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Research Article

The Patients with Nefroangiosclerosis (NAS) Show Urinary Proteins Excretion Similar but Little Higher than That of IgAN with Persistent Non-Nephrotic Proteinuria (IgAN PP): The Comparison Between them May Clarify this Unexpected Data

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Abstract

Background: In 45 patients with Nephroangiosclerosis (NAS) the excretion of some urinary proteins is little higher than that observed in 125 patients with IgAN with persistent non-nephrotic proteinuria (IgAN PP).

Aim of the study: To analyze the mechanism responsible of the higher value of some urinary proteins in NAS and assess if it is the high value of some histologic parameters in NAS patients the determinant of the increased excretion of some proteins.

Results: The higher values of Global Glomerular Sclerosis (GGS%), Tubulo-interstitial damage score (TID score) and Arteriolar Hyalinosis score (AH score) in NAS patients are associated with significantly higher excretion of some proteins in NAS patients.

Conclusion: The higher values of TID and AH score in NAS probably reduce the reabsorption of some proteins by tubular cells with increase of their excretion.

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Introduction

Most cases of nephrosclerosis (NAS) are diagnosed based solely on clinical findings characterized by long-term essential hypertension, hypertensive retinopathy, left ventricular hypertrophy, minimal proteinuria, and progressive kidney failure; but not all the indicated clinical syndromes such as hypertensive retinopathy, left ventricular hypertrophy and progressive kidney failure are associated with nephrosclerosis. Thus it is preferable to assess the diagnosis of suspected nephrosclerosis by renal biopsy as it can assess several clinical functional, histologic and proteinuric parameters of each patient allowing the complete picture of disease severity and the relationship between histologic markers and clinical, functional and proteinuric markers and the identification of the parameters associated with progression to renal failure [1]. In a 2015 review Meyrier [2] cites clinical and experimental evidence that nephrosclerosis, especially in blacks, can be explained by a genetic renovasculopathy that precedes the rise in blood pressure. He argues that the use of the term nephrosclerosis to classify a patient with kidney failure leads to the possibility of an overlooked nephropathy complicated by hypertension and of the mistaken belief that drastic blood pressure control may retard progression to chronic renal failure. Along several years we diagnosed by renal biopsy 45 patients with nephrosclerosis (NAS) and on the basis of the related minimal proteinuria [1] we make a comparison with 125 patients with IgAN and persistent low non-nephrotic proteinuria (PP) with the aim to compare a vascular with a glomerular disease and assess the difference of clinical, functional histologic and proteinuric parameters between them and assess which parameters are associated with disease severity and progression to renal failure in the two types of nephropathy.

Patients and Methods

The patients cohort included in the study was not selected. The patients attending the Nephrology and Dialysis Unit of San Carlo Borromeo Hospital, Milan, Italy, between January 1992 and April 2006 with renal biopsy diagnosis of Nephroangiosclerosis (NAS, n. 45) and IgAN with persistent non nephrotic proteinuria (IgAN PP, n. 125) were included in the study.

Laboratory analysis

Proteinuria was measured in 24 hours urine collection and second morning urine sample by the Coomassie blue method (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 were measured enzymatically and expressed in mg/dL. Urinary albumin, IgG and α1-microglobulin (α1m) were measured by immunonephelometry; urinary proteins were expressed as urinary protein/creatinine ratio (IgG/C, Alb/C, α1m/C). Estimated glomerular filtration rate (eGFR) was measured by the

	Age	eGFR	High BP	GGS%	TID score	AH score	24hours/P	TUP/C	IgG/C	Alb/C	α1m/C
NAS n. 45	56.9±12.9	63.9±12.2	40 (89%)	21.4±17.8%	2.70±1.50	1.91±0.79	1.35±1.25	783±783	58±98	637±466	17.7±19.8
IgAN & PP n. 125	42.6±17.0	71.6±26.2	53 (42%)	13.9±23.6	1.88±1.68	0.76±0.92	0.69±0.88	487±547	32±47	372±478	10.0±10.7
P value	<0.0001	0.06	0.006	0.017	0.003	<0.0001	0.03	0.02	0.09	0.02	0.016

Table 1: Comparison of all 45 NAS patients with all 125 IgAN PP patients.

	Age	eGFR	High BP	TUP/C	IgG/C	α2-m/C	Alb/C	α1-m/C
NAS all pts n. 45	56.9	63.9	40 (89%)	783	58	0.14	636	17.7
TID score 0 & 1 n. 7 (16%)	54.3	72.1	6 (86%)	529	25	0	360	9.7
TID score 2 & 3 n. 22 (49%)	60.1	67.8	19 (86%)	506	30	0.14	434	27.8
TID score 4 & 6 n. 16 (36%)	42.6	54.8	15 (94%)	1055	81	0	838	30.5
TID score 0 & 1 vs. 4 & 6	0.8	0.06	n.s.	0.02	0.03		0.014	0.09
IgAN PP all patients n. 125				487			372	
P value: all NAS vs. all IgAN PP				0.02			0.02	0.016
IgAN PP all patient n. 125	42.6	71.6	53 (42%)	487	32	0.49	372	10
TID score 0 & 1 n. 55 (44%)	44.8	88.8	16 (29%)	307	17	0.34	207	6.3
TID score 2 & 3 n. 47 (38%)	40.9	66.6	22 (47%)	446	26	0.4	336	8.7
TID score 4 & 6 n. 23 (18%)	40.5	45.5	15 (65%)	999	79	0.99	841	21.7
IgAN PP TID 0 & 1 vs 4 & 6				0.0006	0.001		0.0003	0.0005

Table 2: Comparison of urinary proteins excretion in patients with NAS and IgAN PP according to values of TID score: TUP/C and Alb/C are significantly higher in NAS.

	Age	eGFR bas.	High BP	TUP/C	IgG/C	Alb/C	α1-m/C	GGS%	TID score	AH score
NAS all pts n. 45	56.9	63.9	40 (89%)	783	58	637	17.7	21.4	2.7	1.91
NAS eGFR ≥60 n. 25 (56%)	54.3	79.1	22 (88%)	552	32.3	469	9.7	19.4	2.5	1.96
NAS eGFR< 60 n. 20 (44%)	60.1	44.8	18 (90%)	1071	89.5	846	27.8	23.8	3	1.85
NAS p between eGFR ≥60 and <60	0.14	< 0.0001	0.83	0.04	0.07	0.1	0.005	0.43	0.24	0.64

IgAN PP all pts n. 125	42.6	71.6	53 (42%)	487	31.7	372	10	13.9	1.88	0.76
IgAN PP eGFR≥60 n. 83 (66%)	44.1	85.2	27 (33%)	334	18.7	235	6.3	7.8	1.2	0.51
IgAN PP eGFR<60 n. 42 (34%)	39.6	44.8	26 (62%)	788	57.3	644	17.5	26.1	3.2	1.26
IgA PP p value eGFR ≥ and < 60	<0.0001	0.06	0.006	0.02 ---	0.0002	0.0001	<0.0001	< 0.0001	< 0.0001	<0.0001

Table 3: Comparison of patients with eGFR ≥60 ml/min or <60 ml/min in NAS and IgAN PP.

IgANPP and eGFR<60 n. 42	**Age**	**Basel. eGFR**	**Last eGFR**	**GGS%**	**TID score**	**AH score**	**TUP/C**	**IgG/C**	**Alb/C**	**α1m/C**
IgAN PP eGFR<60 n. 34 (81%) No ESRD n. 34 (81%)	41.2±17.0	47.8±9.4	42.7±17.1	24.3±17.9	3.20±1.4	1.24±0.98	815±627	62±56	671±532	17.6±14.9
IgAN PP eGFR<60 ESRD n. 8 (19%)	41.7±13.5	32.0±5.8	10.5±3.6	38.2±20.4	4.00±1.0	1.87±0.96	1225±1021	102±85	1051±854	18.1±22.0
P 8 ESRD vs 34 no ESRD	0.17	<0.0001	<0.0001	0.08	0.04	0.016	0.12	0.18	0.12	0.84
NAS eGFR < 60 n. 11										
ESRD n. 1* (9%)	73	29	22	50	4	3	4583	542	4002	54.2
eGFR<50% of bas. n.1(9%)	65	38	16	70	4	2	1081	69	1168	9.1

Table 4: Comparison in 42 patients IgAN PP with <60 ml/min not progressing to ESRD [n. 34 (81%)] or progressing to ESRD [n.8 (19%)] and 11 NAS patients with eGFR <60 progressing to ESRD [n. 1 (9%)], not progressing to ESRD [n. 10 (91%)].

1*: This patient is the only NAS patient with proteinuria in nephrotic range.

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [3]. Three types of renal lesions markers of disease severity were evaluated: percentage of glomeruli with global glomerulosclerosis (GGS%); extent of tubulo-interstitial damage (TID) evaluated semi-quantitatively by a score: tubular atrophy, interstitial fibrosis and inflammatory cell infiltration graded 0, 1 or 2 if absent, focal or diffuse (TID global score: 0-6) and extent of Arteriolar Hyalinosis (AH) evaluated semiquantitatively by a score: 0, 1, 2, 3 if absent, focal, diffuse, diffuse with lumen reduction, respectively (AH global score 0-4) [4-5].

Statistical analysis

Continuous variables are expressed as mean±SD. Categorical variables are expressed as the number of patients (%). The differences of mean were determined by t-test; categorical variables by the chi-square test. All statistical analyses were performed using Stata 15.1 (StataCorp LP, TX, USA). Two-sided $p<0.05$ was considered statistically significant [6].

Results

In 45 patients with biopsy diagnosis of nephrosclerosis (NAS) all clinical, functional, proteinuric and histologic parameters were evaluated to visualize the complete picture of characteristics of NAS patients. The age was 56.9±12.9 (29-83), arterial hypertension is present in 40 patients (89%), at biopsy arterial hypertension was present from a mean time of 5.4 years (1-20), the eGFR was 63.9±22.2 (19-108), the value of proteinuric parameters was low: total urinary proteins/C (TUP/C 696±534 :78-2267), IgG/C 98±65 (2.9-305), Alb/C 436±489 (3-1957), α1m 17.7±19.2 (0-69). Global Glomerular Sclerosis (GGS) was 21.4±17.8% (0-70%) tubulo-interstitial-damage score (TID score) 2.70±1.50 (0-6) and Arteriolar hyalinosis score (AH) score was 1.91±0.79 (1-3). Thus the complete evaluation of the characteristics of NAS patients show: higher age, higher frequency of arterial hypertension and rather long duration of arterial hypertension before biopsy, mean value of baseline eGFR little higher than 60 ml/min, low values of proteinuric parameters, high values of GGS%, TID score and AH score. The low urinary excretion of proteinuric parameters and the high values of histologic parameters are in contrast with current opinion: at least in glomerulonephritis the severity of renal lesions is dependent on entity of proteinuria. With the aim to clarify this strange divergence the NAS patients were compared with 125 IgAN patients with non-nephrotic proteinuria (PP) similar to that observed in NAS patients. This comparison shows that the majority of proteinuric markers (24hours/P, TUP/C, IgG/C, Albumin/C and α1m/C) (Table 1) are significantly higher in the vascular disease NAS than in the glomerular disease IgAN PP in contrast with the hypothesis that loos of urinary proteins should be higher in a glomerular disease such as IgAN PP in comparison to a vascular disease mainly characterized by arteriolar hyalinosis.

A possible hypothesis is that the severity of renal lesions in NAS may be dependent from older age in comparison with IgAN PP patients (56.9±12.9 vs 42.6±17.0, $p<0.0001$), higher frequency of high blood pressure (89% vs. 42%; $p = 0.006$) and prolonged duration of arterial hypertension (mean 5.4 years) before renal biopsy. The higher values of proteinuric markers in NAS

versus IgAN PP could be dependent on lower reabsorption of proteins by tubular cells consequent to more severe tubulo-interstitial damage in NAS patients versus IgAN PP patients (TID score 2.70±1.50 vs 1.88±1.68, p= 0.003) (Table 2). The role of histologic pattern in determining the higher values of proteinuric markers in NAS is confirmed by comparison in NAS and IgAN PP the patients with eGFR ≥60 ml/min and those with eGFR < 60 ml/min. In NAS and IgAN PP patients with eGFR < 60 ml/min the histologic pattern and the proteinuric parameters are similar and not significantly different between NAS and IgAN PP. In NAS and IgAN PP with GFR ≥ 60 ml/min the histologic pattern is significantly lower in IgAN PP and values of proteinuric markers are significantly higher in NAS (Table 3). Thus these more severe histological patterns in NAS with eGFR ≥ 60 ml/min reduces the tubular reabsorption of proteins filtered by the glomerular filtration barrier and increase the urinary protein loss [7], presumably mainly for the higher values of tubulo-interstitial-damage score (Table 3).

Discussion and Conclusion

The patients with NAS and IgAN PP rather similar for values of urinary proteins are very different for clinical (age, frequency of high blood pressure) and histologic parameters (GGS%, TID score, AH score). The functional outcome (Table 4) was valuable only in few NAS patients (n. 11) and 42 IgAN PP but unespectedly the progression to renal failure (ESRD, eGFR reduction >50% of baseline) is very similar (18% and 19% respectively). as reported in a study of Carriazo who suggest that hypertensive nephrosclerosis as a cause of end-stage renal disease (ESRD) may not exist at all.

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