Bazzi C, et al., J Nephrol Renal Ther 2021, 7: 055
DOI: 10.24966/NRT-7313/100055

HSOA Journal of Nephrology & Renal Therapy

Research Article

Combined Urinary Excretion of IgG and α2-Macroglobulina Very Simple Marker to Assess Disease Severity, Outcome Prediction and Responsiveness to Steroids and Cyclophosphamide in Patients with Chronic Glomerulonephritis and Nephrotic Syndrome

Claudio Bazzi[1,2]* and Masaomi Nangaku[3]

[1]D'Amico Foundation for Renal Disease Research, Milan, Italy

[2]Retired from Nephrology and Dialysis Unit, San Carlo Borromeo Hospital, Via Pio II, 3, Milan, Italy

[3]Division of Nephrology and Endocrinology, the University of Tokyo Graduate School of Medicine, Tokyo, Japan

Abstract

Background: In Glomerulonephritis (GN) with Nephrotic Syndrome (NS) proteinuric and molecular biomarkers don't reach 100% of outcome prediction and treatment responsiveness. Aim of study: verify whether combined excretion of IgG/C and α2m/C, markers of damage of glomerular filtration barrier, assess disease severity, outcome prediction and responsiveness to steroids and cyclophosphamide.

Methods: 178 GN and NS patients, 151 with long-term outcome, 84 treated with steroids and cyclophosphamide were classified in 4 groups according to excretion of IgG/C and α2m/C: IgG/C0 & α2m/C0, IgG/C0 & α2m/C1, IgG/C1 & α2m/C0, IgG/C1 & α2m/C1. Outcomes were considered in combination: Remission combined with persistent NS with long lasting NRF was indicated "Remission & persistent NRF"; ESRD, eGFR ≤ 50%, persistent NS and progressive eGFR reduction, indicated "Progression & progression risk".

Results: The 4 groups realize a picture of disease severity showing from IgG/C1 & α2m/C1 to IgG/C0 & α2m/C0 eGFR increase and histologic and proteinuric parameters decrease. In 151 patients outcomes were: IgG/C1 & α2m/C1 & high Blood Pressure (BP1): "Remission & persistent NRF": 15%; "Progression & progression risk": 85%; IgG/C0 & α2m/C0 & normal Blood Pressure (BP0): "Remission & persistent NRF": 96%; "Progression & progression risk": 4%. In patients Steroids and Cyclophosphamide treated IgG/C1 & α2m/C1 & BP1: "Progression & progression risk": 100%: "Remission & persistent NRF": 0%; IgG/C0 & α2m/C0 & BP0: "Remission & persistent NRF": 100%: "Progression & progression risk": 0%.

Conclusion: Urinary IgG/C and α2m/C in combination with BP realizes 100% prediction of outcome and responsiveness to Steroids and Cyclophosphamide treatment.

Keywords: Cyclophosphamide; Glomerulonephritis; Nephrotic Syndrome; Urinary Excretion

***Corresponding author:** Claudio Bazzi, D'Amico Foundation for Renal Disease Research, Milan, Italy; Retired from Nephrology and Dialysis Unit, San Carlo Borromeo Hospital, Via Pio II, 3, Milan, Italy, Tel: +39 3388319049; E-mail: claudio.bazzi@alice.it

Citation: Bazzi C, Nangaku M (2021) Combined Urinary Excretion of IgG and α2-Macroglobulina Very Simple Marker to Assess Disease Severity, Outcome Prediction and Responsiveness to Steroids and Cyclophosphamide in Patients with Chronic Glomerulonephritis and Nephrotic Syndrome. J Nephrol Renal Ther 7: 055.

Received: June 16, 2021; **Accepted:** June 23, 2021; **Published:** June 30, 2021

Introduction

Prediction of functional outcome and responsiveness to treatments in Glomerulonephritis (GN) with Nephrotic Syndrome (NS) is of paramount importance in clinical practice and has been the object of several studies in last decades. Some proteinuric biomarkers, mainly low and high Molecular Weight (MW) urinary proteins (α1-microglobulin, β2-microglobulin, IgG, IgM), have been useful to predict remission and progression to ESRD [1-12]. Fractional Excretion of IgG (FE IgG), according to cut offs assessed by ROC analysis, predicted Remission and ESRD in several types of GN (IMN, FSGS, IgAN, Crescentic IgAN, MPGN) [13-21], but no one of these proteinuric markers reachs 100% prediction. Thus it would be very useful for clinical practice to identify a new marker with 100% predictive power. A recent review by Remuzzi et al. [22], 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 the assessment of urinary proteins excretion remains a useful target, taking into account that the excretion of high MW proteins (IgG/C and α2m/C) may be marker of damage of the final Glomerular Filtration Barrier (GFB) (podocytes and slit diaphragms) to filtration of macromolecules [23-26]. A reliable conclusion about predictors of responsiveness to various treatments in GN with NS has not been reached. A large systematic review and meta-analysis [27], of 36 clinical trials including 1762 patients with IMN compared several immuno-suppressive treatments (steroids, steroids in combination with alkylating agents, cyclosporine, tacrolimus, mycophenolate mofetil, adreno-corticotropic hormone, azathioprine and mizoribine) and concluded that corticosteroids in combination with alkylating agents

significantly reduced all-cause mortality and ESRD. In NS the elevated urinary excretion of the high Molecular Weight (MW) proteins IgG (150 kDa) and α2-macroglobulin, (720 kDa) is associated with severe renal disease. The comparison of 4° to 1° quartile of IgG/C shows: highly significant eGFR increase (from 48.3 to 89.7 ml/min/1.73m2, $p < 0.0001$) and significant reduction of GGS% (from 17.5 to 8.3%, $p = 0.005$), TID score (from 2.57 to 1.17, $p = 0.0001$), AH score (from 0.83 to 0.26, $p < 0.0001$) and marked reduction of IgG/C (from 664 to 43, $p < 0.0001$) and α2m/C (from 24.0 to 9.0, $p < 0.0001$). Similar results comparing 4° to 1° quartile of α2m/C. Aim of this study is verify whether the combined excretion of these two proteins, also in association with normal or high Blood Pressure (BP), may be suitable for evaluation of disease severity, prediction of outcome and responsiveness to treatment with steroids and cyclophosphamide.

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 GN with NS were 204; 26 patients with Acute Reversible Renal Failure (ARF) at biopsy were excluded from analysis as do not meet the inclusion criterion (chronic glomerulonephritis); thus 178 patients were the object of this study with the following types of chronic primary Glomerulonephritis (GN) and Lupus Nephritis (LN) with NS (Table 1): Focal Segmental Glomerulosclerosis (FSGS, n. 34), Idiopathic Membranous Nephropathy (IMN, n.74), Minimal change disease (MCD, n. 14), Membrano-proliferative glomerulonephritis (MPGN, n. 18: type I n. 11; type II n. 1; type III n. 4; fibrillary type n. 2); IgA nephropathy (IgAN, n. 2), Crescentic IgAN (CIgAN, n. 13)] and Lupus Nephritis [LN, n. 23: (LN classes: 3+5 n. 3, 4 n. 13; 4+5 n. 2; 5 n. 5)]. Inclusion criteria: nephrotic syndrome (proteinuria ≥ 3.5 g/24h and/or serum albumin < 3.0 g/dL); at least six glomeruli in renal biopsy; typical features at light and immunofluorescence microscopy; no clinical signs of secondary GN except for LN. The functional outcome was available for 151 patients with rather long follow up: mean 85 ± 70 months (2-311). Five types of outcome were considered: 1) Remission of NS: complete: proteinuria ≤ 0.30 g/24h; partial: proteinuria ≤ 2.0 g/24h; 2) persistent NS with long lasting normal Renal Function (NRF) after a follow up of 80 ± 52 months; 3) progression to End-Stage Renal Disease (ESRD); 4) eGFR reduction ≤ 50% of baseline; 5) persistent NS with Chronic Renal Failure (CRF) and progressive eGFR reduction (from 49.3 to 39.1 ml/min/1,72 m2). Usually in prediction studies the outcomes considered are Remission and ESRD (often in combination with eGFR ≤ 50% of baseline). We decided to evaluate not only each type of outcome considered independently but also the combination of outcomes with similar prognostic significance: thus Remission was evaluated in combination with persistent NS with long lasting NRF, afterwards indicated as "Remission & persistent NRF"; ESRD and eGFR ≤ 50% were evaluated in combination with persistent NS with CRF characterized by eGFR reduction from 49.3 to 39.1 ml/min/1,72 m2 and thus candidate for progression to ESRD, afterwards indicated as "Progression & progression risk". 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).

	Nephrotic syndrome (n=178)
Age, years	41.5 ± 17.6
Men, n (%)	94 (84)
Hypertension (BP>140/90), n (%)	124 (60%)
eGFR ml/min/1.73m2	72.3 ± 33.3
Serum albumin, mg/dL (n=401)	2.4 ± (0.7)
Serum IgG, mg/dL (n=401)	688 ± 527
Urinary protein, g/24hour	6.7 ± 4.4
Total urinary protein/Cre, mg/gCre	4538 ± 3108
Urinary α2m/Cre	9.99 ± 16.79
Urinary IgG/Cre	254.6 ± 316.0
Urinary albumin/Cre	3754 ± 2505
Urinary α1m/Cre	49.2 ± 50.3
Diagnosis, n (%)	
CIgAN	13 (7)
FSGS	34 (19)
IgAN	2 (1)
IMN	74 (42)
LN	23 (13)
MCD	14 (8)
MPGN	18 (10)

Table 1: Diagnosis and clinical, functional and proteinuric parameters in 178 patients with glomerulonephritis and nephrotic syndrome.

Serum and urinary creatinine were measured enzymatically and expressed in mg/dL. Serum albumin and IgG and urinary IgG, α2-macroglobulin (α2m), Albumin and α1-microglobulin (α1m) were measured by immunonephelometry; urinary proteins were expressed as urinary protein/creatinine ratio (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 [28]. Three types of renal lesion that are markers of disease severity in any type of GN 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 ordiffuse (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). For all the 178 patients and the 151 with functional outcome was calculated the median of IgG/C (IgG/C0 < median and IgG/C1 > median); the median of α2m/C was calculated independently in IgG/C1 and IgG/C0 patients, respectively and defined α2m/C0 and α2m/C1 if < or > the median; thus 4 groups were defined: IgG/C1 & α2m/C1, IgG/C1 & α2m/C0, IgG/C0 & α2m/C1, IgG/C0 & α2m/C0).

Statistical analysis

Continuous variables are expressed as means±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.

Results

In the 178 patients those with high blood pressure (BP 1, n. 106) show significantly lower values of eGFR, and significantly higher values of TUP/C, IgG/C, α2m/C and α1m/C, GGS%, TID score and AH score in comparison with patients with normal blood pressure (BP 0, n. 72) (Table 2). The patients with IgG/C lower than median (IgG/C0, n. 89) show significantly higher values of eGFR and significantly lower values of TUP/C, IgG/C, α2m/C, Alb/C, α1m/C, GGS%, TID and AH scores in comparison with patients with IgG/C higher than median (IgG/C1, n. 89) (Table 3). The patients with α2m/C lower than median (α2m/C 0, n. 89) showed significant higher values of eGFR and significant lower values of all the proteinuric parameters and TID and AH score in comparison with patients with α2m/C higher than median (α2m/C1, n. 89). The 4 groups defined by combination of IgG/C and α2m/C (IgG/C1 & α2m/C1, IgG/C1 & α2m/C0, IgG/C0 & α2m/C1, IgG/C0 & α2m/C0) realize a reliable picture of disease severity in all 178 patients showing a progressive increase of eGFR and reduction of GGS%, TID score and AH score, TUP/C, IgG/C, α2m/C, Alb/C and α1m/C (Table 4). In 151 patients with functional outcome were reported the clinical, functional, proteinuric and histological data of the 5 type of functional outcome alone and in combination (Table 5); in the same patients were evaluated also the rates of functional outcomes (Table 6): the patients with IgG/C1 & α2m/C1 in combination with BP 1 show 15% of "Remission & persistent NRF" and 85% of "Progression & progression risk"; the patients with IgG/C0 & α2m/C0 in combination with BP 0 show 96% of "Remission & persistent NRF" and 4% of "Progression & progression risk". In 84 patients treated with Steroids and Cyclophosphamide the treatment improves the functional outcome (Table 7): in patients IgG/C1 & α2m/C1 & BP 1 "Remission & persistent NRF" is 0% and "Progression & progression risk" is 100%; in patients with IgG/C0, α2m/C0 and BP 0 "Remission & persistent NRF" is 100% and "Progression & progression risk" is 0%. Very similar results in 30 patients with IMN and NS treated with Steroids and Cyclophosphamide (Table 8).

	Normal BP (BP 0) n. 72 (40%) <140/90 mmHg	High BP (BP 1) n. 106 (60%) ≥ 140/90 mmHG	P
Age yrs	37.6 ± 16.3	44.1±18.1	0.014
eGFR baseline	93. ± 24.8	58.1 ± 30.8	<0.0001
TUP/C	3920 ± 2630	4958 ± 3343	0.02
IgG/C	158 ± 211	320 ± 357	0.0002
α2m/C	7.6 ± 16.9	11.6 ± 16.5	0.12
Alb/C	3355 ± 2357	4025 ± 2577	0.07
α1m/C	30.2 ± 31.4	62.4 ± 56.4	<0.0001
Renal Biopsy	Normal Blood pressure n. 68	High Blood pressure n. 97	
GGS%	4.9±8.5	16.6±18.5	
GGS% 0%	40 (59%)	27 (28%)	
GGS ≥1 < 20%	24(35%)	34 (35%)	
GGS% ≥ 20%	4(6%)	36 (37%)	0.00001
TID score	1.10±1.27	2.45±1.76	
TID score 0	27 (40%)	17 (18%)	
TID score 1-3	37 (54%)	51 (53%)	
TID score 4-6	4 (6%)	29 (30%)	0.0002
AH score	0.24±0.52	0.77±0.85	
AH score 0	55 (81%)	44 (45%)	
AH score 1	10 (15%)	35 (36%)	
AH score 2-3	3 (4%)	18 (19%)	0.00005

Table 2: Baseline clinical, functional, histologic and proteinuric data in 178 patients with chronic glomerulonephritis (GN) and nephrotic syndrome (NS) with normal or high blood pressure.

Discussion

The prediction of functional outcome and responsiveness to treatments in GN and NS is of paramount importance in clinical practice. Several studies in last decades evaluated the predictive power of functional outcome of several proteinuric and novel molecular biomarkers but none of them reached 100% prediction. The identification of a new marker with high outcome prediction would be useful also to assess responsiveness to new therapies introduced recently such as Rituximab. A recent article [28], "New insight into podocyte slit diaphragm, a therapeutic target of proteinuria" reviews the extracellular molecular components forming a molecular sieve of the slit diaphragm and the cytoplasmic molecules that link the slit diaphragm to the cytoskeleton; on the basis of increased knowledge of molecular components of podocytes and slit diaphragm, the Authors hope the definition of novel therapeutic strategy for proteinuria reduction but at present no one proteinuric or molecular marker may evaluate the extent of damage of podocytes and slit diaphragm and predicts outcome and treatment responsiveness. The proteinuric marker proposed for the first time in this study evaluating the combined excretion of two high MW proteins (IgG, 150 kDa and α2-macroglobulin, 720 kDa), may be considered on the basis of functional, histologic and proteinuric data a reliable marker of disease severity and damage of the epithelial cell layer of GFB (podocytes and slit-diaphragms) and may be useful to predict outcome and responsiveness to treatments. The IgG/C1 & α2m/C1 group, associated with the highest excretion of IgG/C (577) and α2m/C (29.52), suggest severe alteration of the epithelial cell layer of GFB (podocytes and slit-diaphragms) and the association with the lowest value of baseline eGFR (47.7 ml/min/1.72 m2) and the highest values of the histologic and proteinuric parameters (GGS% 17.7%, TID score 2.73 and AH score 0.78, TUP/C 6562, Alb/C 5023 and α1m/C 96.8). These data suggest the ability of this marker to identify the patients with the highest level of disease severity. By contrast the marker IgG/C0 & α2m/C0 associated with the lowest excretion of IgG/C (53) and α2m/C (0) and with the highest value of baseline eGFR (92.3 ml/min/1,72 m2) and the lowest values of the histologic and protenuric parameters (GGS%, 5.1%, TID score 0.90, AH score 0.24; TUP/C 2620, IgG/C 53, α2m/C 0, Alb/C 2330 and α1m/C 17.5) suggest the ability of this marker to identify the patients with the lowest level of disease severity. The 4 groups of IgG/C and α2m/C in combination, show a high predictive value of functional outcome both for "Remission &persistent NRF" and "Progression & progression risk". In 84 patients treated with Steroids and Cyclophosphamide the combination of IgG/C0 & α2m/C0 with normal blood pressure (BP 0) is associated with the highest values of eGFR and the lowest values of histologic and proteinuric parameters; the functional outcome reachs 100% of "Remission & persistent NRF" and 0% of "Progression & progression risk". The combination of IgG/C1 & α2m/C1 with high blood pressure (BP 1) is associated with worsening of all the parameters and 100% of "Progression & progression risk" and 0% of "Remission & persistent NRF". To reach the highest rate of functional outcome it is necessary a combination

	IgG/C < Median n. 89	IgG/C > Median n. 89	P	α2m/C < Median n. 89	α2m/C > Median n. 89	P
Age yrs	41.6±17.7	41.3±17.7	0.90	41.3±17.1	41.6±18.2	0.90
eGFR baseline	85.2±29.4	59.4±32.0	<0.0001	82.0±30.3	62.6±33.4	<0.0001
TUP/C	2820±1718	6256±3242	<0.0001	3503±2563	5573±3271	<0.0001
IgG/C	72±34	437±364	<0.0001	124±132	385±387	<0.0001
α2m/C	3.35±7.57	16.56±20.48	<0.0001	0.49±1.56	19.6±19.6	<0.0001
Alb/C	2563±1796	4945±2555	<0.0001	3020±2291	4488±2508	<0.0001
α1m/C	23.2±17.6	76.5±58.3	<0.0001	29.5±26.4	69.2±60.0	<0.0001
Renal Biopsy	n. 82	n. 83		n. 83	n. 81	
GGS%	9.5±15.6	14.1%		10.6±16.7	13.0±15.6	
GGS% 0%	41 (50%)	26 (31%)		39(47%)	28 (35%)	
GGS% ≥ 1 < 20%	26 (32%)	32 (39%)		28 (34%)	29 (36%)	
GGS% ≥ 20%	15 (18%)	25 (30%)	0.09	16 (19%)	24 (29%)	0.33
TID score	1.50±1.64	2.29				
TID score 0	31 (38%)	13 (16%)		31 (37%)	13 (16%)	
TID score 1-3	38 (46%)	50 (60%)		42 (51%)	45 (56%)	
TID score 4-6	13 (16%)	20 (24%)	0.014	10 (12%)	23 (28%)	0.0056
AH score	0.40±0.73	0.70				
AH score 0	59 (72%)	40 (48%)		56 (67%)	42 (52%)	
AH score 1	15 (18%)	30 (36%)		20 (24%)	25 (31%)	
AH score 2-3	8 (10%)	13 (16%)	0.02	7 (8%)	14 (17%)	0.18
High blood pressure	41 (46%)	65 (73%)	0.13	44 (49%)	65 (73%)	0.11

Table 3: Baseline clinical, functional, histologic and proteinuric data in 178 patients with chronic Glomerulonephritis (GN) and Nephrotic Syndrome (NS) with IgG/C < and > its median and α2m/C < or > its respective median.

	IgG/C1 & α2m/C1 n. 45 RB n. 41	IgG/C1 & α2m/C0 n. 44	IgG/C0 & α2m/C1 n. 44	IgG/C0 & α2m/C0 n. 45 RB n. 41	IgG/C1 & α2m/C1 vs. IgG/C0 & α2m/C0 p
Age yrs	39.7±17.7	42.9±17.8	40±17	43.7±18.5	0.31
eGFR baseline	47.7±30.2	71.4±29.7	77.8±32.1	92.3±24.7	<0.0001
TUP/C	6562 ±2862	5942±3597	3025±1411	2620±1968	<0.0001
IgG/C	577±447	294±158	90±28	53±28	<0.0001
α2m/C	29.52±21.91	3.32±3.40	6.85±9.71	0±0	<0.0001
Alb/C	5023±2227	4865 ±2877	2802±1579	2330±1975	<0.0001
α1m/C	96.8±69.8	53.7±31.9	28.9±19.9	17.5±12.9	<0.0001
GGS 0%	8			25	
GGS >1 < 20%	16			13	
GGS ≥ 20%	17			3	0.0002
TID score 0	4			22	
TID score 1-3	23			17	
TID score 4-6	14			2	0.00005
AH score 0	18			32	
AH score 1-4	23			9	0.006
BP 1 ≥ 140/90	32 (71%)	33 (75%)	26 (59%)	15 (33%)	
BP 0 < 140/90	13 (29%)			30 (67%)	0.001

Table 4: Disease severity in 178 patients with GN and NS classified in 4 groups according to the following combination:

1) (IgG/C1 & α2m/C1): IgG/C > median and α2m/C > median n. 45 patients.

2) (IgG/C1 & α2m/C0): IgG/C > median and α2m/C < median n. 44 patients.

3) (IgG/C0 & α2m/C1): IgG/C < median and α2m/C > median n. 44 patients.

4) (IgG/C0 & α2m/C0: IgG/C < median and α2m/C < median n. 45 patients.

	Remission n. 76	PNS & last NRF n. 11	ESRD n. 39	PNS CRF n. 15	eGFR ≤ 50% n. 10	Remission & PNS NRF n. 87	ESRD & PNSCRF& eGFR≤50% n. 64	P value
Age yrs	42.0±17.6	34.7±13.5	41.4±19.7	44.7±15.8	40.1±17.2	41.1±17.2	42.0±18.3	n.s.
eGFR baseline	87.9±24.5	95.1±18.8	45.6±29.0	48.4±20.9	66.1±27.1	88.8±28.9	49.5±27.6	<0.0001
eGFR last	79.6±23.6	88.1±20.7	8.0±2.7	38.5±12.7	26.2±10.6	80.7±23.3	18.0±15.1	<0.0001
Follow up months	112±85	79±59	41.0±32	59.0±61	106±56	108±83	55±49	<0.0001
TUP/C	3888±2611	3195±1921	6956±3596	4446±1510	3228±2426	3800±2535	5785±3552	0.0002
IgG/C	144±143	150±159	383±315	354±452	283±460	145±144	361±370	<0.0001
α2m/C	4.9±13.6	6.8±8.8	18.9±20.4	11.3±18.3	10.0±13.3	5.2±13.1	15.8±19.3	0.0002
Alb/C	3335±2311	2766±1729	5498±2679	3675±2057	2619±1716	3263±2246	4621±2648	0.001
α1m/C	28.6±25.3	20.6±15.7	86.7±46.1	56.4±49.0	48.6±44.5	27.6±24.4	73.7±48.7	<0.0001
GGS%	5.8±4.6	4.6±6.0	19.7±20.9	21±12	26±23	6±8	21±19	<0.0001
TID score	1.21±1.12	1.09±1.81	2.79±1.97	3.38±1.71	2.40±1.43	1.19±1.22	2.86±1.83	<0.0001
AH score	0.29±0.57	0.09±0.30	0.94±0.77	1.00±1.15	0.60±0.84	0.26±0.54	0.89±0.88	<0.0001
Last 24/ hour proteinuria	0.54±0.53	5.76±4.71	7.30±6.15	4.08±2.81	3.54±2.05	1.20±2.42	5.96±5.30	<0.0001
BP 1 blood pressure ≥ 140/90 mmHg	36 (47%)	2 (18%)	33 (85%)(	13 (87%)	65 (60%)	38 (44%)	52 (81%)	0.02

Table 5: Clinical, functional, proteinuric and histologic parameters in 151 patients with different functional outcome.

	IgG/C1 & α2m/C1 & BP 1 n. 26	IgG/C1 & α2m/C1 n. 38	IgG/C1 & α2m/C0 n. 38	IgG/C0 & α2m/C1 n. 37	IgG/C0 & α2m/C0 n. 38	IgG/C0 & α2m/C0 & BP 0 n. 26	IgG/C1 & α2m/C1 vs. IgG/C0 & α2m/C0 p
Age yrs	41.1±18.9	38.0±17.4	42.5±17.5	42±.4±18.0	43.0±17.8	42.8±18.4	0.22
eGFR basel	36.0±21.4	49.7±29.6	71.2±27.9	73.8±31.1	93.9±23.8	99.9±21.5	<0.0001
eGFR last	21.2±22.6	31.6±34.0	44.1±33.0	59.1±34.9	81.9±26.1	88.8±23.5	<0.0001
FU up months	70±75	68±71	77±58	77±70	113±78	117±73	0.011
TUP/C	6331±2817	6292±2708	6180±3897	3384±1820	2677±1958	2917±2232	<0.0001
IgG/C	489±358	439±315	319±339	128±140	57±28	56±28	<0.0001
α2m/C	29.83±20.67	28.74±23.46	5.15±6.87	2.95±4.34	1.43±3.30	1.17±3.33	<0.0001
Alb/C	4979±2003	4896±1940	5068±3013	2973±1758	2394±2014	2635±2309	<0.0001
α1m/C	93.9±48.2	80.4±49.7	54.3±42.4	35.3±30.9	18.2±12.4	18.7±14.4	<0.0001
GGS%	23.5±16.5	18.1±16.6	10.1±13.1	14.0±19.7	6.0±10.6	4.9±10.9	0.0009
TID score	3.52±1.58	2.89±1.71	1.78±1.66	1.75±1.68	1.11±1.31	0.85±0.97	0.0009
AH score	1.16±0.85	0.89±0.87	0.50±074	0.59±0.84	0.14±0.35	0.15±0.37	0.0008
BP 1 ≥ 140/90 mmHg		26 (68%)	33 (75%)	26 (59%)	12 (32%)	12 (32%)	0.06
Remission & PNS NRF	4 (15%)	10 (26%)	17 (45%)	25 (68%)	34 (89%)	25 (96%)	
ESRD &PNS CRF & eGFR ≤ 50%	22 (85%)	28 (74%)	21 (55%)	12 (32%)	4 (11%)	1 (4%)	

Table 6: Disease severity in 151 patients with GN and NS and functional outcome evaluated by eGFR, proteinuric and histologic data according to the 4 groups of IgG/C and α2m/C in combination between them and with BP 1 or 0.

of normal or high blood pressure also in patients treated with steroids and cyclophosphamide. Very similar results in 30 patients with IMN and NS treated with Steroids and Cyclophosphamide.

Conclusion

The combined urinary excretion of IgG/C and α2m/C realizes a reliable evaluation of disease severity in 178 patients with chronic glomerulonephritis and NS, in 151 patients with a long term functional outcome and in 84 patients treated with Steroids and Cyclophosphamide; in these last patients not only assess disease severity but also achieves 100%of outcome prediction: the patients with IgG/C1 & α2m/C1 & and BP 1 show 100% of "Progression & progression risk" and 0% of "Remission & persistent NRF"; the patients with IgG/C0 & α2m/C0 & and BP 0 show 100% of "Remission & persistent NRF"

	IgG/C1 & α2m/C1 & BP 1 n. 14	IgG/C1 & α2m/C1 n. 21	IgG/C1 & α2m/C0 n. 21	IgG/C0 & α2m/C1 n. 21	IgG/C0 & α2m/C0 n. 21	IgG/C0 & α2m/C0 & BP 0 n. 15	IgG/C1 & α2m/C1 vs. IgG/C0 & α2m/C0 p
Age yrs	46±20	42±18	37±18	38±16	41±19	37±18	0.83
eGFR baseline	31.2±19.1	46.0±29.9	74.1±27.4	67.1±26.6	97.9±25.3	105.9±22.4	<0.0001
eGFR last observ.	16.3±14.8	33.8±37.4	48.5±35.5	46.8±34.3	85.7±25.7	93.9±20.1	<0.0001
Follow up months	66±72	68±70	96±79	85±85	117±76	114±67	0.03
TUP/C	5933±2125	5795±2043	7373±4406	3781±2223	3194±2423	3543±2683	0.0005
IgG/C	448±196	434±181	101±148	112±41	63±32	53±31\	<0.0001
α2m/C	24.97±13.3	26.64±23.0	6.00±4.34	6.76±7.65	0.12±0.54	0±0	<0.0001
Alb/C	4823±1645	4639±1676	3376±5982	3310±1975	3258±2592	3408±2881	0.02
α1m/C	91.6±37.3	79.4±45.3	56.2±29.3	37.9±20.8	18.8±10.4	19.2±10.8	<0.0001
GGS%	29.8	22.2	9.05	16.3	4.5	5.0	0.003
TID score	4.15	3.32	2.33	2.57	1.15	0.87	0.011
AH score	1.08	0.79	0.57	0.71	0.30	0.13	0.017
BP 1 ≥ 140/90 mmHg	14 (100%)	14(67%)	14 (67%)	15 (71%)	6 (29%)	6 (40%)	0.13
Remission & persistent NS with NRF	0 (0%)	(19%)	(48%)	(62%)	34 (89%)	(100%)	
ESRD &PNS CRF & eGFR ≤ 50%	14 (100%)	(81%)	(52%)	(38%)	1 (4%)	(0%)	

Table 7: Baseline functional, proteinuric and histologic parameters and functional outcome according to the 4 groups of IgG/C and α2m/C also in combination with BP 1 or BP 0 in 84 patients treated with Steroids and cyclophosphamide.

	IgG/C1 & α2m/C1 & BP 1 n. 5	IgG/C1 & α2m/C1 n. 8	IgG/C1 & α2m/C0 n. 7	IgG/C0 & α2m/C1 n. 8	IgG/C0 & α2m/C0 n. 7	IgG/C0 & α2m/C0 & BP 0 n. 5	IgG/C1 & α2m/C1 vs IgG/C0 & α2m/C0 p
Age yrs	54.2±16.1	47.1±18.1	41.3±18.1	46.4±19.9	54.9±17.3	54.4±20.9	0.41
eGFR baseline	40.4±15.6	51.7±27.7	56.9±18.4	70.6±21.6	90.7±20.9	88.6±26.0	0.008
eGFR last observ	25.4±18.7	42.2±37.6	47.6±22.8	41.7±28.5	83.7±21.8	81.4±26.0	0.02
Follow up months	74±59	90±70	103±62	101±95	128±85	124±71	0.37
TUP/C	6522±1355	5903±1696	4163±1319	4010±1646	2404±1398	2250±2035	0.002
IgG/C	505±140	465±156	270±105	106±31	44±24	41±21	0.0001
α2m/C	19.7±8.3	18.6±7.2	4.9±2.6	6.6±5.0	0±0	0±0	0.0001
Alb/C	5929±1236	5283±1673	3449±954	3608±1587	2254±1648	2021±1709	0.004
α1m/C	121.4±22.0	103.5±52.6	42.5±5.8	36.4±13.1	15.1±7.2	13.9±8.4	0.002
GGS%	28.6±20.8	21.0±19.0	13.4±16.6	14.3±27.4	3.1±4.3	4.4±4.6	0.04
TID score	3.40±1.34	2.75±1.39	1.43±1.40	1.37±1.06	0.57±0.79	0.60±0.89	0.04
AH score	1.00±0.71	0.75±0.71	1.14±1.07	0.50±0.53	0.29±0.49	0.40±0.55	0.55
BP≥ 140/90 mmHg	5 (100%)	5 (62,5%)	5 (71%)	5 (62.5%)	2 (29%)	0 (0%)	0.42
Remission & PNS NRF	0 (0%)	2 (25%)	5 (71%)	4 (50%)	7 (100%)	5 (100%)	
ESRD & PNS CRF & eGFR ≤ 50%	5 (100%)	6 (75%)	2 (29%)	(50%)	(0%)	(0%)	

Table 8: Baseline functional, proteinuric and histologic parameters and functional outcome according to IgG/C and α2m/C groups in combination with BP 1 and BP 0 in 30 patients with IMN and NS treated with Steroids and cyclophosphamide.

and 0% of "Progression & progression risk". This new proteinuric marker could be very useful to assess functional outcome with new treatments such as Rituximab.

Acknowledgment

We thank Dr. Pietro Napodano for the analysis of renal biopsies.

References

1. Branten AJ, du Buf-Vereijken, Klasen IS, Bosch FH, Feith GW, et al. (2005) Urinary excretion of beta2-microglobulin and IgG predict prognosis in idiopathic membranous nephropathy: A validation study. J Am Soc Nephrol 16: 169-174.

2. Deegens JK, Wetzels JF (2007) Fractional excretion of high- and low-molecular weight proteins and outcome in primary focal segmental glomerulosclerosis. Clin Nephrol 68: 201-208.

3. Tofik R, Torffvit O, Tippe B, Bakoush O (2009) Increased urine IgM excretion predicts cardiovascular events in patients with type 1 diabetic nephropathy. BMC Med 7: 39.

4. Tofik R, Aziz R, Reda A, Rippe B, Bakoush O (2011) The value of IgG-uria in predicting renal failure in idiopathic glomerular diseases. A long-term follow up study. Scand J Clin Lab Invest 71: 123-128.

5. Tofik R, Ekelund U, Torffvit O, Sward P, Rippe B, et al. (2013) Increased urinary IgM excretion in patients with chest pain due to coronary artery disease. BMC Cardiovasc Disord 13: 72.

6. van der Brand JAJG, Hofstra JM, Wetzels JFM (2011) Low-molecular-weight proteins as prognostic markers in idiopathic membranous nephropathy. Clin J Am Soc Nephrol 6: 2846-2853.

7. Bakoush O, Grubb A, Rippe B, Tencer J (2001) Urine excretion of protein HC in proteinuric glomerular diseases correlates to urine IgG but not to albuminuria. Kidney Int 60: 1904-1909.

8. Bakoush O, Torffvit O, Rippe B, Tencer J (2001) High proteinuria selectivity index based upon IgM is a strong predictor of poor renal survival in glomerular diseases. Nephrol Dial Transplant 16: 1357-1363.

9. Bakoush O, Tencer J, Tapia J, Rippe B, Torffvit O (2002) Higher urinary IgM excretion in type 2 diabetic nephropathy compared to type 1 diabetic nephropathy. Kidney Int 61: 203-208.

10. Bakoush O, Torffvit O, Rippe B, Tencer J (2003) Renal function in proteinuric glomerular diseases correlates to the changes in urine IgM excretion but not to the changes in the degree of albuminuria. Clin Nephrol 59: 345-352.

11. Bakoush O, Segelmark M, Torffvit O, Ohlsson S, Tencer J (2006) Urine IgM excretion predicts outcome in ANCA-associated renal vasculitis. Nephrol Dial Transplant 21: 1263-1269.

12. Irazabal MW, Eirin A, Lieske J, Beck LH, Sethi S, et al. (2013) Low- and high-molecular weight proteins as predictors of response to rituximab in patients with membranous nephropathy: A prospective study. Nephrol Dial Transplant 28: 137-146.

13. Bazzi C, Petrini C, Rizza V, Paparella M, Pisano L, et al. (2002) In Membrano-Proliferative Glomerulonephritis (MPGN) fractional excretion of IgG correlates with tubulo-interstitial damage and predicts ESRF and remission in response to therapy. Journal of American Society of Nephrology.

14. D'Amico G, Bazzi C (2003) Pathophysiology of proteinuria. Kidney Int 63: 809-825.

15. Bazzi C, Petrini C, Rizza V, Napodano P, Paparella M, et al. (2003) Fractional excretion of IgG predicts renal outcome and response to therapy in primary focal segmental glomerulosclerosis: A pilot study. Am J Kidney Dis 41: 328-335.

16. Bazzi C, Rizza V, Raimondi S, Casellato D, Napodano P, et al. (2009) In crescentic IgA nephropathy fractional excretion of IgG in combination with nephron loss is the best predictor of progression and responsiveness to immunosuppression. Clin J Am Soc Nephrol 4: 929-935.

17. Park EY, Kim TY (2011) Fractional excretion of protein may be a useful predictor of decline of renal function in pan-chronic kidney diseases. Nephrol Dial Transplant 26: 1746-1747.

18. Mc Quarrie EP, Shakerdi L, Jardine AG, Fox JG, Mackinnon B (2011) Fractional excretions of albumin and IgG are the best predictors of progression in primary glomerulonephritis. Nephrol Dial Transplant 26: 1563-1569.

19. Bazzi C, Rizza V, Casellato D, Stivali G, Rachele G, et al. Validation of some pathophysiological mechanisms of the CKD progression theory and outcome prediction in IgA nephropathy. J Nephrol 25: 810-818.

20. Bazzi C, Rizza V, Casellato D, Stivali G, Rachele G, et al. (2013) Urinary IgG and α2-macroglobulin are powerful predictors of outcome and responsiveness to steroids and cyclophosphamide in idiopathic focal segmental glomerulosclerosis with nephrotic syndrome. Biomed Res Int 2013: 941831.

21. Bazzi C, Rizza V, Casellato D, Tofik R, Berg AL, et al. (2014) Fractional excretion of IgG in idiopathic membranous nephropathy with nephrotic syndrome: A predictive marker of risk and drug responsiveness. BMC Nephrol 15: 74.

22. Gentile G, Remuzzi G (2016) Novel biomarkers for renal diseases? None for the moment (but One). J Biomol Screen 21: 655-670.

23. Menon MC, Chuang PY, He CJ (2012) The glomerular filtration barrier: Components and crosstalk. Int J Nephrol 2012: 749010.

24. Haraldsson B, Nystrom J, Deen WM (2008) Properties of the glomerular barrier and mechanisms of proteinuria. Physiol Rev 88: 451-487.

25. Miner JH (2011) Glomerular basement membrane composition and filtration barrier. Pediatr Nephrol 26: 1413-1417.

26. Kawachi H, Fukusumi Y (2020) New insight into podocyte slit diaphragm, a therapeutic target of Proteinuria. Clin Exp Nephrol 24: 193-204.

27. Chen Y, Schieppati A, Cai G, Chen X, Zamora J, et al. (2013) Immunosuppression for membranous nephropathy: A systematic review and meta-analysis of 36 clinical trials. Clin J Am Soc Nephrol 8: 787-796.

28. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, et al. (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150: 604-612.

HERALD

Advances In Industrial Biotechnology | ISSN: 2639-5665

Advances In Microbiology Research | ISSN: 2689-694X

Archives Of Surgery And Surgical Education | ISSN: 2689-3126

Archives Of Urology

Archives Of Zoological Studies | ISSN: 2640-7779

Current Trends Medical And Biological Engineering

International Journal Of Case Reports And Therapeutic Studies | ISSN: 2689-310X

Journal Of Addiction & Addictive Disorders | ISSN: 2578-7276

Journal Of Agronomy & Agricultural Science | ISSN: 2689-8292

Journal Of AIDS Clinical Research & STDs | ISSN: 2572-7370

Journal Of Alcoholism Drug Abuse & Substance Dependence | ISSN: 2572-9594

Journal Of Allergy Disorders & Therapy | ISSN: 2470-749X

Journal Of Alternative Complementary & Integrative Medicine | ISSN: 2470-7562

Journal Of Alzheimers & Neurodegenerative Diseases | ISSN: 2572-9608

Journal Of Anesthesia & Clinical Care | ISSN: 2378-8879

Journal Of Angiology & Vascular Surgery | ISSN: 2572-7397

Journal Of Animal Research & Veterinary Science | ISSN: 2639-3751

Journal Of Aquaculture & Fisheries | ISSN: 2576-5523

Journal Of Atmospheric & Earth Sciences | ISSN: 2689-8780

Journal Of Biotech Research & Biochemistry

Journal Of Brain & Neuroscience Research

Journal Of Cancer Biology & Treatment | ISSN: 2470-7546

Journal Of Cardiology Study & Research | ISSN: 2640-768X

Journal Of Cell Biology & Cell Metabolism | ISSN: 2381-1943

Journal Of Clinical Dermatology & Therapy | ISSN: 2378-8771

Journal Of Clinical Immunology & Immunotherapy | ISSN: 2378-8844

Journal Of Clinical Studies & Medical Case Reports | ISSN: 2378-8801

Journal Of Community Medicine & Public Health Care | ISSN: 2381-1978

Journal Of Cytology & Tissue Biology | ISSN: 2378-9107

Journal Of Dairy Research & Technology | ISSN: 2688-9315

Journal Of Dentistry Oral Health & Cosmesis | ISSN: 2473-6783

Journal Of Diabetes & Metabolic Disorders | ISSN: 2381-201X

Journal Of Emergency Medicine Trauma & Surgical Care | ISSN: 2378-8798

Journal Of Environmental Science Current Research | ISSN: 2643-5020

Journal Of Food Science & Nutrition | ISSN: 2470-1076

Journal Of Forensic Legal & Investigative Sciences | ISSN: 2473-733X

Journal Of Gastroenterology & Hepatology Research | ISSN: 2574-2566

Journal Of Genetics & Genomic Sciences | ISSN: 2574-2485

Journal Of Gerontology & Geriatric Medicine | ISSN: 2381-8662

Journal Of Hematology Blood Transfusion & Disorders | ISSN: 2572-2999

Journal Of Hospice & Palliative Medical Care

Journal Of Human Endocrinology | ISSN: 2572-9640

Journal Of Infectious & Non Infectious Diseases | ISSN: 2381-8654

Journal Of Internal Medicine & Primary Healthcare | ISSN: 2574-2493

Journal Of Light & Laser Current Trends

Journal Of Medicine Study & Research | ISSN: 2639-5657

Journal Of Modern Chemical Sciences

Journal Of Nanotechnology Nanomedicine & Nanobiotechnology | ISSN: 2381-2044

Journal Of Neonatology & Clinical Pediatrics | ISSN: 2378-878X

Journal Of Nephrology & Renal Therapy | ISSN: 2473-7313

Journal Of Non Invasive Vascular Investigation | ISSN: 2572-7400

Journal Of Nuclear Medicine Radiology & Radiation Therapy | ISSN: 2572-7419

Journal Of Obesity & Weight Loss | ISSN: 2473-7372

Journal Of Ophthalmology & Clinical Research | ISSN: 2378-8887

Journal Of Orthopedic Research & Physiotherapy | ISSN: 2381-2052

Journal Of Otolaryngology Head & Neck Surgery | ISSN: 2573-010X

Journal Of Pathology Clinical & Medical Research

Journal Of Pharmacology Pharmaceutics & Pharmacovigilance | ISSN: 2639-5649

Journal Of Physical Medicine Rehabilitation & Disabilities | ISSN: 2381-8670

Journal Of Plant Science Current Research | ISSN: 2639-3743

Journal Of Practical & Professional Nursing | ISSN: 2639-5681

Journal Of Protein Research & Bioinformatics

Journal Of Psychiatry Depression & Anxiety | ISSN: 2573-0150

Journal Of Pulmonary Medicine & Respiratory Research | ISSN: 2573-0177

Journal Of Reproductive Medicine Gynaecology & Obstetrics | ISSN: 2574-2574

Journal Of Stem Cells Research Development & Therapy | ISSN: 2381-2060

Journal Of Surgery Current Trends & Innovations | ISSN: 2578-7284

Journal Of Toxicology Current Research | ISSN: 2639-3735

Journal Of Translational Science And Research

Journal Of Vaccines Research & Vaccination | ISSN: 2573-0193

Journal Of Virology & Antivirals

Sports Medicine And Injury Care Journal | ISSN: 2689-8829

Trends In Anatomy & Physiology | ISSN: 2640-7752