and/or segmental glomerulosclerosis, prominent tubulointerstitial lesions, high glomerular and/or tubular scores in the Lee and/or Haas classifications, and being in a high-grade damage stage are all considered strong indicators of poor prognosis (11-14).

Interstitial fibrosis was found in the pathological specimens of 21% of patients, which is consistent with other reports (20–30%) (15). Crescent formation was observed in 9 patients (17%), which is higher than the >5% rate reported in some literature (9). Widespread global and/or segmental glomerulosclerosis was identified in 20 patients (38%), consistent with published data (15). Glomerulosclerosis, interstitial fibrosis, and crescent formation—associated with poor prognosis—were more frequently observed in patients with proteinuria ≥1 g/day compared to those with proteinuria <1 g/day.

Although clinical features may vary with age, hematuria is the most common finding, particularly in younger patients (6). In our patient group, hematuria was also the most frequently observed urinary abnormality (86.5%). Mixed nephrotic syndrome was present in 6 patients (11.5%), and nephrotic syndrome alone was seen in 1.9%; both are considered rare in IgA nephropathy (6).

Hypertension, especially when accompanied by proteinuria, is an important indicator of risk for progression in renal function impairment. It has been reported that in cases with daily protein excretion ≥1 g, blood pressure levels above 130/80 mmHg increase the risk of progression (11). In our study, hypertension at the time of diagnosis (BP >130/80 mmHg) was observed in 25% of the group with proteinuria <1 g/day, and in 42% of the group with proteinuria ≥1 g/day. Reported rates in the literature vary between 6% and 49% (12). This variability may be due to differences in the disease stage at diagnosis and the definition of hypertension.

Renal dysfunction at the time of diagnosis is considered a significant indicator of poor prognosis (7, 11, 14). In our study, initial serum creatinine levels did not significantly differ between the two groups ($p>0.05$), but in the final follow-up, creatinine levels were significantly higher in patients with proteinuria ≥1 g/day compared to those with proteinuria <1 g/day ($p<0.05$). At diagnosis, elevated creatinine levels (≥1.3 mg/dl) were found in 12.5% of patients with proteinuria <1 g/day and in 21% of those with proteinuria ≥1 g/day. These rates are within the range of 2% to 59% reported in the literature (16).

Although IgA nephropathy was previously referred to as benign hematuria, more recent publications have established it as a common cause of end-stage renal disease (ESRD). Despite variability across studies, 20–30% of patients are reported to develop ESRD within 20 years, and 20–40% show renal function loss (2). These differences may be attributed to disease course variability and differences in biopsy indications between centers. In our patient group, 12.5% of those with initial proteinuria <1 g/day experienced renal function loss, but none developed ESRD. Among those with proteinuria ≥1 g/day, 21% experienced renal function loss, and 10% progressed to ESRD.

According to three different endpoints (1. serum creatinine ≥1.3 mg/dl, 2. development of ESRD, 3. doubling of initial creatinine level), the five-year renal survival rate was calculated as 87.5% in the

proteinuria <1 g/day group and 69% in the proteinuria ≥1 g/day group. In previous studies, ten-year survival rates have been reported between 57% and 94% (16). Publications from Asia and Europe report survival rates of around 80%, while studies from the U.S. report rates of approximately 60%. These discrepancies may stem from differences in defining disease onset (symptom onset vs. pathological diagnosis), biopsy indications across centers, and initial clinical characteristics of patient populations.

A 2007 Canadian study comparing renal function loss based on proteinuria levels found that patients with proteinuria ≥1 g/day had significantly greater renal function loss compared to those with <1 g/day, and that proteinuria level correlated with renal function loss (17). In our study, creatinine clearance calculated using the MDRD formula also showed a significant decrease in patients with proteinuria ≥1 g/day compared to those with proteinuria <1 g/day.

5. Conclusıon

The patients included in the evaluation were divided into two groups based on their proteinuria levels at the time of diagnosis: proteinuria <1 g/day and proteinuria ≥1 g/day. No significant differences were observed between the two groups in terms of demographic characteristics. The presenting complaints of the patients were similar in both groups. Histopathological examination of kidney biopsies revealed a higher frequency of glomerulosclerosis, interstitial fibrosis, and crescent formation—findings associated with poor prognosis in the literature—in the group with proteinuria ≥1 g/day.

Hypertension and elevated creatinine levels, both known to be associated with disease progression and poor prognosis, were found to be more frequent in the group with proteinuria ≥1 g/day compared to those with proteinuria <1 g/day. In our study, the five-year renal survival rate—calculated based on three different endpoints (1. serum creatinine ≥1.3 mg/dl, 2. development of end-stage renal disease [ESRD], 3. doubling of the initial creatinine level)—was higher in the group with proteinuria <1 g/day than in the group with proteinuria ≥1 g/day.

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