Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Urinary excretion of low-molecular-weight proteins as prognostic markers in IgA nephropathy

H.P.E. Peters*, J.A.J.G. van den Brand, J.F.M. Wetzels

Department of Nephrology, Radboud University Nijmegen Medical Center Nijmegen, PO Box 9101, 6500 HB Nijmegen, the Netherlands, *corresponding author: e-mail: H.Peters@aig.umcn.nl

ABSTRACT

Background: Immunoglobulin A nephropathy (IgAN) is characterised by high variability in clinical course and outcome. Accurate prediction of prognosis is needed to optimise treatment. Urinary α1-microglobulin and β2-microglobulin are markers of tubulointerstitial injury and predict the risk of end-stage renal disease (ESRD) in idiopathic membranous nephropathy. We questioned the relevance of these markers in IgAN. Methods: We included patients with biopsy proven IgAN, who were evaluated for proteinuria in our centre between 1995 and 2007. Data were analysed using univariate and multivariate Cox regression for the outcome variables ESRD and progression (rise in serum creatinine of >50% or start of immunosuppressive therapy). Results: Seventy patients (71% men) were selected. Median age was 39 years, median serum creatinine 140 μmol/l, and median proteinuria 2.4 g/day. Median urinary α1-microglobulin excretion was 23.5 μg/min (range 3.5-275.3) and median urinary β2-microglobulin excretion was 0.4 μg/min (range 0.1-62.1). Both α1m and β2m correlated significantly with serum creatinine (r = 0.65, p<0.01 and r = 0.62, p<0.01) and total proteinuria (r = 0.35, p<0.01 and r = 0.28, p<0.05). During follow-up (median 75 months) 25 patients (36%) developed ESRD, and 46 patients (66%) showed progression. 19 patients (27%) were treated with immunosuppressive agents. In univariate analysis urinary α1- and β2-microglobulin predicted ESRD and progression. In multivariate analysis only serum creatinine and urinary protein were independent predictors of both outcomes. Conclusion: Urinary excretion of low molecular weight proteins did not offer an advantage over total proteinuria and serum creatinine in predicting prognosis in patients with IgAN.

KEYWORDS

α1-microglobulin, β2-microglobulin, end-stage renal disease, IgA nephropathy, prognosis, progression

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis worldwide. The natural history is quite variable and published data must be interpreted with caution since many patients with mild disease may never come to clinical attention or undergo a renal biopsy. End-stage renal disease (ESRD) develops in 20 to 30% of patients with IgAN within 20 years after diagnosis.[1-4]

Although there is a lack of randomised controlled trials, data suggest that a minority of patients may benefit from immunosuppressive treatment.[5-8] Ideally, such treatment should be restricted to patients who will progress to ESRD. Several variables have been identified as predictors of prognosis i.e. elevated serum creatinine concentration,[3,9-13] severe proteinuria,[9,14-17] arterial hypertension[9,15,16] and histological characteristics.[3,10,14,15] Few studies have showed that clinical features evaluated after one year of follow-up predicted prognosis more accurately than at the time of presentation.[17,18] Recently Reich *et al.* reported that persistent proteinuria is the strongest predictor of poor renal outcome in IgAN and that sustained reduction of proteinuria to <1 g/24 hour is associated with a good prognosis.[19] Unfortunately, most markers are not very accurate, with low sensitivity and specificity.

In idiopathic membranous nephropathy, high-risk patients can be identified in an early stage by measuring low-molecular-weight proteins such as α_1-microglobulin

(α_1m) and β_2-microglobulin (β_2m) with a sensitivity of 83% and a specificity of 97%.[20-22] We aimed to determine whether the excretion of low-molecular-weight (LMW) proteins adds to predicting prognosis in patients with IgAN.

SUBJECTS AND METHODS

Population

Since 1995, we have performed standardised protein measurements in patients with proteinuria due to glomerular diseases.[20,21] Patients are referred to our medical centre from hospitals located mainly in the south-eastern part of the Netherlands. For the present study we analysed the data of adult patients with biopsy proven IgA nephropathy who were evaluated for proteinuria in our centre between 1995 and 2007, and followed thereafter. Patients with other causes of IgA-positive glomerular staining (systemic lupus erythematosus, Henoch-Schönlein purpura or liver disease) or a follow-up of less than 12 months, were excluded from analysis.

Baseline measurement

Gender, ethnicity, age, body weight and height were recorded at the time of measurement. Details of the measurements have been described.[21] Two 24-hour urine samples were obtained for measurement of creatinine and total protein. The excretion of the low- and high-molecular-weight proteins was measured under standardised conditions. A urinary pH >6.0 is necessary to allow reliable measurements of urinary β_2m. Therefore, patients took 4000 mg of oral sodium bicarbonate the evening before the measurement. On arrival at the ward, the patients took an additional 2000 to 4000 mg sodium bicarbonate and up to 500 ml of tap water was given to enforce diuresis. The patients remained supine for two hours except for voiding. Blood pressure measurements were taken using an automated device (DINAMAP, Criticon, Tampa FL) with six consecutive readings registered every five minutes after ten minutes rest; these readings were used to calculate the mean arterial pressure (MAP). Measurement of urinary pH, β_2m, α_1m, immunoglobulin G (IgG), transferrin, albumin, total protein and creatinine was performed. Beta-2-microglobulin excretion was only measured in urine with a pH >6.0. Laboratory parameters were measured in blood samples collected in the middle of the urine collection period.

The use of angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin II type 1 receptor antagonists (ARBs), calcium channel blockers, other antihypertensive agents, diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs), as well as HMG-CoA-reductase inhibitors, was recorded. Current or previous use of corticosteroids, other immunosuppressive agents or fish oil was registered.

Serum creatinine, cholesterol, urinary total protein and creatinine were measured with standard automated techniques. Urinary proteins were measured as described before.[23]

Follow-up

After baseline measurements, patients were commended to the care of their local physicians. Immunosuppressive therapy was advised to patients with progressive renal disease. We collected data on serum creatinine, albumin, cholesterol and urea, total urinary protein and creatinine levels, blood pressure, body weight and exposure to medication during follow-up from medical records.

Calculations and definitions

Body mass index (BMI) was calculated from body weight and height at baseline. MAP during follow-up was calculated as the diastolic pressure plus one third of the pulse pressure. The glomerular filtration rate at baseline and follow-up was estimated (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) equation.[24,25] Start of follow-up was defined as the time of standardised measurement of proteinuria, regardless of the first assessment suggestive of renal disease. We defined the following two renal outcomes: ESRD and progression of renal disease. ESRD was defined as initiation of dialysis, renal transplantation or an eGFR <15 ml/min per 1.73 m^2. Progression of renal disease was defined as an elevation in serum creatinine of 50% or more since the baseline measurement, the start of immunosuppressive therapy or the development of ESRD.

Statistical analysis

Missing values for urinary protein concentration in the 24-hour urine samples were imputated by using the urinary protein-creatinine ratio which was obtained from the two-hour sample, and by using serum albumin. Missing values for low-molecular-weight proteins were not imputated.

All baseline variables were compared for patient groups by χ^2-test if dichotomous, one-way ANOVA if continuous and after log transformation if skewed. Each continuous baseline variable was divided into tertiles and plotted in a Kaplan-Meier curve for visual inspection.

Possible collinearity for univariate significant predictors was checked. Predictors that had a Spearman's rho smaller than 0.800 were entered into a multivariate Cox model. A backward stepwise selection algorithm, criteria for exclusion being a likelihood ratio test with p-value greater than 0.05 and smaller than 0.10 for inclusion, was used.

Possible interactions, based on plausible mechanism, were entered and tested too. The most parsimonious model with the best fit, using generalised R^2, was considered most appropriate.[26] Internal validation of the selected model was done with a bootstrapping procedure using 1000 samples. The predictive value of this model was investigated by the area under the receiver operating characteristics (ROC) curve.

RESULTS

Baseline characteristics and outcome variables

Initial demographic, clinical and laboratory data of 70 patients are listed in *table 1*. In the majority of patients (57%) proteinuria was >2.0 g/day and the estimated GFR <60 ml/min/1.73 m^2. Eighty percent of the population were taking ACEIs or ARBs at the time of evaluation for proteinuria. Median duration of follow-up was 74 months. The time period between onset of renal disease or biopsy and subsequent referral to our centre varied. In 60% of patients the time between biopsy and referral was less than six months.

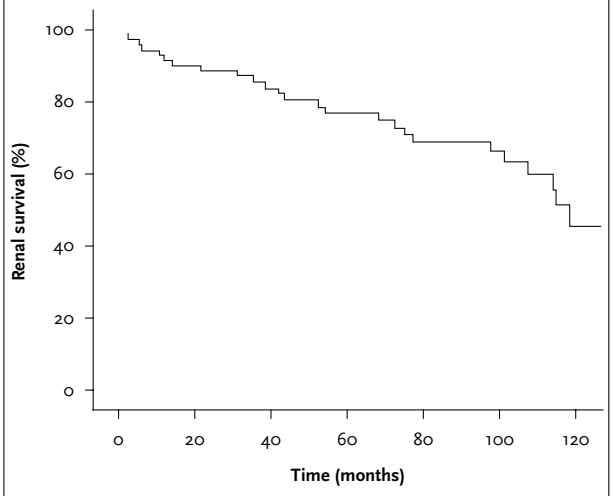
During follow-up all patients were treated with ACEIs and/or ARBs. Immunosuppressive therapy was initiated in 19 patients, the majority of them (74%) were treated with cyclophosphamide combined with prednisone. Twenty-five patients (36%) developed ESRD, with the shortest survival time being two months. Five- and eight-year renal survival rates from baseline were 78 and 66% (*figure 1*). In 46 (66%) patients progression of renal disease occurred based on an increase in serum creatinine of >50% (n=35), or initiation of immunosuppressive therapy (n=11). Thus, of 19 patients who received immunosuppressive therapy during follow-up, eight patients were treated because of a rise in serum creatinine of more than 50%. In 11

Table 1. *Clinical and demographic characteristics at baseline*

	Total group	Progression		No progression	
		Rise in serum creatinine >50%	Therapy		p
n (% male)	70 (71.4%)	35 (74.3%)	11 (81.8%)	24 (62.5%)	0.436
Age (years)	39 (17-70)	36.0 (17-70)	37 (25-59)	45.5 (20-66)	0.164
BMI (kg/m^2)	26.2 (19.4-41.0)	26.1 (20.4-31.1)	27.5 (21.2-33.2)	26.3 (19.4-41.0)	0.605
MAP (mmHg)	101.3 (73-133.7)	104 (83-133.7)	99.8 (73-112)	94.3 (80.0-133.2)	0.113
Urinary protein (g/d)	2.4 (0.4-24.4)	2.9 (0.5-12.6)	3.6 (0.4-24.3)	1.7 (0.4-9.6)	0.090
Protein-creatinine ratio (g/10 mmol)	2.9 (0.5-18.2)	3.5 (1.0-16.1)	4.5 (0.6-18.2)	1.2 (0.5-13.3)	0.093
Serum creatinine (µmol/l)	139.5 (70-366)	149 (76-366)	186 (100-274)	112 (70-172)	<0.001
Serum urea (µmol/l)	8.3 (4-36)	9.1 (4-36)	11.1 (6-22)	6.3 (4-14)	0.007
Serum albumin (g/l)	38.0 (21-46)	38.0 (21-46)	37.0 (29-45)	39.0 (30-44)	0.847
Serum cholesterol (mmol/l)	5.7 (3.5-8.9)	5.9 (3.6-8.7)	5.1 (3.6-8.9)	5.7 (3.5-7.2)	0.468
MDRD4 (ml/min/1.73 m^2)	48.2 (16.5-95.5)	44.9 (16.5-86.7)	37.1 (22.3-82.0)	54.7 (36.3-95.5)	0.003
α_1-microglobulin excretion (µg/min)	23.5 (3.5-275.3)	30.6 (3.5-275.3)	48.0 (7.8-192.0)	14.9 (4.1-48.4)	0.010
β_2-microglobulin excretion (µg/min)	0.4 (0.1-62.1)	1.1 (0.1-62.1)	1.15 (0.1-36.0)	0.30 (0.1-27.0)	0.077
IgG excretion (mg/d)	111.4 (11.3-1327.2)	144.8 (16.2-1327.2)	111.4 (11.3-900.1)	68.2 (13.5-786.9)	0.038
ESRD	35.70%	65.70%	18.20%	0%	<0.001
Time until ESRD of last follow-up (months)	74.6 (2.2-145.6)	72.7 (2.2-145.6)	97.5 (6.1-135.5)	76.9 (12.9-125.9)	0.676
Time until progression or last follow-up (months)	39.4 (0.2-125.9)	28.1 (0.5-114.5)	2.1 (0.2-75.6)	76.9 (12.9-125.9)	<0.001
Interval between biopsy and referral* (months)	2.0 (0-209.7-)	5.0 (0-187.5)	0.7 (0-98.9)	1.8 (0-209.7)	0.965
Interval between onset and referral (months)	29.3 (219.7-2.0)	38.6 (195.9-4.1)	36.0 (179.7-2.3)	8.8 (219.7-2.0)	0.592
Use of ACEIs/ARBs before baseline	80.00%	80.00%	81.80%	79.20%	0.984
Use of diuretics before baseline	30.00%	34.30%	27.30%	25.00%	0.729
Use of other antihypertensive medication	34.30%	37.10%	45.50%	25.00%	0.437
Use of immunosuppressive treatment before baseline	4.30%	5.70%	9.10%	0.00%	0.393
Use of ACEIs/ARBs during follow-up	100.00%	100.00%	100.00%	100.00%	
Use of diuretics during follow-up	68.60%	71.40%	90.90%	54.20%	0.082
Use of other antihypertensives during follow-up	54.30%	62.90%	63.60%	37.50%	0.126
Use of immunosuppressive drugs during follow-up	27.14%	22.86%	100.00%	0.00%	<0.001

Data expressed as median (range). *In a few patients biopsy was performed after evaluation for proteinuria.
BMI = body mass index; MAP = mean arterial blood pressure; MDRD4 = modification of diet in renal disease equation; ESRD = end-stage renal disease; ACEI= angiotensin-converting enzyme inhibitors; ARB=angiotensin II type 1 receptor antagonist.
P values are from χ^2-test or ANOVA comparing the three groups: rise in serum creatinine, therapy and non-progressors.

Figure 1. *Renal survival curve in patients with IgAN*



Renal survival was defined as onset of ESRD.

patients treatment was started earlier. These patients were characterised by higher serum creatinine values at baseline and more severe proteinuria (*table 1*).

Low-molecular-weight proteins

Alpha-1-microglobulin levels were not available for two patients, while β_2m levels could not be measured in nine patients due to a urinary pH <6.0. The urinary excretion of both α_1m and β_2m was increased in patients with IgAN, with median levels of 23.5 µg/min (reference value <10 µg/min) and 0.4 µg/min (reference value <0.2 µg/min).

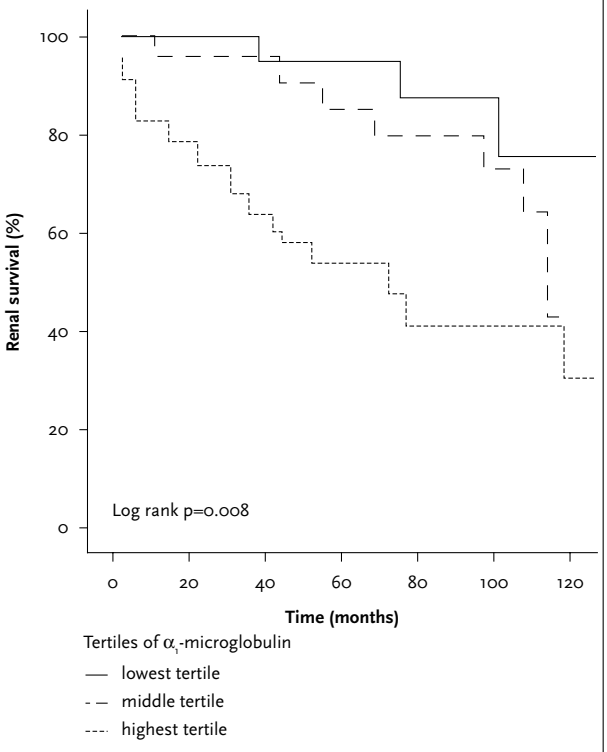
There was a high correlation between α_1m and β_2m ($r = 0.86$, $p<0.01$). Both α_1m and β_2m correlated significantly with serum creatinine ($r = 0.65$, $p <0.01$ and $r = 0.62$, $p<0.01$), IgG excretion ($r = 0.59$, $p<0.01$ and $r = 0.58$, $p<0.01$), and total proteinuria ($r = 0.35$, $p<0.01$ and $r = 0.28$, $p<0.05$).

Predictors of outcome

End-stage renal disease

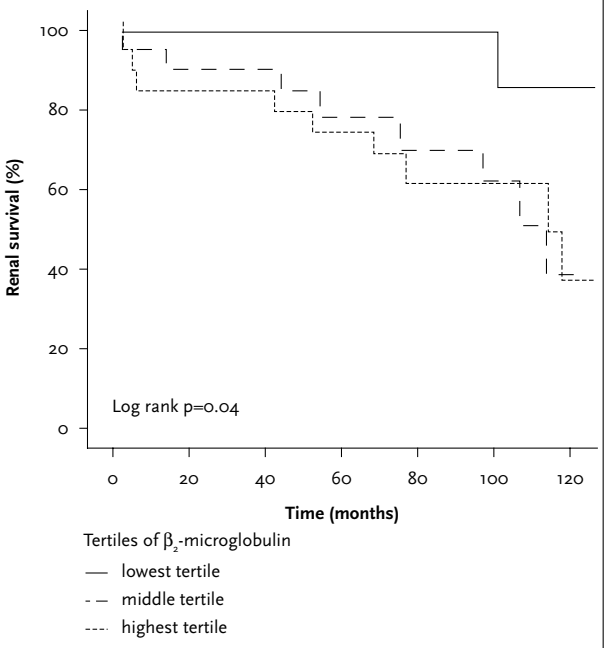
Urinary α_1-microglobulin, β_2-microglobulin and IgG excretion, serum creatinine and urea levels, total urinary protein, eGFR and the use of diuretics before baseline were all significantly associated with ESRD. When evaluating tertiles of α_1m, renal survival in the highest tertile was markedly lower compared with that in the lowest and middle tertiles (94 *vs* 63% at five years, 85 *vs* 44% after eight years, p=0.001) (*figure 2*). Only one patient within the lowest tertile of urinary β_2m developed ESRD. Therefore, renal survival in the lowest tertile of β_2m was higher than in the middle and highest tertile (*figure 3*). After multivariate Cox regression analysis only baseline serum creatinine and total proteinuria proved significant predictors of ESRD when correcting for therapy (*table 2*). Thus, neither α_1-microglobulin nor β_2-microglobulin

Figure 2. *Renal survival curve for tertiles of α_1-microglobulin in patients with IgAN*



Renal survival was defined as onset of ESRD.

Figure 3. *Renal survival curve for tertiles of β_2-microglobulin in patients with IgAN*



Renal survival was defined as onset of ESRD.

Table 2. *Hazard ratios (HR) and confidence intervals (CI) of significant baseline predictors of ESRD or progression of renal disease after univariate and multivariate analysis*

	Variable	Univariate analysis		Multivariate analysis	
		HR	(95% CI)	HR	(95% CI)
ESRD	α_1-microglobulin (µg/min)	1.015	(1.008 – 1.023)		
	β_2-microglobulin (µg/min)	1.06	(1.022 – 1.099)		
	IgG excretion (mg/d)	1.002	(1.001 – 1.004)		
	Use of diuretics before referral	2.922	(1.197 – 7.132)		
	$MDRD_4$ ml/min/1.73 m^2	0.929	(0.897 – 0.962)		
	Protein-creatinine ratio (g/10 mmol)	1.133	(1.022 – 1.255)		
	Serum urea (mmol/l)	1.161	(1.099 – 1.226)		
	Serum creatinine (µmol/l)	1.018	(1.012 – 1.025)	1.022	(1.013 – 1.038)
	Total urinary protein (g/d)	1.160	(1.061 – 1.268)	1.241	(1.029 – 1.781)
	Immunosuppressive therapy	0.843	(0.336 – 2.115)	0.179	(0.010 – 0.921)
Generalised R^2 = 0.508					
Progression	α_1-microglobulin (µg/min)	1.013	(1.008 – 1.018)		
	β_2-microglobulin (µg/min)	1.033	(1.006 – 1.061)		
	IgG excretion (mg/d)	1.002	(1.001 – 1.003)		
	$MDRD_4$ ml/min/1.73m^2	0.972	(0.955 – 0.990)		
	Protein-creatinine ratio (g/10 mmol)	1.119	(1.039 – 1.205)		
	Serum urea (mmol/l)	1.102	(1.055 – 1.151)		
	Serum creatinine (µmol/l)	1.009	(1.005 – 1.013)	1.009	(1.005 – 1.014)
	Total urinary protein (g/d)	1.216	(1.116 – 1.325)	1.213	(1.112 – 1.362)
Generalised R^2 = 0.368					

ESRD = end-stage renal disease; MDRD = modification of diet in renal disease equation, IgG = immunoglobulin G.

were independent predictors of ESRD. Of note, patients who were treated with immunosuppressive agents during follow-up were less likely to develop ESRD.

Progression of renal disease

Urinary α_1-microglobulin, β_2-microglobulin and IgG excretion, serum creatinine and urea levels, total urinary protein, eGFR and age, were significant predictors of progression in univariate analysis. Multivariate Cox regression showed that only serum creatinine and total urinary protein were independent significant predictors of progression (*table 2*).

DISCUSSION

Our data clearly indicate that the urinary excretion of low-molecular-weight proteins does not predict prognosis in IgAN more accurately than total proteinuria. To our knowledge we are the first to report on the prognostic value of urinary excretion of α_1-microglobulin and β_2-microglobulin in IgAN. Others have found a highly significant relation between tubulointerstitial damage and the presence of unspecified, urinary LMW proteins, in a small cohort of patients with IgAN.[27] Woo *et al.* reported a higher incidence of chronic renal failure in 60 patients with IgAN who presented with LMW proteinuria and were followed for six years.[28] However, patients with LMW proteinuria had more severe proteinuria and higher serum creatinine levels.

In our patients with IgAN urinary excretion of α_1m and β_2m exceeded normal values. Renal survival was significantly lower in patients with values of urinary α_1m and β_2m in higher tertiles. We observed a difference when comparing renal survival curves for tertiles of urinary α_1m and β_2m excretion. This apparent discrepancy can be explained by the fact that β_2m could not be measured in nine patients due to a low urinary pH. These patients were characterised by higher serum creatinine levels and more severe proteinuria. Thus, missing values are not at random but reflect an impairment of renal function and bicarbonate excretion. This illustrates the limitations of β_2m as a prognostic marker. Both urinary α_1m and β_2m predicted ESRD and progression of renal disease in univariate analysis. However, in multivariate analysis they did not prove to be independent predictors of either outcome. These findings are in contrast with previous reports on the good performance of LMW proteins as prognostic markers in patients with idiopathic membranous nephropathy. Urinary α_1m and β_2m are considered to reflect tubulo-interstitial injury. In general, the presence and extent of tubulo-interstitial injury determines renal outcome. From this perspective, the difference in the predictive value of LMW proteins between IgAN and idiopathic membranous nephropathy is remarkable. Of note, the predictive value of LMW proteins (such as α_1m) in idiopathic membranous nephropathy was validated in patients with no or moderate renal impairment, defined as a serum

creatinine <135 µmol/l. However, even within the subgroup of patients with IgAN and a serum creatinine level of <135 µmol/l, α_1m does not allow identification of high-risk patients. This difference is illustrated in the panels of *figure 4*. From the figure it is evident that levels of α_1m are higher in patients with idiopathic membranous nephropathy. These patients presented more frequently with nephrotic range proteinuria. Thus, the prognostic value of these LMW proteins may be confined to glomerulopathies characterised by nephrotic range proteinuria.

We found baseline serum creatinine and proteinuria to predict ESRD and progression of renal disease. The relation between serum creatinine and ESRD is to be expected, since a patient with a higher serum creatinine concentration will develop ESRD at an earlier time-point, even if the rate of renal function deterioration is similar. To overcome this problem we defined a 50% or more increase of serum creatinine concentration as progression. We chose a 50% rise to be sure that no patients who had a minor increase were marked as progressors. Since multivariate analysis regarding the outcome ESRD implied that the natural progression of IgAN is influenced by immunosuppressive therapy, this was considered an end-point. The use of initiation of immunosuppressive therapy as an end-point can be debated. In our study, 19 out of 70 patients received immunosuppressive therapy during follow-up. In eight patients, treatment was started after serum creatinine had increased by 50% or more. The remaining 11 patients received immunosuppressive treatment before reaching this 50% rise in serum creatinine. These patients were characterised by high serum creatinine and more severe proteinuria at baseline. Further delay of treatment was considered inappropriate by their physicians. As such, these patients reflect current treatment practice in our region. At the start of therapy, mean serum creatinine was 221 µmol/l, clearly pointing to the severity of IgAN. Even with progression as outcome, serum creatinine level and total urinary protein excretion remained significant, independent predictors.

The observation that serum creatinine concentration is a significant, independent predictor of progression of renal disease implies that an accelerated rather than a linear decline in renal function occurs in the course of the disease. In order to correct for the possible confounding effect of using initiation of immunosuppressive therapy as an end-point, we reanalysed the data using an increase of serum creatinine of >50% as only end-point. Serum creatinine concentration remained a significant predictor, which possibly reflects that patients with an increased serum creatinine are more likely to progress or progress at a faster rate than those with no renal impairment. Our findings support observations reported by others and are in line with the hypothesis that loss of nephrons gives rise to hyperfiltration of a reduced number of nephrons leading to further destruction of nephrons and an accelerated deterioration of renal function.[29,30]

Although data are scarce, immunosuppressive medication may be of benefit for patients failing a supportive approach

Figure 4A. *Correlation between α_1-microglobulin and proteinuria in patinets with iMN*

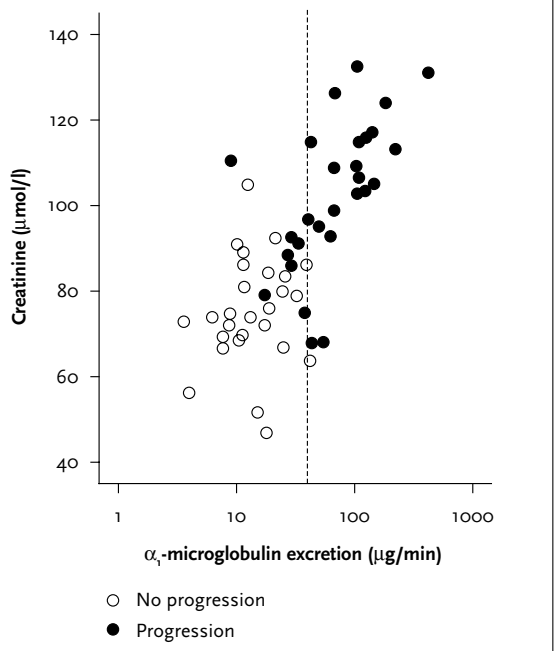
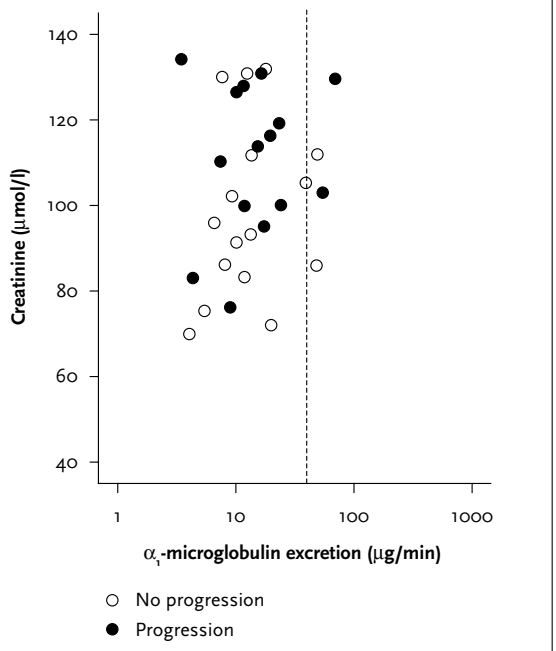


Figure 4B. *Correlation between α_1-microglobulin and proteinuria in patinets with IgAN*



and at high risk for progressive loss of renal function. In order to avoid unnecessary immunosuppressive therapy, a model with a high specificity is required to guide clinical decisions regarding treatment. When constructing a receiver operating characteristics curve (ROC), our model predicting ESRD using serum creatinine concentration and urinary protein concentration has an area under the curve (AUC) of 0.88 (95% CI 0.78 to 0.95). When predicting progression of renal disease using the same variables, the AUC was 0.80 (95% CI 0.69 to 0.91). Although these values indicate a reasonably good performance of our models, closer examination of data shows that a specificity of 90% is accompanied by a low sensitivity (50 to 60%). Our models are therefore unsuitable to guide clinical decisions. The identification of more accurate prognostic markers remains essential.

Admittedly, this study has several limitations. First, it describes a relatively small number of patients. Second, when compared with other reported populations, eGFR is lower and proteinuria is more severe in our cohort despite a comparable blood pressure. A large percentage of patients showed fast progression and many patients developed ESRD. This may be due to a selection bias since patients with stable serum creatinine and moderate proteinuria are less likely to be biopsied and/or referred to our medical centre. Since many patients were biopsied in another hospital and material was unavailable, we were unable to correlate urinary α_1m and β_2m with histopathological characteristics. On the other hand, in contrary to earlier populations examined, this cohort is comprised of patients who were all treated with ACEIs and/or ARBs, an important element of therapy nowadays. Furthermore, we ruled out an effect of therapy while analysing data. Finally, the lack of a validation group, as in every other study evaluating the prognostic predictors for progression of IgAN, was corrected for by bootstrapping.

CONCLUSION

Urinary excretion of the low-molecular-weight proteins α_1-microglobulin and β_2-microglobulin does not add to predicting prognosis of IgAN. Serum creatinine concentration and urinary protein excretion are the most potent predictors of progression of IgA nephropathy.

ACKNOWLEDGMENTS

H.P.E. Peters is supported by a grant from the Dutch Kidney Foundation.

We thank G. Feith and M. Den Hartog, Gelderse Vallei Hospital, Wageningen; J. Beutler, D. Hollander, J. Jansen and M. Koolen, Jeroen Bosch Hospital, 's-Hertogenbosch; M. Ten Dam, I. Go and J. van de Leur, Canisius Wilhelmina Hospital, Nijmegen; A. van den Wall Bake, St Joseph Hospital, Veldhoven; R. van Leusen and L. Reichert, Rijnstate Hospital, Arnhem; W. van Kuijk and V. Verstappen, VieCurie Medical Center, Venlo; R. Smeets, St Anna Hospital, Geldrop; A. Lückers, Maas Hospital, Boxmeer; H. Krepel, Lievensberg Hospital, Bergen op Zoom, for their participation in this study.

REFERENCES

1. D'Amico G. Clinical features and natural history in adults with IgA nephropathy. Am J Kidney Dis. 1988;12:353-7.
2. D'Amico G, Colasanti G, Barbiano di BG, et al. Long-term follow-up of IgA mesangial nephropathy: clinico-histological study in 374 patients. Semin Nephrol. 1987;7:355-8.
3. Radford MG, Jr, Donadio JV, Jr, Bergstralh EJ, Grande JP. Predicting renal outcome in IgA nephropathy. J Am Soc Nephrol. 1997;8:199-207.
4. Frimat L, Briancon S, Hestin D, et al. IgA nephropathy: prognostic classification of end-stage renal failure. L'Association des Nephrologues de l'Est. Nephrol Dial Transplant. 1997;12:2569-75.
5. Pozzi C, Bolasco PG, Fogazzi GB, et al. Corticosteroids in IgA nephropathy: a randomised controlled trial. Lancet. 1999;353:883-7.
6. Pozzi C, Andrulli S, Del VL, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. J Am Soc Nephrol. 2004;15:157-63.
7. Yoshikawa N, Honda M, Iijima K, et al. Steroid treatment for severe childhood IgA nephropathy: a randomized, controlled trial. Clin J Am Soc Nephrol. 2006;1:511-7.
8. Ballardie FW, Roberts IS. Controlled prospective trial of prednisolone and cytotoxics in progressive IgA nephropathy. J Am Soc Nephrol. 2002;13:142-8.
9. Beukhof JR, Kardaun O, Schaafsma W, et al. Toward individual prognosis of IgA nephropathy. Kidney Int. 1986;29:549-56.
10. Bogenschutz O, Bohle A, Batz C, et al. IgA nephritis: on the importance of morphological and clinical parameters in the long-term prognosis of 239 patients. Am J Nephrol. 1990;10:137-47.
11. Koyama A, Igarashi M, Kobayashi M. Natural history and risk factors for immunoglobulin A nephropathy in Japan. Research Group on Progressive Renal Diseases. Am J Kidney Dis. 1997;29:526-32.
12. Li PK, Ho KK, Szeto CC, Yu L, Lai FM. Prognostic indicators of IgA nephropathy in the Chinese--clinical and pathological perspectives. Nephrol Dial Transplant. 2002;17:64-9.
13. Manno C, Strippoli GF, D'Altri C, Torres D, Rossini M, Schena FP. A novel simpler histological classification for renal survival in IgA nephropathy: a retrospective study. Am J Kidney Dis. 2007;49:763-75.
14. D'Amico G, Minetti L, Ponticelli C, et al. Prognostic indicators in idiopathic IgA mesangial nephropathy. Q J Med. 1986;59:363-78.
15. Alamartine E, Sabatier JC, Guerin C, Berliet JM, Berthoux F. Prognostic factors in mesangial IgA glomerulonephritis: an extensive study with univariate and multivariate analyses. Am J Kidney Dis. 1991;18:12-9.
16. Haas M. Histologic subclassification of IgA nephropathy: a clinicopathologic study of 244 cases. Am J Kidney Dis. 1997;29:829-42.
17. Donadio JV, Bergstralh EJ, Grande JP, Rademcher DM. Proteinuria patterns and their association with subsequent end-stage renal disease in IgA nephropathy. Nephrol Dial Transplant. 2002;17:1197-203.
18. Bartosik LP, Lajoie G, Sugar L, Cattran DC. Predicting progression in IgA nephropathy. Am J Kidney Dis. 2001;38:728-35.
19. Reich HN, Troyanov S, Scholey JW, Cattran DC. Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol. 2007;18:3177-83.
20. Reichert LJ, Koene RA, Wetzels JF. Urinary excretion of beta 2-microglobulin predicts renal outcome in patients with idiopathic membranous nephropathy. J Am Soc Nephrol. 1995;6:1666-9.

21. Branten AJ, du Buf-Vereijken PW, Klasen IS, et al. Urinary excretion of beta2-microglobulin and IgG predict prognosis in idiopathic membranous nephropathy: a validation study. J Am Soc Nephrol. 2005;16:169-74.

22. Bazzi C, Petrini C, Rizza V, et al. Urinary excretion of IgG and alpha(1)-microglobulin predicts clinical course better than extent of proteinuria in membranous nephropathy. Am J Kidney Dis. 2001;38:240-8.

23. Jacobs EM, Vervoort G, Branten AJ, Klasen I, Smits P, Wetzels JF. Atrial natriuretic peptide increases albuminuria in type I diabetic patients: evidence for blockade of tubular protein reabsorption. Eur J Clin Invest. 1999;29:109-15.

24. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130:461-70.

25. Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine. J Am Soc Nephrol. 2000;11:0828.

26. Nagelkerke NJD. A note on a general definition of the coefficient of determination. Biometrika. 2008;78:691.

27. Nagy J, Miltenyi M, Dobos M, Burger T. Tubular proteinuria in IgA glomerulonephritis. Clin Nephrol. 1987;27:76-8.

28. Woo KT, Lau YK, Lee GS, Wei SS, Lim CH. Pattern of proteinuria in IgA nephritis by SDS-PAGE: clinical significance. Clin Nephrol. 1991;36:6-11.

29. Geddes CC, Rauta V, Gronhagen-Riska C, et al. A tricontinental view of IgA nephropathy. Nephrol Dial Transplant. 2003;18:1541-8.

30. Fellin G, Gentile MG, Duca G, D'Amico G. Renal function in IgA nephropathy with established renal failure. Nephrol Dial Transplant. 1988;3:17-23.