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In Crescentic IgAN with Cellular Crescents the Urinary Excretion of the High MW Protein α2-Macroglobulin may be considered a Proteinuric Marker of Podocytes Damage Induced by Cellular Crescents

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ABSTRACT

Background: In Glomerulonephritis (GN) several urinary proteins with different molecular weights (MW: IgM, IgG, α1-microglobulin, β2-microglobulin) have been evaluated for their ability to predict outcomes and a possible association with renal lesions; no study has evaluated the clinical significance of the urinary excretion of the high MW protein α2-macroglobulin (α2m, MW 720 kDa). Aim of the study: assess the clinical significance of α2m urinary excretion in IgAN with crescents (ClgAN).

Patients & Methods: 58 patients with ClgAN (37 with cellular and 21 with fibrous crescents) were compared with each other and with 125 patients with IgAN and non-nephrotic proteinuria (PP).

Results: A comparison between 125 IgAN PP patients and with 58 ClgAN patients and versus 37 with cellular crescents shows that the groups did not differ with respect to baseline eGFR; there were significant differences in all proteinuric parameters and GGS%, TID score, and percentage of cellular and fibrous crescents (higher in ClgAN). In all ClgAN patients, the α2m/C value is 13.6 times higher than in all IgAN PP patients and 18.76 times higher in ClgAN patients with cellular crescents; TUP/C, IgG/C, Alb/C and α1m/C were about 3 times higher in ClgAN. A comparison of the first to the fourth quartile of the 37 patients with cellular crescents showed that the progressive increase in the percentage of glomeruli with cellular crescents is associated with increasing α2m/C levels. The functional outcome of 34 patients with cellular crescents was evaluated according to α2m/C quartiles; in the first quartile, remission was 67% and ESRD 0%; in the fourth quartile remission was 0% and ESRD 67% (Table 6). Outcome prediction according to quartiles of cellular crescents was lower and worse: first quartile: remission 62.5% and ESRD 25%; fourth quartile: remission 25% and ESRD 37%.

Conclusions: In ClgAN with cellular crescents the excretion of α2m may be considered dependent on podocyte damage induced by crescents and thus used as a marker for podocyte damage. In ClgAN with cellular crescents, α2m/C quartiles predict outcome more effectively than quartiles of cellular crescents probably due to the difference between α2m excretion, dependent on overall GFB damage, and the percentage of glomeruli with cellular crescents dependent on the different sizes of biopsy samples.

INTRODUCTION

In Glomerulonephritis (GN) several urinary proteins with different molecular weights (MW: IgM, IgG, α1-microglobuin, β2-microglobulin) have been evaluated for their ability to predict functional outcomes and their association with renal lesions such as percentage of Global Glomerular Sclerosis (GGS%), degree of Tubulo-Interstitial Damage (TID) and Arteriolar Hyalinosis (AH) [1-19]. Surprisingly no study has so far evaluated the clinical significance of the urinary excretion of the high MW protein α2-macroglobulin (α2m, MW 720 kDa). Several studies have been published on the role of podocytes and slit-diaphragm damage as the main factors responsible for the amount and composition of proteinuria [20-22], but at present, in clinical practice, no single proteinuric marker can assess the extent of podocyte damage. The urinary excretion of the high MW protein α2m presupposes a severe abnormality of the Glomerular Filtration Barrier (GFB) including podocytes damage. Our group evaluated the clinical significance of the urinary excretion of α2-macroglobulin by comparing 125 patients with IgAN and with persistent non-nephrotic proteinuria (PP) with 58 patients with crescentic IgAN (ClgAN: 37 patients with cellular crescents; 21 with fibrous crescents). Results would suggest α2-macroglobulin as a marker for podocyte damage. The excretion of α2m is significantly higher in ClgAN patients with crescents compared to IgAN PP patients (18.76x) and also in ClgAN patients with cellular crescents compared to patients with fibrous crescents (7.07 x). Similar results were observed in Lupus Nephritis (LN) with cellular crescents [23] versus patients without crescents. Also in Membranoproliferative Glomerulonephritis (MPGN) characterized by crescents in a few patients and by the immunofluorescent pattern of massive granular deposits of C3 and IgG along the capillary wall [24], the excretion of α2m is markedly high. The aim of this study is to evaluate the role of α2m excretion as a possible marker for podocyte damage by comparing 58 ClgAN patients, 37 with cellular crescents and 21 with fibrous crescents, versus 125 patients with IgAN and PP.

PATIENTS AND METHODS

All patients attending the Nephrology and Dialysis Unit of San Carlo Borromeo Hospital, Milan, Italy, between January 1992 and April 2006 with Renal Biopsy (RB) diagnosis of IgA nephropathy (IgAN, n. 125 pts) and Crescentic IgAN, n. 58 pts) were included in the study (n. 183 pts). The IgAN patients had persistent non-nephrotic proteinuria; of the ClgAN patients with cellular crescents 15 (41%) had Nephrotic Syndrome (NS) and 22 had PP (59%); of the patients with fibrous crescents 20 (95%) had PP and 1 had NS (5%).

Table 1: Clinical, functional, proteinuric and histologic data in 125 patients with IgAN and PP and 58 patients with ClgAN.

	IgAN with PP (n.125)	Crescentic IgAN (n. 58)	P
Age (years)	43 ± 17	33 ± 13	< 0.001
Sex (m/f) n.	82/43	37/21	0.92
eGFR	71.6 ± 26.2	61.3 ± 31.5	0.03
TUP/C	487 ± 547	1455 ± 1406	< 0.0001
IgG/C	32 ± 47	95 ± 116	0.0001
α2m/C	0.49± 1.47	6.30 ± 11.12	0.0002
Albumin /C	372 ± 478	1208 ± 1135	< 0.0001
α1m/C	10.0 ±10.7	24.4 ± 32.0	0.001
GGS%	14 ± 17	22 ± 18	0.01
TID score	1.88 ± 1.68	3.46 ± 1.89	0.01
AH score	0.76 ± 0.92	0.84 ± 0.98	0.58
High blood pressure	42%	54%	0.23
Cellular crescents	0	19 ± 15	< 0.0001
Fibrous crescents	0	6 ± 11	0.0006

Table 2: Renal lesions severity scores: percentage of Global Glomerular Sclerosis (GGS%); extent of Tubulo-Interstitial Damage (TID) evaluated by a score: absent (score 0), focal (score1-3), diffuse (score 4-6) in 125 IgAN PP patients and 58 patients with Crescentic IgAN (ClgAN).

	IgAN PP patients n. 125	ClgAN patients n. 58	P
Global Glomerular Sclerosis % (GGS%)			0.01
0	51 (41%)	10 (17%)	
1-19	39 (31%)	20 (34%)	
≥ 20	35 (28%)	28 (48%)	
Tubulo-interstitial Damage score, n. %			0.01
0	36 (29%)	4 (7%)	
1	19 (15%)	6 (10%)	
2	31 (25%)	12 (21%)	
3	16 (13%)	4 (7%)	
4	14 (11%)	11 (19%)	
5	4 (3%)	11 (19%)	
6	5 (4%)	10 (17%)	

Laboratory analysis

Proteinuria was measured by 24-ur urine collection and second morning urine sample using the Coomassie Blue method

In Crescentic IgAN with Cellular Crescents the Urinary Excretion of the High MW Protein α2-Macroglobulin may be considered a Proteinuric Marker of Podocytes Damage Induced by Cellular Crescents. Journal Of Nephrology & Kidney Diseases. 2022; 4(1):128.

(modified with sodium-dodecyl-sulphate) and expressed as 24/hour proteinuria and protein creatinine/ratio (mg urinary protein/g urinary creatinine). Serum and urinary creatinine levels were measured enzymatically and expressed in mg/dL. Serum and urinary IgG, α2-Macroglobulin (α2m), Albumin and α1-microglobulin (α1m) were measured by immunonephelometry and expressed as urinary protein/creatinine ratios (IgG/C, α2m/C, Alb/C, α1m/C). Estimated Glomerular Filtration Rate (eGFR) was measured by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Renal biopsy was performed at the same time as the assessment of clinical, functional and proteinuric data in all patients.

Pathological/Morphological Examination

Three types of renal lesions that are markers for renal disease severity of any type of CKD were evaluated: percentage of glomeruli with global glomerulosclerosis (GGS%), extent of Tubulo-Interstitial Damage (TID) evaluated by semi-quantitative scoring: tubular atrophy, interstitial fibrosis and inflammatory cell infiltration were graded 0, 1 or 2 if absent, focal or diffuse; TID global score: 0-6; extent of Arteriolar Hyalinosis (AH) evaluated by semi-quantitative scoring: 0, 1, 2, 3 if absent, focal, diffuse, diffuse with lumen reduction, respectively.

Functional outcomes

Functional outcomes were available in 55 ClgAN patients (95%); two types of outcome were considered: End-Stage Renal Disease (ESRD) and remission: in NS: complete: proteinuria ≤0.30 g/24h; partial: proteinuria ≤2.0 g/24h; remission in PP: proteinuria ≤0.30 g/24h and normal renal function (NRF) at last observation. The follow-up of patients with outcomes was: IgAN PP 64±36 months (7-155) and ClgAN patients 59 ± 46 months (2-248).

Statistical analysis

Continuous variables are expressed as means ± SD. Categorical variables are expressed as the number of patients (%). Differences in means were determined by t-test and categorical by the chi-square test. All statistical analyses were performed using Stata 15.1 Software (StataCorp LP, TX, USA). Two-sided $p < 0.05$ was considered significant.

RESULTS

The comparison of 125 IgAN PP patients with 58 ClgAN patients (Table 3) and with 37 patients with cellular crescents (Table 3) shows that the two groups were not significantly different in term of baseline eGFR; there was a significant difference for age, all proteinuric parameters, GGS%, and TID score, percentage of cellular and fibrous crescents (all parameters being higher in ClgAN). The α2m/C value in all ClgAN patients was 13.6 times higher than in the IgAN PP patients and 18.76 times higher in patients with cellular crescents, while TUP/C, IgG/C, Alb/C and α1m/C values were less than 3 times higher in ClgAN. The comparison of 125 IgAN PP patients with 21 ClgAN patients with fibrous crescents (Table 3) shows that the two groups were not significantly different in terms of baseline eGFR; there was a significant difference only for TUP/C, Alb/C and TID score. The α2m/C value in ClgAN patients with fibrous crescents was 2.65 times higher than in IgAN PP patients, while the TUP/C, IgG/C and Alb/C values were about 2 times higher in ClgAN. The comparison of 37 ClgAN patients with cellular crescents with 21 patients with fibrous crescent (Table 4) shows a significant difference for age, TUP/C, IgG/C and α2m/C, while eGFR, α1m/C, GGS%, TID score and AH score were not significantly different. The comparison of first to fourth quartiles for cellular crescents in 37 patients showed a progressively higher percentage of glomeruli with cellular crescents from 1° to 4° quartile (Table 5). The comparison between 4° to 1° quartile showed in the fourth quartile a significantly lower baseline eGFR, and a significant increase in all proteinuric parameters, mainly α2m/C, while the histological parameters were not significantly different between 4° vs 1° quartile. The functional outcome in 34 of 37 ClgAN patients with cellular crescents evaluated according to quartiles of α2m/C shows in 1° quartile remission 67% and ESRD 0%; in 4° quartile remission 0%, ESRD 67% (Table 6). By contrast, the functional outcome according to quartiles of cellular crescents (Table 7) shows a lower predictive value: in 1° quartile Remission is 62.5% and ESRD 25%; in 4° quartile Remission 25% and ESRD 37%.

In Crescentic IgAN with Cellular Crescents the Urinary Excretion of the High MW Protein α2-Macroglobulin may be considered a Proteinuric Marker of Podocytes Damage Induced by Cellular Crescents. Journal Of Nephrology & Kidney Diseases. 2022; 4(1):128.

Table 3: Comparison of clinical, functional, proteinuric. histologic parameters and percentage of cellular and fibrous crescents in 125 IgAN PP patients and 58 patients with ClgAN, 37 with cellular crescents and 21 ClgAN with fibrous crescents.

	Age	Basel eGFR	TUP/C	IgG/C	α2m/C	Alb/C	α1m/C	GGS%	TID score	AH Score	High BP	CellularCresc	Fibrous Cresc. %
IgAN with PP n. 125	42.6±17.0	71.6±26.2	487±547	32±47	0.49±1.47	372±478	10.0±10.7	14.0	1.88	0.76	53 (42%)	0%	0%
P value vs IgAN PP	<0.0001	0.03	<0.0001	0.0001	0.0002	<0.0001	0.001	0.01	0.01	0.58	0.23	<0.0001	0.0006
ClgAN n. 58	33.0±12.6	61.3±31.5	1455±1406 x 2.98	95±116 x 2.96	6.30±11.12 x 12.9	1208±1135 x 3.24	24±32.0 x 2.44	22.0	3.57	0.84	30 (52%)	12.4%	5.7%
P value vs IgAN PP	**<0.0001**	**0.13**	**<0.0001**	**0.0004**	**0.0003**	**<0.0001**	**0.003**	**0.02**	**<0.0001**	**0.72**	**0.21**	**<0.0001**	**0.0006**
ClgAN with cellular cresc. n. 37	30.4±11.3	62.5±33.1	1752±1566 x 3.59	118±134 x 3.67	8.94±12.9 x 18.76	1451±1259 x 3.90	26±29 x 2.57	21.2	3.46	0.70	20 (54%)	19%	5.8%
P value vs IgAN PP	**0.15**	**0.08**	**0.03**	**0.10**	**0.22**	**0.02**	**0.15**	**0.08**	**0.006**	**0.22**	**0.78**		
ClgAN with Fibrous cresc. n. 21	37.8±13.6	59.3±29.1	929±876 x 1.91	55±61 x 1.71	1.38±3.11 x 2.81	780±718 x 2.09	22±37 X 2.21	22.4	3.76	1.09	10 (48%)	0%	17.0%

Table 4: Comparison of clinical, functional, proteinuric. histologic parameters and percentage of cellular and fibrous crescents in 58 ClgAN patients, 37 with cellular crescents and 21 with fibrous crescents.

	Age	Basel eGFR	TUP/C	IgG/C	α2m/C	Alb/C	α1m/C	GGS%	TID score	AH score	High BP	cellular cresc.%	fibrous cresc. %
ClgAN with cellular crescents n. 37	30.4±11.3	62.5±33.1	1752±1566 x 1.88	118±134 x 2.12	8.94±12.91 x 7.07	1451±1259 x 1.98	25.7±29.4	21.2	3.46	0.70	(54%)	19%	5.8%
P value	0.04	0.71	0.01	0.02	0.001	0.01	0.70	0.81	0.66	0.19	0.63	0.002	0.001
ClgAN with fibrous crescents n. 21	37.8±13.6	59.3±29.1	929±876	55±61	1.38±3.11	780±718	22.1±36.9	22.4	3.48	1.09	(48%)	0%	17.0%

Table 5: Clinical, functional, proteinuric. histologic parameters and percentage of cellular and fibrous crescents in quartiles of cellular crescents in 37 ClgAN patients.

	Age years	Basel eGFR	TUP/C	IgG/C	α2m/C	Alb/C	α1m/C	GGS%	TID score	AH score	High BP	Cell. cresc.%	Fibrous cresc. %
ClgAN with cellular crescents n. 37	30.4±11.3	62.5±33.1	1752±1566	118±134	8.9±12.9	1451±1259	25.7±29.4	21.2	3.46	0.70	54%	19%	5.8%
1° quart. cell cresc. n. 10	29.1±7.6	74.8±31.0	994±796	59±49	2.9±4.1	859±731	14.7±12.4	22.6	3.10	0.70	30%	6.2%	8.1%
2° quart. cell cresc n. 9	36.0±20.5	50.6±41.1	1798±1799	125±132	14.1±22.2	1430±1191	39.9±45.4	11.0	3.40	0.80	60%	10.0%	5.2%
3° quart. cell cresc n. 9	31.0±10.4	64.6±27.9	2065±1830	149±185	9.3±13.7	1384±1399	16.1±15.6	21.8	3.54	0.77	62%	17.6%	3.8%
4° quart. cell cresc n. 9	29.6±9.6	49.6±38.1	2765±1642	185±144	12.2±11.2	2216±1338	43.7±39.1	24.2	3.78	0.56	67%	41.8%	4.2%
1° vs 4° quartile p	0.81	0.08	0.01	0.03	0.04	0.02	0.06	0.64	0.25	n.s.	0.33	0.0006	0.73

In Crescentic IgAN with Cellular Crescents the Urinary Excretion of the High MW Protein α2-Macroglobulin may be considered a Proteinuric Marker of Podocytes Damage Induced by Cellular Crescents. Journal Of Nephrology & Kidney Diseases. 2022; 4(1):128.

Table 6: Functional outcome and clinical, functional, proteinuric parameters in 34 patients with CIgAN and cellular crescents according to quartiles of ⟨2m/C.

Quartiles of α2m/C in 34 patients with Cellular Crescents	Remission NRF	ESRD	Cellular crescent %
1° quartile n. 12	8 (67%)	0 (0%)	15.7
2° quartile n. 5	3 (60%)	2 (40%)	11.8
3° quartile n. 8	5 (56%)	2 (22%)	20.9
4° quartile n. 9	0 (0%)	6 (67%)	27.1
P			

Quartiles of α2m/C Cell. Cresc. n.34	Age	Basel eGFR	TUP/C	IgG/C	α2m/C	Alb/C	α1m/C	GGS%	TID score	AH score	High BP
1° quartile n. 12	31.0±12.5	80.1±34.0	714±543	41±39	0±0	632±562	9.5±9.1	16.7	2.25	0.58	25%
2° quartile n. 5	28.4±8.8	60.8±29.1	811±516	43±26	1.91±1.12	727±493	16.3±19.6	27.0	3.60	0.80	60%
3° quartile n. 9	30.2±9.3	62.1±28.9	1419±908	95±119	6.41±2.46	1169±797	25.5±27.5	18.6	3.67	0.67	67%
4° quartile n. 8	31.9±16.0	31.4±18.1	3932±1061	286±133	26.69±12.9	3163±730	60.1±35.7	26.4	4.75	1.12	100%
1° vs 4° quart. p	0.89	0.0001	<0.0001	0.001	0.0006	<0.0001	0.005	0.11	0.0001	0.13	0.0001

Table 7: Functional outcome and clinical, functional, proteinuric parameters in 34 patients with CIgAN according to quartiles of cellular crescents.

Quartiles of cellular crescents in 34 pts with functional outcome	Remission with NRF	ESRD	Cellular crescent%
1° quartile n. 8	5 (62.5%)	2 (25%)	6.2
2° quartile n. 9	5 (56%)	2 (22%)	11.4
3° quartile n. 8	4 (44%)	2 (22%)	19.6
4° quartile n. 9	2 (25%)	3 (37.5%)	40.4
P			

Quartiles of Cell. Crescents n.34	Age	Basel eGFR	TUP/C	IgG/C	α2m/C	Alb/C	α1m/C	GGS%	TID score	AH score	High BP
1° quartile n. 10	32.1±12.6	67.6±34.1	1235±1522	97±104	8.9±15.1	1249±1187	23.3±28.0	17.8	2.92	0.85	46%
2° quartile n. 9	31.5±13.4	71.0±26.9	610±238	34±10	2.4±3.02	518±142	8.6±8.8	13.7	2.25	0.25	50%
3° quartile n. 9	30.5±10.9	66.7±28.7	1670±1489	119±173	9.2±13.3	1459±1320	18,6±18.1	23.0	3.87	0.87	75%
4° quartile n. 9	28.1±9.8	45.9±36.3	2777±1622	191±152	12.2±11.2	2216±1338	43.7±39.1	27.0	4.22	0.78	67%
1° vs 4° quart. p	0.43	0.25	0.03	0.07	0.35	0.03	0.25	0.13	0.08	0.85	0.11

In Crescentic IgAN with Cellular Crescents the Urinary Excretion of the High MW Protein α2-Macroglobulin may be considered a Proteinuric Marker of Podocytes Damage Induced by Cellular Crescents. Journal Of Nephrology & Kidney Diseases. 2022; 4(1):128.

DISCUSSION

The comparison between IgAN PP patients and patients with ClgAN and cellular crescents and between ClgAN patients with cellular versus fibrous crescents shows that in ClgAN with crescents the excretion of α2m/C is markedly higher than other urinary proteins, including the high MW protein IgG/C. The four quartiles of glomeruli with cellular crescents show that the increased number of glomeruli with cellular crescents is associated with increased excretion of α2m/C. Urinary excretion of the high MW protein α2m/C presupposes a severe abnormality of the Glomerular Filtration Barrier (GFB); this suggests that cellular crescents localized in the space between the parietal epithelial cells of Bowman's capsule and podocytes may damage the podocytes and slit-diaphragm allowing the passage of the high MW protein α2m/C. Thus α2m/C excretion may be used as a proteinuric marker for podocyte damage due to the presence of cellular crescents. The role of excretion of α2m/C is further underlined by observing the predictive value of functional outcomes: the 1° quartile of α2m/C in ClgAN patients with cellulars crescents is associated with a 67% remission rate and 0% of progression to ESRD, respectively; by contrast the fourth quartile of α2m/C is associated with 0% remission and 67% progression to ESRD, respectively. The quartiles of glomeruli with cellular crescent show a lower predictive value: 1° quartile: remission 62.5% and ESRD 25%; 4° quartile remission 25% and ESRD 37%. This data suggests that in patients with ClgAN and cellular crescents the urinary excretion of α2m/C is a better outcome predictor than the number of glomeruli with cellular crescents. This difference may depend on the degree of excretion of α2m reflecting an overall global of GFB abnormality; conversely, the number of glomeruli with cellular crescents may depend on the size of the biopsy sample which may differ markedly between patients. Some studies have examined outcomes in Crescentic glomerulonephritis [25] and specifically in IgA Nephropathy [26]. Increases of α2m/C similar to those of ClgAN are observed in Lupus Nephritis with cellular crescents [23] and in MPGN characterized in some patients by the presence of crescents and by an immunofluorescent pattern of granular deposits of C3 and IgG along the capillary walls with a lobular distribution [24].

CONCLUSION

In ClgAN with cellular crescents the excretion of the high MW protein α2m may be considered dependent on the damage induced by crescents on podocytes. In ClgAN with cellular crescents the α2m/C quartiles show a markedly better ability to predict outcomes than the quartiles of glomeruli with cellular crescents, probably due to the difference between α2m excretion associated with overall GFB damage, while the percentage of glomeruli with cellular crescents may be dependent on the various size of the biopsy samples from different patients.

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In Crescentic IgAN with Cellular Crescents the Urinary Excretion of the High MW Protein α2-Macroglobulin may be considered a Proteinuric Marker of Podocytes Damage Induced by Cellular Crescents. Journal Of Nephrology & Kidney Diseases. 2022; 4(1):128.

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