The Functional Outcome of Normal or High Blood Pressure in Patients with Chronic Glomerulonephritis and Nephrotic Syndrome is Dependent on Association with Functional, Histologic and, Proteinuric Parameters

Claudio Bazzi

Received: 31 December 2021 Accepted: 27 January 2022 Published: 8 February 2022

Abstract

Background: Normal (BP0)or high blood pressure (BP1)are variably present in patients with chronic glomerulonephritis (GN) and Nephrotic Syndrome (NS). At biopsy each BP0 or BP1 patient is associated with different values of renal function, urinary proteins excretion and renal lesions severity [GGS

Index terms—

1 Introduction

he clinical significance of arterial hypertension in renal diseases has been evaluated in several studies (1)(2) **??**3) **??**4) **??**5)(6)(7)(8)(9)(10)(11)(12). In a cohort of 151 patients with chronic glomerulonephritis (GN) and nephrotic syndrome (NS) normal (BP 0) and high blood pressure (BP 1) are present with variable percentage according to several factors: eGFR ? or < 60 ml /min73.1 m2; GGS: 0% vs ? 20%; TID score 0 vs 4 -6; AH score 0 vs 2-3, TUP/C <vs ? median and combined excretion of IgG/C and ?2m/C groups (for these groups definition see later in Laboratory analysis Section).The combination of each patient with one or more functional, histologic and proteinuric parameters and eventual treatment with Steroids and Cyclophosphamide is associated with different percentages of favourable outcome (Remission and PNS with long lasting NRF": briefly defined "noprogr.") or unfavourable outcome (ESRD & eGFR< 50% of baseline & PNS with CRF: briefly defined "progr"). Aim of the study: assess how high blood pressure increases according to lower values of eGFR and increased values of the main histological parameters such as Global Glomerular Sclerosis (GGS%), extent of tubulo-interstitial damage (TID score) and Arteriolar Hyalinosis (AH score) and how functional outcome may improve or worse according with the association with these functional, proteinuric and histologic parameters.

2 II.

3 Patients and Methods

The patients cohort included in the study was not selected.

4 Laboratory Analysis

Proteinuria was measured in 24 hour urine collection and second morning urine sample by the Coomassie blue method (modified with sodiumdodecyl-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 albumin and IgG and urinary IgG, ?2macroglobulin (?2m), Albumin and ?1-microglobulin (?1m) were measured by immunonephelometry; urinary proteins were expressed as urinary protein/creatinine ratio (IgG/C, ?2m/C, Alb/C, ?1m/C). Estimated glomerular filtration rate (eGFR) was measured by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (13). Three types of renal lesions that are markers of disease severity in any type of GN were evaluated: percentage of glomeruli

9 OUTCOME IN BP0 AND BP1 PATIENTS ACCORDING TO VALUE OF TID SCORE [0 (ABSENT) VERSUS TUBULAR ATROPHY, INTERSTITIAL FIBROSIS AND INFLAMMATORY CELL INFILTRATION DIFFUSE (SCORE 4-6)].

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); 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). In our recent study (14)in151 patients with GN and NS, were calculated the median of IgG/C (IgG/C 0<median and IgG/C1>median); the median of ?2m/C was calculated independently in IgG/C 1 and IgG/C 0 patients, respectively and defined ?2m/C 0 and ?2m/C 1 if < or > the median. On the basis of combination of IgG/C and ?2m/C medians were defined 4 groups:IgG/C 1 & ?2m/C 1, IgG/C 1 & ?2m/C 0, IgG/C 0 & ?2m/C 1, IgG/C 0 & ?2m/C 0) more briefly defined (1+1, 1+0, 0+1, 0+0

). These groups assess disease severity of all patients: moreover the combination of BP 1 with (1+1) group and BP 0 in combination with (0+0) group predict 100% of "progr" and 100% of "noprogr" respectively (Table 3).

IV.

5 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 chisquare test. All statistical analyses were performed using Stata 15.1 (StataCorp LP, TX, USA). Two-sided p<0.05 was considered statistically significant.

V.

6 Results

The functional outcome has been evaluated according to the highest and lowest values of eGFR (?vs< 60 ml/min), GGS 0% vs ? 20%, TID score 0 vs 4-6 and AH score 0 vs 2-3. The outcome was classified as "noprog" (remission and persistent NS with long lasting normal renal function) and "progr" (ESRD, eGFR< 50% of baseline and persistent NS with CRF). In general the patients with more severity of renal function and histological parameters show an increase of percentage of patients with high blood pressure, while the patients with eGFR ? 60 ml/min, GGS 0%, TID score 0 and AH score 0 usually show an increase of patients with normal blood pressure. The functional outcome was also evaluated according to groups of combined urinary excretion of IgG/C & ?2m/C (0+0, 0+1, 1+0, 1+1).

7 Outcome in BP 0 and BP 1 patients according to level of renal function eGFR ? or < 60 ml/min.

In all the 151 patients with GN and NS 61 patients (40%) have normal blood pressure (BP 0) and 90 patients (60%) have high blood pressure (BP 1); In 61 BP 0 patients "No progr" is 80% and "Progr." 20%; in 90 BP 1 patients "no progr." 42% and "progr." is 58% (Table 2). BP 0 and BP 1 are highly significant different for baseline and last eGFR, IgG/C, ?1m/C, GGS%, TID score and AH score (Table 1).

In eGFR ? 60 ml/min/1.73 m2 the patients are 97: BP 0 n. 57 (59%) and BP 1 n. 40 (41%); in BP 0 "no progr" is 82% and "progr" 18%;in 40 patients BP 1 "noprogr " is 72.5% and "progr" 27.5%. In eGFR< 60 ml/min the patients are 54: BP 0 are n. 4 (7%) and BP 1 are n. 50 (93%); in the 4 BP 0 "noprogr" is 25% and "progr" 75%;in the 50 patients BP 1 "no progr" is 18% and " Progr" is 82% (Table 2).

8 Outcome in BP0 and BP1 patients according to percentages of global glomerular sclerosis (GGS 0% versus GGS ? 20%).

The patients with GGS 0% (n. 53) were compared with patients with GGS ?20% (n. 34). In patients with GGS 0% (n.53) the BP 0 are 34 (64%) and BP1 19 (36%); the 34 BP0 show 85% of "noprogr" and 15 % progr". The 19 BP1show: 15 (79%) of "noprogr" and 4 (21%) of "progr". In patients with GGS? 20% (n. 34) the BP 0 are 2(6%) and BP1 are 32 (94%); the 2 BP0 show 1 "noprogr" (50%) and 1 "progr" (50%); the 25 BP1 patients show 78% of "noprogr" and (22%) of "progr".

9 Outcome in BP0 and BP1 patients according to value of TID score [0 (absent) versus tubular atrophy, interstitial fibrosis and inflammatory cell infiltration diffuse (score 4-6)].

The patients with absent tubulo-interstitial damage (TID score: 0, n. 39) were compared with patients with focal or diffuse tubular atrophy, interstitial fibrosis and inflammatory cell infiltration (TID score: 4-6, n. 27). In patients with TID 0 the BP 0 are 24 (62%) and BP1 15 (38%); the 24 BP0 show 96% of "noprogr" and 4% of "progr" ; the 15 BP1show 53% of "noprogr" and 47% of "progr". In patients with TID score 4-6 BP 0 are 2 (7%) and the BP 1 are 25 (93%): the BP 0 Show 0% of "noprogr" (0%) and 1(100%) of "progr"; the BP1 show 4% of

"no progr" and 96% of "progr". Thus the functional outcomes are rather different as in the BP1 patients with TID score 0 "progr" is 47%, while in BP1 patients with TID score 4-6 the "progr" is 96%.

10 Outcome in BP0 and BP1 patients according to value of AH (arteriolar hyalinosis) absent (0) and arteriolar hyalinosis diffuse (2) and diffuse with lumen reduction (3).

In patients with AH score 0 the patients are n. 86 with BP 0 is n.48 (56%) and BP 1 n. 38 (44%): the 48 BP 0 patients show 41 (85%) of "no progr" and 7 (15%) of "Progr". In patients with BP 1 (n.38) "noprogr" is 22 (58%) and "progr" is 16 (42%).

In patients with AH score 2-3 (2: diffuse arteriolar hyalinosis, 3: diffuse arteriolar hyalinosis with lumen reduction) BP 0 are2 (outcome not valuable); the BP1 patients are n. 14: "noprogr" n. 2 (14%) and "Progr." n. 12 (86%).

11 Outcome in BP 0 and BP 1 patients according to the groups of combined urinary excretion of IgG/C & ?2m/C (0+0, 0+1, 1+0, 1+1).

The 0+0 group in combination with BP0 and with Steroids and Cyclophosohamide treatment (n. 15 patients) show 100% of "noprogr" and 0% of "progr". The 1+1 group in combination with BP1 and Steroids and Cyclophosphamide treatment (n. 14 patients) "noprogr" is 0% and "progr." is 100%.

In the groups 0+1 and 1+0 (n. 55 patients) treated with Steroids and Cyclophosphamide "noprogr" are 32 patients (58%) and "progr" are 23 (42%).

12 VI.

13 Discussion

In 151 patients with GN and NS the percentage of normal blood pressure (BP 0) is lower [n. 61 (40%)] than that of high blood pressure (BP 1) [n. 90 (60%)]. The percentages of BP 0 and BP 1 are influenced by level of renal function (eGFR ? or $<$ 60 ml/min) with increase of percentages of BP 0 in patients with eGFR ? 60 ml/min (59%) and increase of percentages of BP 1 (93%) in patients with eGFR$<$ 60 ml/min. These variations in percentages of BP 0 and BP 1 changes the outcome: "noprogr" is reduced from 42% to 18% in BP 1 patients associated with eGFR$<$ 60 ml/min and "progr" increases from 58% to 82% in BP 0 associated with eGFR ? 60ml/min. Similar observations by comparison of GGS 0% with GGS ? 20% that show a reduction of "noprogr" from 42% to 22% and increases the percentage of "progr" from 58% to 78%. Similar observations evaluating TID score and AH score. These data show that the functional outcome in BP 0 and BP 1 is dependent on association with functional, proteinuric and histologic parameters. This observation allow to suggest that the combination in evry patient of BP with eGFR, GGS%, TID score and AH score may be a predictor functional outcome at diagnosis (for example prediction of ESRD) and this prediction may influence the choice of treatment.

14 VII.

15 Conclusions

Considering only the percentage of normal blood pressure (BP 0, n. 61) and high blood pressure (BP 1, n 90) as such in 151 patients with GN and NS the BP 0 patients show better outcome: "noprog." 80%and "Progr." 20%, while in BP 1 patients "no Progr." is 42% and "Progr" 58%. The highest percentage of "noprogr" are observed in BP 0 associated with eGFR ? 60 ml/min ("noprogr" 82%), GGS 0% ("noprogr" 85%), TID score 0 ("noprogr" 96%) and AH score 0 ("noprogr" 85%). The highest percentages of "progr" are observed in BP1 patients associated with eGFR$<$60 ml/min ("progr" 82%), TID score 4-6 ("progr" 96%) and AH score 2-3 ("progr" 86%). Thus the most powerful parameters associated with worse renal function are eGFR$<$60, TID score 4-6 and AH score 2-3. These results show that outcome of BP 0 and BP 1 patients are associated with eGFR$<$vs ? 60 ml/min, TID score 0 vs 4 -6 and AH score 0 vs 2-3. In evry single patients the combination at diagnosis of these 4 parameters may be able to predict the functional outcome and suggest that patients whose combination predict ESRD should not treated with immunosuppression.

(CIgAN) n. 12, Focal Segmental Glomerulosclerosis (FSGS, n. 32), IgAN (2), Idiopathic Membranous Nephropathy (IMN, n. 66), Minimal change disease (MCD, n. 11), Membrano-proliferative glomerulonephritis (MPGN, n. 15): Lupus Nephritis [LN, n. 13: (WHO LN classes: 4: n. 11; 5 n. 2)].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 evaluated in all 151 patients with rather long follow up[mean 91±77 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 (PNS NRF) after a follow up of 91±73 months (30-200); 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. We decided to evaluate not only each type of outcome considered alone but the combination of outcomes with similar prognostic significance: thus Remission was evaluated in combination with persistent PNS with long lasting NRF, afterwards indicated as ""noprog."; ESRD and eGFR? 50% were evaluated in combination with persistent PNS 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 "progr".
III.

Figure 1:

1

Figure 2: Table 1 :

2

	Normal BP (BP 0) n. 61 (40%) <140/90 mmHg	High BP (BP 1) n. 90 (60%) ? 140/90 mmHG		P
Age yrs	38.4± 16.5	43.6±18.1		
eGFR baseline	94.3 ± 22.4	57.1 ±28.9		<0.0
eGFR last	75.2 ±33.4	39.8± 32.5		<0.0
eGFRbasel. ? 60	n. 57		n. 40	
eGFRbasel. < 60	n. 4		n. 50	
TUP/C	4086± 2731	5018± 3375		0.06
IgG/C	142± 140	296± 335		0.00
?2m/C	6.64± 16.50	11.64± 16.76		0.07
Alb/C	3469±2397	4089± 2563		0.13
?1m/C	28.9±26.8	59.4 ± 47.6		<0.0
GGS%	4.7±8.2	17.0± 17.7		<0.0
TID score	1.01±1.18	2.48±1.76		<0.0
AH score	0.19±0.44	0.76±0.85		< 0.00
IgG/C &?2mC 0+0	26 (43%)	12 (13%)		
IgG/C &?2m/C 0+1	12 (20%)	25 (28%)		
IgG/C &?2m/C 1+0	11 (18%)	27 (30%)		
IgG/C &?2m/C 1+1	12 (20%)	26 (29%)		
	Remission & PNS NRF		ESRD & eGFR<50% & PNS C	
		”no progr”	”Progr”	
All pts BP n.151				
All ptsBP 0	BP 0 n. 61 (40%)	80%	20%	
All pts BP 1	BP 1 n. 90 (60%)	42%	58%	
eGFR ?60 all BP 97	BP0 n. 57 (59%)	82%	18%	
eGFR ?60 all BP 97	BP1 n. 40 (41%)	72.5%	27.5	
eGFR<60 all BP 54	BP0 n. 4 (7%)	25%	75%	
eGFR<60 all BP 54	BP1 n. 50 (93%)	18%	82%	

Figure 3: Table 2 :

3

Figure 4: Table 3 :

4

of combined IgG/C & ?2m/C excretion (1+1, 1+0, 0+1, 0+0) in combination with BP 1 and BP 0

Figure 5: Table 4 :

[Williams et al. ()] , B Williams , G Mancia , W Spiering , E Agabiti Rosei , M Azizi , M Burnier , D L Clement , A Coca , G De Simone , A Dominiczak . 2018.

[Am. J. Kidney Dis ()] , doi: 10.1053/ j.ajkd.2019.02.015. *Am. J. Kidney Dis* 2019. 74 p. .

[(Dec)] , 10.5049/EBP.2015.13.2.41. Dec. 13 p. .

[Levey et al. ()] 'A new equation to estimate glomerular filtration rate'. A S Levey , L A Stevens , C H Schmid , Y L Zhang , A F Castro , H I Feldman , J W Kusek , P Eggers , F Van Lente , T Greene . 10.7326/0003-4819-150-9-200905050-00006. *Ann. Intern. Med* 2009. 150 p. .

[Haruhara et al. ()] 'Ambulatory blood pressure and tubulointerstitial injury in patients with IgA nephropathy'. K Haruhara , N Tsuboi , K Koike , G Kanzaki , Y Okabayashi , Y Miyazaki , T Kawamura , M Ogura , T Yokoo . 10.1093/ckj/sfv083. *Clin. Kidney J* 2015. 8 p. .

[Yu et al.] *Association Between Hypertension and Kidney Function Decline: The Atherosclerosis*, Z Yu , C M Rebholz , E Wong , Y Chen , K Matsushita , J Coresh , M E Grams . (Risk in Communities (ARIC) Study)

[Bazzi et al.] *Blood Pressure Is Associated with Tubulointerstitial Damage along with Glomerular Damage in Glomerulonephritis. A large Cohort Study 3*, C Bazzi , T M Seccia , P Napodano , C Campi , B Caroccia , L Cattarin , L A Calò , ; High , T M Seccia , B Caroccia , L Calò .

[Agarwal ()] 'Caring for individuals with hypertension in CKD, especially those with low education'. R Agarwal . 10.1016/j.kint.2019.06.009. *Kidney Int* 2019. 96 p. .

[Chun-Gyooihm ()] Chun-Gyooihm . *Hypertension in Chronic Glomerulonephritis*, 2015. Electrolyte Blood Press.

[Bazzi and Nangaku ()] 'Combined Urinary Excretion of IgG and ?2-macroglobulin Very Simple Marker to Assess Disease Severity, Outcome Prediction and Responsiveness to Steroids and Cyclophosphamide in Patients with Chronic Glomerulonephritis and Nephrotic Syndrome'. C Bazzi , M Nangaku . 10.24966/NRT-7313/100055. *HSOA Journal of Nephrology & Renal Therapy* 2021. 7 p. 55.

[Alencar De Pinho et al. ()] 'Considerable international variation exists in blood pressure control and antihypertensive prescription patterns in chronic kidney disease'. N Alencar De Pinho , A Levin , M Fukagawa , W E Hoy , R Pecoits-Filho , H Reichel , B Robinson , C Kitiyakara , J Wang , K.-U Eckardt . 10.1016/j.kint.2019.04.032. *Kidney Int* 2019. 96 p. .

[Parikh et al. ()] 'Disease Risk Factors in Chronic Kidney Disease'. N I Parikh , S.-J Hwang , M G Larson , J B Meigs , D Levy , C S Fox , Cardiovascular . 10.1001/archinte.166.17.1884.8. *Arch. Intern. Med* 2006. 166 p. 1884.

[Malhotra et al. ()] 'Effects of Intensive Blood Pressure Lowering on Kidney Tubule Injury in CKD: A Longitudinal Subgroup Analysis in SPRINT'. R Malhotra , T Craven , W T Ambrosius , A A Killeen , W E Haley , A K Cheung , M Chonchol , M Sarnak , C R Parikh , M G Shlipak . 10.1053/j.ajkd.2018.07.015.]. *Am. J. Kidney Dis* 2019. 73 p. .

[Esc/Esh ; De La Sierra et al. ()] 'Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension'. A Esc/Esh ; De La Sierra , J Segura , J R Banegas , M Gorostidi , J J De La Cruz , P Armario , A Oliveras , L Ruilope . 10.1097/HJH.0000000000001940.55. doi: 10.1161/HYPERTENSIONAHA.110.168948. *J. Hypertens* 2018. 1979. 2011. 36 p. . (Hypertension)

[Muntner et al. ()] 'Hypertension awareness, treatment, and control in adults with CKD: Results from the Chronic Renal Insufficiency Cohort (CRIC) Study'. P Muntner , A Anderson , J Charleston , Z Chen , V Ford , G Makos , A O'connor , K Perumal , M Rahman , S Steigerwalt . 10.1053/j.ajkd.2009.09.014. *Am. J. Kidney Dis* 2010. 55 p. . (11)

[Ikee et al. ()] 'Impact of Hypertension and Hypertension-Related Vascular Lesions in IgA Nephropathy'. R Ikee , S Kobayashi , T Saigusa , T Namikoshi , M Yamada , N Hemmi , T Imakiire , Y Kikuchi , S Suzuki , S Miura . 10.1291/hypres.29. *Hypertens Res* 2006. 29 p. .

[Hypertensivenephropathy ()] 'Moving from classic to emerging pathogenetic mechanisms'. Hypertensivenephropathy . 10.1097/HJH.00000. *J. Hypertens* 2017. 35 p. .