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Research Article

The Different Degree of Severity Intrinsically Present in Each Type of Renal Lesions [Arteriolar Hyalinosis (Ah Score), Tubulo-Interstitial-Damage Score (TID Score), Global Glomerular Sclerosis (GGS%) are a Very Simple Predictor of Functional Outcome and High Blood Pressure Frequency in Glomerulonephritis Patients

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Abstract

Background: In chronic glomerulonephritis (GN) the patients have different types of renal lesions: the more frequent lesions are: Global Glomerular Sclerosis evaluated by percentage (GGS%); Tubulo- Interstitial-Damage evaluated 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); Arteriolar Hyalinosis evaluated by a score: 0, 1, 2, 3 if absent, focal, diffuse, diffuse with lumen reduction, respectively (AH global score 0- 3). The aim of the study was to assess the predictive value of outcome and high blood pressure according to the data of different severity in each type of renal lesion.

Methods: 363 patients were evaluated according to GGS%, 362 according to TID score, 361 according to AH score.

Results: Remission was 76% in patients with AH score=0; 80% in patients with TID score =0; 81% in patients with GGS % =0. Progression to ESRD was 48% in patients with TID score 5+6, 45% in GGS≥50% and 12% in AH score=3. The frequency of high blood pressure (BP1) was 38% vs 81% in AH =0 vs AH=3; 70% vs 86% in patients with TID score=0 vs TID score 5+6; 32% vs 83% in GGS=0% and GGS≥50%. In every type of renal lesion, the patients with remission and progression to ESRD are very different for baseline and last eGFR and for all proteinuric parameters.

Conclusion: In chronic glomerulonephritis and nephroangiosclerosis the different degrees of severity that characterize evry single renal lesion are a very simple and useful marker for prediction of functional outcome and high blood pressure frequency in comparison to renal lesion as such.

Introduction

The key role of renal lesions assessed by renal biopsy for CKD progression is widely recognized. In patients with glomerulonephritis are present different types of renal lesions; the more frequent are : Global Glomerular Sclerosis evaluated by percentage (GGS%), Tubulo-Interstitial-Damage valuable by a score of severity: tubular atrophy, interstitial fibrosis and inflammatory cell infiltration graded 0, 1 or 2 if absent, focal or diffuse (TID global score: 0-6); Arteriolar Hyalinosis evaluated by a score: 0, 1, 2, 3 if absent, focal, diffuse, diffuse with lumen reduction, respectively (AH global score 0-3). The role of each renal lesion may be considered as such or taking into account that each type of lesion includes different degree of severity that are useful to identify different percentages of the various outcomes. In the majority of previous studies, the prediction of functional outcome was mainly based on urinary excretion of various types of proteins with different molecular weight (2-28). To my knowledge no one publication evaluated the clinical significance of the different degree of severity of renal lesion. Aim of this study is to assess which is the percentage of the main functional outcome [Remission and Progression to ESRD] according to the different severity that characterizes evry renal lesions. The patients with 0 value in any type of renal lesion are associated with the highest percentage of Remission: 81% in GGS%=0, 80% in TID score=0, 76% in AH score=0; ESRD is 52% in TID score 5+6, 45% in GGS≥50% and 12% in AH score=3. The outcomes Remission and ESRD in each type of renal lesion are characterized by different values of clinical parameters such as age, baseline and last eGFR, percentage of GGS, values of TID and AH score, excretion of

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total proteinuria (TUP/C) and of proteins of different molecular weight.

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 were 469; the patients with acute reversible renal failure (ARF) at biopsy were excluded from analysis as do not meet the inclusion criterion (chronic glomerulonephritis); for the objective of the present study were selected only the patients with a follow up and outcome; thus 363 patients were the object of this study with the following types of chronic primary glomerulonephritis (GN), Nephroangiosclerosi (n. 20) and Lupus Nephritis (LN n. 36; [WHO classes: 3+5 n. 5, 4 n. 16; 5 n. 5, 3 n. 5, 2 n. 5)], (Table 1): Focal Segmental Glomerulosclerosis (FSGS, n. 38), Idiopathic Membranous Nephropathy (IMN, n. 81), Minimal change disease (MCD, n. 12), Membrano-proliferative glomerulonephritis (MPGN, n. 18); IgA nephropathy (IgAN, n. 124), Crescentic IgAN (CIgAN, n. 34), Nephroangosclerosis (n. 20). Inclusion criteria: at least six glomeruli in renal biopsy; typical features at light and immunofluorescence microscopy; no clinical signs of secondary GN except for LN. The patients evaluated by TID score are 362, by GGS% are 363 and by Arteriolar Hyalinosis score are 361.

The functional outcome was available for the 361-363 patients with rather long follow up: mean 74±60 months (12-354). Four types of outcomes were considered: 1) Remission 2) progression to end-stage renal disease (ESRD); 3) eGFR reduction ≤ 50% of baseline). We decided to consider as outcomes Remission and ESRD. Diagnosis and clinical presentation of patients are reported in Table 1.

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: UP/C). Serum and urinary creatinine were measured enzymatically and expressed in mg/dL. Urinary albumin IgG and α1-microglobulin (α1m) were measured by immunonephelometry and expressed as urinary protein/creatinine ratio (IgG/C, Alb/C, α1m/C). Estimated glomerular filtration rate (eGFR) was measured by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (1). Three types of renal lesions as 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 semi-quantitatively by a score: 0, 1, 2, 3 if absent, focal, diffuse, diffuse with lumen reduction, respectively (AH global score 0- 4) (Table 2).

Results

Remission was 76% in patients with AH score=0; 80% in patients with TID scor =0; 81% in patients with GGS %=0. Progression to ESRD was 48% in patients with TID score 5+6, 45% in GGS≥50% and 12% in AH score 3. The frequency of high blood pressure (BP1) was 38% vs 81% in AH =0 vs AH=3; 70% vs 86% in patients with TID score=0 vs TID score 5+6; 32% vs 83% in GGS=0% and GGS≥50%. In evry type of renal lesion the patients with remission were very different from patients with ESRD for baseline and last eGFR and for all proteinuric parameters.

Table 1: Diagnosis of patients included in the study and comparison between normal and high blood pressure.

GN diagnosis	NAS	CIgaN	IgAN	FSGS	MCD	IMN	LN	MPGN
N. patients 363	20	34	124	38	12	81	36	18

	Age	eGFR	eGFR last	Follow up	AH score	GGS%	TID score	TUP/C	IgG/C	α2m/C	Alb/C	α1m/C
Pts with normal BP n. 175	39.2	87.2	80.6	78.8	0.41	7.5	1.30	1790	74	2.77	1954	21.0
Pts with high BP n. 188	44.7	57.6	51.2	70.0	0.92	18.6	2.57	2933	198	7.86	1983	34.6
	<0.0001	<0.0001	<0.0001	0.17	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	0.0003	0.90	0.0004

Table 2: Functional Outcome and High Blood Pressure according to Arteriolar Hyalinosis (AH) score, Tubulo-interstitial damage (TID) score and percentages of Global Glomerular Sclerosis (GGS%).

Art. Hyalinosis. Sc. / n. patients n. 361	Remission	ESRD	High BP
AH = 0 n. 198	151 (76%)	11 (6%)	38%
AH = 1 n. 99	55 (56%)	21 (21%)	63%
AH = 2 n. 48	13 (27%)	14 (29%)	73%
AH = 3 n. 16	5 (31%)	2 (12%)	81%

TID score n. 362	Remission	ESRD	High BP
TID sc = 0 n. 90	72 (80%)	6 (7%)	70%
TID sc 1 & 2 n. 153	112 (73%)	12 (8%)	44%
TID sc 3 & 4 n. 90	36 (40%)	17 (19%)	74%
TID sc 5 & 6 n. 29	4 (14%)	14 (48%)	86%

GGS% n. 263	Remission	ESRD	High BP
GGS% = 0 n. 141	114 (81%)	9 (6%)	32%
GGS%>1%<20% n. 127	83 (65%)	13 (10%)	51%
GGS% ≥ 20 <50 n. 66	22 (33%)	15 (23%)	82%
GGS% ≥ 50 n. 29	5 (17%)	13 (45%)	83%

Table 3: Percentages of Remission and progression to ESRD in patients according to Arteriolar hyalinosis score (n.361).

Art. Hyalinosis. Sc. n. 361 patients in pts n. 361	Age	eGFR basel	eGFR last	Foll.up	High BP	GGS%	TID score	UPC/C	IgG/C	α2m/C	Alb/C	α1m/C	Last 24h/P
AH = 0 n. 198	40	85.7	79.8	79	38%	5.5	1.22	2428	122	4.79	2014	20.7	1.62
AH = 1 n. 99	44.9	79	54.9	74	63%	20.1	2.46	2547	176	6.87	2111	35.7	1.9
AH= 2 n. 48	42.5	47.7	38.9	64	73%	25.8	3.31	1962	93	5.76	1565	31.4	1.74
AH= 3 n. 16	46.9	45.2	37.9	55	81%	24.2	3.6	1977	224	5.24	1595	39.4	1.6

Art. Hyalinosis. Sc.	Age	eGFR bas	eGFR last	Foll. up	High BP	GGS%	TID score	UTP/C	IgG/C	α2m/C	Alb/C	α1m/C	Last 24h/P
AH = 0 Remission n. 151	38.9	91.1	90.8	84	20%	4.2	0.64	1960	88	3.66	1669	15.5	0.48
AH = 1 Remission n. 55	45.6	76.2	76.7	81	33%	14.4	1.91	2108	122	3.5	1697	21.4	0.65
AH = 2 Remission n. 13	41.3	64.8	76	78	61%	13.5	2.38	811	45	3.67	652	17.9	0.47
AH 3 Remission n. 5	50.6	55.6	51.2	66	81%	18.4	3	1066	91	1.35	941	20.7	1.16
AH = 0 ESRD n. 11	39.8	63.4	6.7	36	73%	2.6	1	8166	412	17.04	5999	78.4	10.37
AH = 1 ESRD n. 21	45.6	34.2	9.3	55	81%	29.9	3.42	4525	364	14.07	3817	79.3	4.97
AH = 2 ESRD n. 14	37.7	33.1	9	43	79%	30.6	4.21	3516	137	10.94	2864	46.2	3.33
AH 3 ESRD n. 2	46.5	29.5	10	24	75%	50	4.66	2795	276	0	2314	64	3.25

Table 4: Percentages of Remission and progression to ESRD in patients accoding to Tubulo-interstitial damage score (TID score n. 363 patients).

TID score n. 362	Remission	ESRD	High BP
TID sc= 0 n. 90	72 (80%)	6 (7%)	70%
TID sc =1 n. 67	56 (84%)	4 (6%)	44%
TID sc= 2 n. 86	56 (65%)	8 (9%)	51%
TID sc= 3 n. 45	27 (60%)	5 (11%)	74%
TID sc= 4 n. 45	9 (20%)	12 (27%)	86%
TID sc= 5 n. 18	1 (6%)	11 (61%)	89%
TID sc= 6 n. 11	3 (27%)	4 (36%)	82%

Table 5: Percentages of Remission and progression to ESRD in patients according to Tubulo-Interstitial Damage score (TID score n. 363 patients).

TID score	Age	eGFR	eGFR last	Follow	High BP	GGS%	TID score	UPC/C	IgG/C	α2m/C	Alb/C	α1m/C	Last 24 h P
TID sc = 0 Rem. n. 72	40.8	94	91.7		54 (47%)	1.9	0	1767	64	1.25	1536	13-1	0.42
TID sc= 1 Rem. n. 56	39.8	86.7	84.9		40 (80%)	6.7	1	1972	81	5.35	1620	17.1	0.43
TID sc= 2 Rem. n. 56	43	73.5	70		18 (82%)	11.6	2	1960	113	2.95	1628	23.2	0-70
TID sc= 3 Rem, n. 27	43	60.2	57.4		1 (100%)	16.2	3	2926	224	9.83	2344	37.1	0-70
TID sc= 4 Rem n. 9	44.2	44.5	34.9		5 (83%)	28.3	4	2356	175	7.72	1955	38.2	0.51
TID sc= 5 Rem n. 1	37.7	27.4	19.8		7 (64%)	40.8	5	2490	186	8.36	2064	58.7	0.3
TID sc= 6 Rem n. 3	38.3	58.6	43.1		8 (100%)	25.8	4.5	2576	141	25.05	5488	80.3	0.91
TID sc= 0 ESRD n. 6	38.3	90.2	89.5		54 (47%)	4.3	1.22	3781	165	6.52	3268	26.2	10.5
TID sc= 1 ESRD n. 4	47.2	66.4	66.7		40 (80%)	11.7	1.71	4660	259	6.96	3787	43.5	0.25
TID sc= 2 ESRD n. 8	46	30	51		18 (82%)	35	4	2665	164	13.58	2314	40.3	4.75
TID sc= 3 ESRD n. 5	24	36	79		1 (100%)	50	5	1413	68	6.92	1202	13.5	4.98
TID sc=4 ESRD n. 12	36.9	67.3	6.7		5 (83%)	2.9	0.7	8844	437	18.54	6488	83.6	3.06
TID sc=5 ESRD n. 11	48.1	28.9	8.7		7 (64%)	23.6	3.18	5449	438	17.7	4595	96.3	3.62
TID sc=6 ESRD n. 4	36.5	40.2	7.8		8 (100%)	25.8	4.5	6800	258	25.05	5488	80.3	4.46

Table 6: Percentages of Remission and progression to ESRD according to percentage of Global Glomerular Sclerosis (GGS% n. 361 patients).

GGS% n. 363 patients	Remission	ESRD	High BP
GGS 0% n. 141	114 (81%)	9 (6%)	37 (26%)
GGS≥1<20% n. 127	83 (65%)	13 (10%)	55 (43%)
GGS≥20<50% n. 66	22 (33%)	15 (23%)	34 (52%)
GGS≥50% n. 29	5 (17%)	13 (45%)	23 (79%)

	Age	eGFR	eGFR last	Foll. up	High BP	GGS%	TID score	TUP/C	IgG/C	α2 m/C	Alb/ C	α1m/C
GS 0% n. 141	41.1	90.8	83.5	67.1	37 (24%)	2.55	0	2222	102	3.56	1838	18.8
GGS≥1<20% n. 126	42.9	78.9	73.4	78.7	55 (30%)	9.25	1.58	2163	121	4.69	1818	23.3
GGS≥20<50% n. 67	44.6	54.6	46.1	80.7	34 (31%)	22.7	3.52	2355	175	7.19	1920	34
GGS≥50% n. 29	38.3	42.9	29.3	43.4	34 (76%)	36.5	5.47	2353	186	6.89	1929	46.4

Table 7: Functional outcome in 67 patients with IMN, 35 with FSGS and 14 with MPGN according to Arteriolar Hyalinosis score.

GGS% patients	Age	eGFR	eGFR last	Fol. up	High BP	GGS%	TID score	TUP/C	IgG/C	α2m/C	Alb/C	α1m/C	Last 24hP
GGS 0% Rem. n. 114	38.3	90.2	89.5		54(47%)	4.3	1.22	3781	165	6.52	3268	26.2	0.42
GGS≥1<20% Rem. n. 83	47.2	66.4	66.7		40 80%)	11.7	1.71	4660	259	6.96	3787	43.5	0.6
GGS≥20<50% Rem. n. 22	46	30	51		18(82%)	35	4	2665	164	13.58	2314	40.3	0.94
GGS≥50% Rem. n. 5	41.6	70.4	79.2		3 (60%)	57.2	4.2	667	40	2.27	541	14.5	0.49
GGS 0% ESRD n 9	36.9	67.3	6.7		5 (83%)	2.9	0.7	8844	437	18.54	6488	83.6	13.31
GGS≥1<20% ESRD n. 13	48.1	28.9	8.7		7 (64%)	23.6	3.18	5449	438	17.7	4595	96.3	4.6
GGS≥20<50% ESRD n. 15	36.5	40.2	7.8		8(100%)	25.8	4.5	6800	258	25.05	5488	80.3	3.81
GGS≥50% ESRD n. 13	42	73.5	9.3		11(85%)	56.2	4.6	2367	199	3.56	1990	48.8	3.1

Art. Hyalinosis. Sc. in 67 IMN NS pts	Remission	PNS	ESRD	eGFR<50%
AH = 0 n. 43	25 (58%)	10 (23%)	6 (14%)	2 (5%)
AH = 1 n. 21	10 (48%)	4 (19%)	6 (29%)	1 (5%)
AH = 2 n. 3	1 (33%)	0 (0%)	0 (0%)	2 (67%)

Art. Hyalinosis. Sc. in 35 FSGS NS pts	Remission	PNS	ESRD	eGFR<50%
AH = 0 n. 25	17 (68%)	4 (16%)	4 (16%)	0 (%)
AH = 1 n. 7	5 (71%)	0 (0%)	2 (29%)	0 (0%)
AH = 2 n. 3	0 (0%)	1 (33%)	2 (67%)	0 (0%)

Table 8: Functional outcome according to renal lesions (AH sc., TID sc., GGS%) in combination.

Art. Hyalinosis. Sc. in 14 MPGN NS pts	Remission	PNS	ESRD	eGFR<50%
AH = 0 n. 5	3 (60%)	1 (20%)	0 (0%)	1 (20%)
AH = 1 n. 7	3 (43%)	0 (0%)	3 (43%)	1 (14%)
AH = 2 n. 2	0 (0%)	0 (0%)	2 (67%)	0 (0%)

	Remission	PNS	ESRD	eGFR<50%
AH 0 & GGS 0% n. 55	40 (73%)	8 (15%)	6 (11%)	1 (2%)
GGS 0% & TID sc, 0 n. 27	19 (70%)	5 (19%)	3 (11%)	0 (0%)
AH 0 & TID sc. 0 n. 39	25 (64%)	8 (21%)	5 (13%)	2 (15%)
AH 2 & TID sc. 3-6 n. 13	2 (15%)	3 (23%)	6 (46%)	3 (30%)
AH 2 & GGS% 7-60 n. 13	2 (15%)	3 (23%)	6 (46%)	2 (15%)

Table 9: Percentage of high blood pressure according to quartiles of IgG/C and α1m/C.

Quartili IgG/C	% of High Blood Pressure	Quartili α1m/C	% of High Blood Pressure
1° quart. n. 1 – 117	45 (38%)	1° quar n. 1 – 117	45 (38%)
2° quart n. 118 - 234	63 (54%)	2° quar n. 118-234	63 (54%)
3° quart n. 235 – 351	54 (55%)	3° quar n. 235-351	65 (56%)
4° quart n. 352 – 468	80 (68%)	4° quart n.352-468	79 (68%)

Comparison of patients with nephrotic syndrome (NS) and patients with non-nephrotic proteinuria (PP).

Table 10: Functional outcome in 67 patients with IMN, 35 with FSGS and 14 with MPGN according to Comparison of Remission and ESRD between patients with persistent nephrotic syndrome (NS: KI). according to: no therapy, teraphy with Steroids and Cyclophosphamide and teraphy with only steroids

Pts with NS and PP n. 469	Age	eGFR	eGFR last	Fol. up	High BP	GGS%	TID score	TUP/C	IgG/C	α2m/C	Alb/C	α1m/C	Last 24hP
Remission NS+PP n. 231	40.9	84.9	85.2			7.6	1.37	2021	96	3.47	1692	18.1	0.53
Remission NS n. 98	40.7	82	82.1			6.9	1.42	4100	187	6.42	3474	32.2	0.55
ESRD NS and PP n. 57	41.7	41.6	8.6			29.7	3.18	5276	297	13.51	4182	71.7	5.78
ESRD NS n. 39	41.3	45.6	8.02			19.7	2.79	6956	374	18.95	5497	86.7	7.3

Remission n. 97 patients	Age	eGFR	eGFR last	Fol. up	High BP	GGS%	TID score	TUP/C	IgG/C	α2m/C	Alb/C	α1m/C	Last 24hP
Rem. ther 0 n. 22		90.7	81.8			5.9	1.29	2437	92	3.11	1955	16.6	0.64
P Rem ther0 vs Rem th2		0.86	0.55			0.91	0.37	0.0001	0.001	0.04	<0.0001	<0.0001	0.56
Rem. ster&cyclo2 n. 55	40.8	81,3	85		54 (47%)	6.2	1.58	4454	210	8.41	3836	34.2	0.56
Rem ther steroids n. 20	39.8	86.7	84.9			6.7	1	1972	81	5.35	1620	17.1	0.43
ESRD n. 39 patients													
ESRD ther. 0 n. 14	43	60.2	57.4			21.7	3	2926	224	9.83	2344	37.1	0-70
ESRD st&cyclo 2 n. 23	44.2	45.7	7.7		5 (83%)	21.7	3.09	7134	309	15.76	5862	80.9	8.58
P Rem 2 vs ESRD ther 2		<0.0001	<0.0001			<0.0001	0.002	0.006	0.06	0.05	0.007	<0.0001	<0.0001
ESRD only ster. n. 2													

Discussion

The prediction of functional outcome and responsiveness to treatments in GN patients 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 simple marker with high outcome prediction would be very useful also to assess responsiveness to new therapies introduced recently.

Conclusion

The 3 types of renal lesions considered in this study are all characterized by increasing severity that is for Global Glomerular Sclerosis the percentage of GGS; for Tubulo-Interstitial-Damage the evaluation of a score from 0 to 6 (indicated in the methods paragraph); also Arteriolar hyalinosis is evaluated by a score from 0 to 3 (indicated in methods paragraph); the various markers of severity of each type of renal lesion are a very simple predictors of functional outcome and percentage of high blood pressure.

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