

## Review Article

# Is the Amount of Proteinuria the Main Responsible of Renal Lesion and Renal Function Decline? Insights from Comparison between 204 Patients with Glomerulonephritis and Nephrotic Syndrome and 199 with Persistent Non-Nephrotic Proteinuria

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## Abstract

**Aim:** In Glomerulonephritis (GN) the most frequent clinical presentations are Nephrotic Syndrome (NS) and persistent non-nephrotic Proteinuria (PP) characterized by very different amount of proteinuria.

**Purpose of Study:** Compare renal function and renal lesions severity between NS and PP.

**Patients and Methods:** Out of 403 GN patients, 204 NS were compared with 199 PP for baseline eGFR, percentage of Global Glomerular Sclerosis (GGS%) and extent of Tubulo-Interstitial Damage evaluated by a score (TID score: 0=absent, 1-3=focal, 4-6=diffuse). All patients measured some urinary proteins [IgG,  $\alpha$ 2-macroglobulin ( $\alpha$ 2m), albumin and  $\alpha$ 1-microglobulin ( $\alpha$ 1m)] expressed as protein/creatinine ratio and using a new method: ratio of single protein/C to total urinary proteins (protein/C/TUP/C), subsequently indicated as IgG/TUP,  $\alpha$ 2m/TUP, Alb/TUP,  $\alpha$ 1m/TUP.

**Results:** eGFR was not significantly different between NS and PP (70.5 $\pm$ 32.6 and 75.7 $\pm$ 28.1; p=0.083). The GGS% median (7% vs 9%) (p=0.53) and TID scores distribution (0, 1-3, 4-6) (p=0.31) were not significantly different between NS and PP. In NS GGS% groups (0%,  $\geq$ 1%<20%,  $\geq$ 20%) and TID score groups (0, 1-3, 4-6) show significant increase in IgG/TUP,  $\alpha$ 2m/TUP and  $\alpha$ 1m/TUP; PP groups show significant increase only in Alb/TUP. In NS, 39 ESRD patients compared to 98 remitting patients showed significantly higher IgG/TUP,  $\alpha$ 2m/TUP and  $\alpha$ 1m/TUP, while Alb/TUP was not significantly different.

**Conclusion:** In GN, NS and PP are not significantly different for renal function and renal lesions severity notwithstanding the highly significant difference of proteinuric parameters expressed as protein/creatinine ratio. Proteinuria expressed as ratio of single protein/C to TUP/C shows relevant differences in proteinuric pattern composition between NS and PP.

**Keywords:** Glomerulonephritis; Nephrotic Syndrome; Persistent Non-Nephrotic Proteinuria; Renal Function; Renal Lesion Severity

## Introduction

It is well known that in proteinuric Chronic Kidney Disease (CKD) proteinuria is an independent predictor of progression [1,2]. A recent review by Remuzzi et al. [3] posed a question: "Novel Biomarkers for Renal Diseases?"; their answer was "None for the Moment (but One)" stating that "to date it is still uncertain whether and to what extent novel biomarkers will provide diagnostic and prognostic information over and above what is already granted by established, cheap and easily available biomarkers such as proteinuria". Thus assessment of characteristics of proteinuria remains a useful target. The main determinants of proteinuria [4-6] are alterations in the Glomerular Filtration Barrier (GFB) and impaired protein reabsorption by

Proximal Tubular Epithelial Cells (PTECs). GFB integrity is dependent on structural and functional interactions among its three components: the fenestrated endothelium and its cell surface layer, the Glomerular Basement Membrane (GBM) and the epithelial cell layer (podocytes and slit diaphragms). Tubular proteins reabsorption is dependent on integrity of PTECs and their molecular reabsorption machinery that cannot cope with an increased tubular protein load passing through damaged GFB. Consequent to these processes is the variable composition of proteinuria in high (IgG,  $\alpha$ 2-macroglobulin), medium (Albumin) and low ( $\alpha$ 1-microglobulin) Molecular Weight (MW) proteins that is dependent on the main site and severity of GFB and PTECs alterations. Proteinuria is associated with glomerular and tubulo-interstitial compartment damage [1,2]; excessive protein load

**Table 1:** Glomerulonephritis diagnosis and differences of clinical functional and proteinuric parameters between 204 NS and 199 PP patients.

	N	Non-nephrotic proteinuria (n=199)	N	Nephrotic syndrome (n=204)	P
Age, years	199	38.0 (15.3)	204	43.9 (18.4)	0.0006
Men, n (%)	199	120 (60)	204	105 (51)	0.033
Hypertension (BP>140/90), n (%)	199	79 (39)	204	122 (60)	<0.0001
ml/min/1.73m <sup>2</sup>	199	75.7 (28.1)	204	70.5 (32.6)	0.083
Serum albumin, mg/dL (n=401)	199	4.0 (0.5)	202	2.4 (0.7)	<0.0001
Serum IgG, mg/dL (n=401)	197	1150 (956,1462)	204	581 (381,862)	<0.0001
Urinary protein, g/24hour	199	0.6 (0.3,1.4)	204	5.6 (4.0,8.4)	<0.0001
Urinary protein/Cre, mg/gCre	199	401 (137,897)	204	3924 (2150,6039)	<0.0001
Urinary $\alpha$ 2m/Cre (n=392)	189	0 (0,0)	203	4.65 (0,11.42)	<0.0001
Urinary IgG/Cre	199	17.8 (7.5,48.4)	204	138.0 (72.4,332.3)	<0.0001
Urinary albumin/Cre	199	313 (72,670)	204	3281 (1805,5120)	<0.0001
Urinary $\alpha$ 1m/Cre	199	6.8 (3.1,15.4)	204	33.1 (17.5,61.8)	<0.0001
Diagnosis, n (%)	199		204		
CIgAN		22 (11)		15 (7)	
FSGS		6 (3)		40 (20)	
IgAN		125 (63)		2 (1)	
IMN		20 (10)		80 (39)	
LN		20 (10)		29 (14)	
MCD		0 (0)		18 (9)	
MPGN		6 (3)		20 (10)	

on podocytes induces over-expression of TGF- $\beta$ , which may lead to GBM thickening, podocyte apoptosis and detachment, differentiation of mesangial cells into myofibroblasts, increased extracellular matrix production and dysregulation of the balance between extracellular matrix deposition and breakdown with consequent development of glomerulosclerosis. Excessive tubular proteins reabsorption induces the release of cytokines, chemokines, growth factors and vasoactive molecules, leading to tubular cell apoptosis, interstitial inflammatory cell infiltration and extracellular matrix accumulation, ultimately causing interstitial fibrosis and nephron loss. Tubulo-interstitial injury is also caused by hypoxia due to hemodynamic and vascular alterations that reduce interstitial blood flow [7-9]. Moreover, in CKD nephron mass reduction induces glomerular capillary hypertension and impaired glomerular capillary permeability, leading to increased protein loss [10]. The role of proteinuria as a cause of progression has been confirmed by the renoprotective effects of proteinuria reduction obtained by inhibitors of the Renin-Angiotensin System (RAS) [11].

The most frequent clinical presentations in Glomerulonephritis (GN) are nephrotic syndrome (NS) and persistent non-nephrotic Proteinuria (PP). Surprisingly, to our knowledge a systematic study comparing functional, histologic and proteinuric parameters between these two clinical presentations characterized by very different amounts of proteinuria has not so far been undertaken except for one small, dated study involving 15 FSGS patients [12]. First aim of the present study is to assess these differences in a cohort of 199 PP and 204 NS patients with GN. Second aim was to evaluate whether a new method for expression of proteinuria components [ratio of single protein/C to total urinary proteins/C (TUP/C) (afterwards indicated

as IgG/TUP,  $\alpha$ 2m/TUP, Alb/TUP,  $\alpha$ 1m/TUP) that assess percentage of single proteins in relation to total proteinuria, may point out that NS and PP are different not only quantitatively but also in terms of qualitative composition of the proteinuric pattern.

## Patients and Methods

The patients cohort included in the study was not selected. All patients attending the Nephrology and Dialysis Unit of San Carlo Borromeo Hospital, Milan, Italy, between January 1992 and April 2006 who had Renal Biopsy diagnosis of the following types of primary glomerulonephritis and Lupus Nephritis were included in the study (n. 403) [Focal Segmental Glomerulosclerosis (FSGS), Idiopathic Membranous Nephropathy (IMN), Minimal Change Disease (MCD), Membrano-Proliferative Glomerulonephritis (MPGN: type I n. 19; type II n. 1; type III n. 4; fibrillary type n. 2); IgA nephropathy (IgAN), Crescentic IgAN (CIgAN)] and Lupus Nephritis (LN: classes: 2 n.7, 3 n. 6; 3+5 n. 5, 4 n. 20; 4+5 n. 2; 5 n. 9). All patients with persistent non-nephrotic proteinuria at study inclusion were not preceded by nephrotic syndrome.

### Inclusion criteria

Persistent non-nephrotic proteinuria (199 patients: proteinuria <3.5 g/24h and normal serum albumin) or nephrotic syndrome (204 patients: proteinuria  $\geq$ 3.5 g/24h and/or serum albumin 3.0 g/dL); typical features at light and immunofluorescence microscopy; no clinical, imaging or laboratory signs of secondary GN except for LN; at least six glomeruli in renal biopsy. Functional outcomes: progression to End-Stage Renal Disease (ESRD); remission in NS: complete: proteinuria  $\leq$ 0.30 g/24h; partial: proteinuria  $\leq$ 2.0 g/24h;

**Table 2:** Comparison of severity of renal lesions (percentage of Global Glomerular Sclerosis (GGs%), extent of Tubulo-Interstitial Damage (TID) evaluated by a score [TID score: absent (score 0), focal (score 1-3), diffuse (score 4-6)] in 194 PP and 189 NS patients.

	Non-nephrotic proteinuria	Nephrotic syndrome	P
Renal lesions at biopsy (n = 383)	(n = 194)	(n = 189)	
Global glomerular sclerosis, %	9 (0, 20)	7 (0, 17)	0.53
Tubulo-Interstitial Damage score, n (%)			0.31
0	54 (28)	48 (25)	
1	33 (17)	39 (21)	
2	46 (24)	41 (22)	
3	22 (11)	23 (12)	
4	26 (13)	18 (10)	
5	5 (3)	14 (7)	
6	8 (4)	6 (3)	

Number of patients (%) or median (25 percentile, 75 percentile).

**Table 3:** Association between global glomerular sclerosis % (GGs%) and proteinuric parameters expressed as ratio of single protein/C to total urinary protein/C (TUP/C) in PP and NS.

GGs%	Non-nephrotic proteinuria			p for trend	Nephrotic syndrome			p for trend
	0% (n = 82)	1-19% (n = 60)	20-100% (n = 52)		0% (n = 76)	1-19% (n = 68)	20-100% (n = 45)	
Urinary IgG/TUP×1000	53 (32,76)	45 (30,66)	59 (40, 83)	0.067	33 (21,57)	42 (24,80)	57 (38,94)	0.010
Urinary α2m/TUP×1000	0.72 (0.24,1.46)	0.29 (0.15,0.81)	0.23 (0.11,1.22)	0.073	0.49 (0.04,2.20)	1.44 (0.05,3.42)	2.32 (0.07,4.03)	0.022
Urinary Alb/TUP/×1000	631 (380,797)	714 (580,835)	808 (651,901)	0.020	846 (759,938)	846 (745,906)	829 (764,892)	0.037
Urinary α1m/TUP×1000	18.1 (8.2,40.9)	14.2 (6.6,28.0)	21.3 (9.2,35.5)	0.14	7.0 (5.1,10.2)	7.4 (5.5,11.6)	15.1 (10.5,23.8)	<0.001

Median (25 percentile, 75 percentile).

remission in PP: proteinuria  $\leq 0.30$  g/24h and Normal Renal Function (NRF) at last observation. A rather long follow-up was available for 359 patients (NS: 177, PP: 182); mean follow up: NS  $84 \pm 69$  months (2-298); PP:  $63 \pm 38$  months (6-220). The diagnosis and clinical presentation of patients are reported in Table 1.

### Laboratory analysis

Proteinuria was measured in 24 hour 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. Serum and urinary IgG,  $\alpha 2$ -macroglobulin ( $\alpha 2m$ ), Albumin and  $\alpha 1$ -microglobulin ( $\alpha 1m$ ) were measured by immunonephelometry and expressed as urinary protein/creatinine ratio (IgG/C,  $\alpha 2m$ /C, Alb/C,  $\alpha 1m$ /C). Proteinuria has also been expressed by dividing single protein/creatinine ratio by Total Urinary Protein/Creatinine ratio (TUP/C): this method assesses the percentage of high, medium and low MW proteins in relation to total urinary proteins. 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 of assessment of clinical, functional and proteinuric data in 383 patients (189 NS and 194 PP); 20 patients performed renal biopsy some time before and their histological findings were not included. We decided to evaluate only three types of renal lesion that are markers of renal disease severity in any type of CKD: 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 were graded 0, 1 or 2 if absent, focal or diffuse; TID global score: 0-6; extent of Arteriolar Hyalinosis (AH) evaluated semi quantitatively by a score: 0, 1, 2, 3 if absent, focal, diffuse, diffuse with lumen reduction, respectively.

### Statistical analysis

Continuous variables are expressed as means  $\pm$  SD. Urinary markers are expressed as median (25 percentile, 75 percentile). Categorical variables are expressed as the number of patients (%). The differences of mean were determined by t-test, median between the groups by the Wilcoxon rank-sum test, and categorical 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.

### Results

Baseline eGFR is not significantly different between NS and PP ( $70.5 \pm 32.6$  and  $75.7 \pm 28.1$ , respectively;  $p = 0.083$ ) (Table 1), as are not significantly different the percentages of KDOQI classes in NS and PP: Class 1: 32% vs 34%, Class 2: 38% vs 30%, Class 3: 23% vs 26%, Class 4: 5% vs 8%, Class 5: 4% vs 1%, respectively). Severity of renal lesions was evaluated in 189 NS and 194 PP patients by GGs% and extent of tubulo-interstitial damage assessed by a TID score: absent (score 0), focal (score 1-3), diffuse (score 4-6) (Table 2). The GGs% median was not significantly different between NS and PP (7% vs 9%,  $p = 0.53$ ); the distribution of TID scores was not significantly different between NS and PP ( $p = 0.31$ ). Thus eGFR and renal lesions severity were not significantly different between NS and PP despite the significant differences among all proteinuric parameters expressed as protein/creatinine ratio ( $p < 0.0001$  for all parameters) (Table

**Table 4:** Association between Tubulo-Interstitial Damage (TID) absent (score=0), focal (scores 1-3) and diffuse (scores 4-6) and proteinuria parameters expressed as ratio of single protein/C to total urinary protein/C (TUP/C) in PP and NS.

TID score	Non-nephrotic proteinuria			p for trend	Nephrotic syndrome			p for trend
	0 (n=54)	1-3 (n=101)	4-6 (n=39)		0 (n=48)	1-3 (n=103)	4-6 (n=38)	
Urinary IgG/TUP×1000	54 (32,78)	48 (32,67)	65 (43,86)	0.14	26 (20,54)	42 (26,79)	64 (38,97)	<0.001
Urinary α2m/TUP×1000	0.49 (0.18,0.98)	0.46 (0.17,0.12)	0.18 (0.11,1.52)	0.20	0.18 (0.03,1.63)	1.13 (0.04,3.25)	2.97 (1.07,4.08)	<0.001
Urinary albumin/TUP×1000	622 (387,780)	699 (474,822)	824 (713,927)	0.003	823 (736,907)	847 (768,928)	837 (748,911)	0.38
Urinary α1m/TUP×1000	19.5 (6.7,46.4)	16.5 (8.1,33.6)	20.0 (8.3,35.5)	0.22	6.8 (5.0,10.2)	7.6 (5.9,11.8)	15.1 (10.2,23.8)	<0.001

Median (25 percentile, 75 percentile)

**Table 5:** Comparison in NS patients of proteinuric parameters between patients progressing to ESRD (n. 39) and patients entering remission (n=98).

	Nephrotic syndrome				PR emission vs ESRD
	Remission (n=98)		ESRD (n=39)		
GGs%	94	4 (0, 10)	34	13 (3,33)	<0.001
TID sc. diffuse (4-6), n (%)	94	45 (45)	34	15 (44)	<0.001
Urinary IgG/TUP×1000	98	32.0 (21.4,57.1)	39	52.8 (26.1,85.6)	0.014
Urinary α2m/TUP×1000	98	0.22 (0.04,2.33)	39	2.05 (0.53,5.35)	0.004
Urinary albumin/TUP×1000	98	843 (764,918)	39	783 (701,888)	0.098
Urinary α1m/TUP×1000	98	6.75 (5.39,10.7)	39	11.4 (7.8,19.5)	<0.001
Last 24Hp	98	0.39 (0.12,0.75)	38	5.40 (3.40,9.40)	<0.001
Follow-up, months	98	84 (36,160)	39	39 (16,56)	<0.001

Median (25 percentile, 75 percentile) or number of patients (%).

**Table 6:** Comparison in PP patients of proteinuric parameters between patients progressing to ESRD (n. 16) and patients with remission at last observation (n. 73).

	Non-nephrotic proteinuria			P Last NRF and remission vs. ESRD	
	Last normal renal function (eGFR≥60) and remission (proteinuria ≤0.3g/24h) (n=73)		ESRD (n=16)		
GGs%	72	0 (0,10)	14	42.5 (20,57)	<0.001
TID sc. diffuse (4-6), n (%)	72	3 (4)	14	11 (79)	<0.001
Urinary IgG/TUP×1000	73	57.1 (33.8,78.4)	16	65.5 (54.0,91.3)	0.15
Urinary albumin/TUP×1000	73	519 (270,732)	16	805 (705,884)	0.001
Urinary α1m/TUP×1000	73	29.5 (14.1,50.8)	16	17.5 (13.6,24.7)	0.083
Last 24h P	73	0.12 (0.01,0.19)	16	1.99 (1.48,2.40)	<0.001
Follow-up, months	73	72 (38,100)	16	40 (22,77.5)	0.022

Median (25percentile, 75percentile) or number of patients (%)

α2m/TUP is not reported because in PP is dosable only in 20% of patients.

1). The introduction of a new method for expressing proteinuria, ratio between single protein/C to total urinary protein/C (TUP/C) highlights between NS and PP some clinically relevant differences in proteinuric pattern composition. The percentage of patients with GGS%=0%, ≥1% <20% and ≥20% (40%, 36%, 24%, in NS; 42%, 31%, 27%, in PP) was not significantly different between NS and PP. The three GGS% groups (Table 3) showed a significant increase in IgG/TUP (p=0.010), α2m/TUP (p=0.022), Alb/TUP (p=0.037) and α1m/TUP (p< 0.001); in PP the three GGS% groups showed a significant increase only in Alb/TUP (p=0.020). The percentage of patients with TID score absent, focal and diffuse was not significantly different between NS and PP (25%, 56%, 20% in NS; 28%, 52%, 20% in PP). In NS the TID score groups (Table 4) show a significant increase in IgG/TUP (p<0.001), α2m/TUP (p<0.001) and α1m/TUP/C (p<0.001), but not in Alb/TUP (p= 0.38); in PP the TID groups showed a significant increase only in Alb/TUP (p=0.003). In NS, out of 177 patients with functional outcome (Table 5) 39 progressing to ESRD compared to

98 patients with remission were associated with a higher percentage of GGS (p<0.001) and a diffuse TID score (p<0.001) and higher values of IgG/TUP (p=0.0146), α2m/TUP (p=0.0048) and α1m/TUP (p<0.001), while Alb/TUP was not significantly increased (p=0.098). In PP 16 patients (9%) progressing to ESRD compared with 73 with remission (Table 6) were associated with higher percentages of GGS (p<0.001) and with diffuse TID score (p<0.001) and with increased values only of Alb/TUP (p=0.001). These data suggest that between NS and PP proteinuria is different not only in terms of quantity but also of proteinuric pattern composition.

## Discussion

Amount of proteinuria is considered an independent predictor of progression in proteinuric CKD and lowering it by RAS inhibition an effective reno-protective therapeutic option to reduce progression. Moreover, amount and persistence of proteinuria are associated with glomerular and tubulo-interstitial damage. Due to the important role



attributed to amount of proteinuria it is surprising that no GN studies have so far compared the two most frequent clinical presentations, NS and PP, characterized by very different amounts of proteinuria, to assess differences in renal function, severity of renal lesions and characteristics of the proteinuric pattern. Our observational study of 403 patients with GN showed that the level of renal function, frequency of KDOQI classes, severity of renal lesions and frequency of varying degrees of renal lesions are not significantly different between NS and PP, despite the significant different excretion of high, middle and low MW proteins expressed as urinary protein/creatinine ratio. These results are rather unexpected and in broad contrast with the current opinion that the amount of proteinuria is the main factor associated with CKD progression and renal lesions severity and suggest that the amount of proteinuria is not the main and unique responsible for renal lesions and progression to renal failure. A new approach towards expression of proteinuric markers [ratio of single protein/C to total urinary protein/C (TUP/C)] shows that the GGS% groups (GGS%=0,  $\geq 1$  <20 and  $\geq 20$ ) in NS are characterized by significant increase in IgG/TUP,  $\alpha 2m$ /TUP, Alb/TUP and  $\alpha 1m$ /TUP; by contrast in PP the three GGS% groups were different only for Alb/TUP. Also, the severity of TID (absent, focal and diffuse) in NS is characterized by a significant increase in IgG/TUP,  $\alpha 2m$ /TUP and  $\alpha 1m$ /TUP, while in PP the TID groups are significantly different only for Alb/TUP. How very different amounts of proteinuria and a different proteinuric pattern trigger a similar effect on renal function and renal lesion severity deserves to be clarified, but at present only some hypothesis may be suggested. Many animal and human studies have explored how proteinuria causes progressive renal damage; most of these studies focus on the role of albuminuria; few of them on the role of total proteinuria and IgG [13,14]. These studies show that proteinuria “promote apoptotic response and multiple changes in the phenotype of tubular cells with generation of inflammatory and fibrogenic mediators” and up regulation of inflammatory genes, but to date the differences between the various types of clinical presentations have not been analyzed. The predominance of albumin in non-nephrotic proteinuria as assessed by Alb/TUP may be dependent on major alterations in the endothelial cell layer and minor alterations in other GFB components [GBM and epithelial cell layer (podocytes and slit diaphragms)] [15]. The similar severity of renal lesions in PP and NS might suggest that albumin may be the main cause of renal damage in PP, although its level is much lower than in NS (Alb/C: PP:  $524 \pm 660$ ; NS:  $3787 \pm 2497$ ). In support of the role of albumin as responsible of renal lesions and progression, some studies have shown that “albumin-bound fatty acids but not albumin itself alter redox balance in tubular epithelial cells and induce a peroxide-mediated redox-sensitive apoptosis” [16,17]. In NS the predominant alteration of the epithelial cell layer that is the main cause of increased glomerular permeability and higher excretion of high MW proteins may suggest that the excretion of these proteins is the main cause of renal damage. However, at present how these two very different proteinuric patterns in NS and PP trigger a similar effect on renal function and severity of renal lesions remains largely to be elucidated.

## Conclusion

In conclusion, these data suggest that renal function, frequency of KDOQI classes, severity of renal lesions, and frequency of varying

degrees of renal lesions are not significantly different between NS and PP. The similarity between functional and histological data is associated with very different urinary protein excretion expressed as the protein/creatinine ratio. The expression of proteinuria as a ratio of protein/C to total urinary proteins/C shows that NS and PP are different not only in terms of the amount of proteinuria but also of proteinuric pattern composition.

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