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ORIGINAL ARTICLE

Clinical correlates of renal dysfunction in hypertensive patients without cardiovascular complications: the REDHY study

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Our study was aimed to assess the clinical correlates of different degrees of renal dysfunction in a wide group of non-diabetic hypertensive patients, free from cardiovascular (CV) complications and known renal diseases, participating to the REDHY (REnal Dysfunction in HYpertension) study. A total of 1856 hypertensive subjects (mean age: 47 ± 14 years), attending our hypertension centre, were evaluated. The glomerular filtration rate (GFR) was estimated by the simplified Modification of Diet in Renal Disease Study prediction equation. A 24-h urine sample was collected to determine albumin excretion rate (AER). Albuminuria was defined as an AER greater than 20 μg min^{-1}. We used the classification proposed by the US National Kidney Foundation's guidelines for chronic kidney disease (CKD) to define the stages of renal function impairment. In multiple logistic regression analysis, the probability of having stage 1 and stage 2 CKD was significantly higher in subjects with greater values of systolic blood pressure (SBP) and with larger waist circumference. SBP was also positively related to stage 3 CKD. Stage 3 and stages 4–5 CKD were inversely associated with waist circumference and directly associated with serum uric acid. Age was inversely related to stage 1 CKD and directly related to stage 3 CKD. The factors associated with milder forms of kidney dysfunction are, in part, different from those associated with more advanced stages of renal function impairment.
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Introduction

Recent guidelines for the management of hypertension have recognized the relevance of albuminuria and an estimated glomerular filtration rate (eGFR) value $<60\,ml\,min^{-1}$ per $1.73\,m^2$ on cardiovascular (CV) prognosis of hypertensive patients.[1–3] The presence or absence of albumin in urine and the level of eGFR allow patients to be allocated to one of the five stages of chronic kidney disease (CKD), described by the US National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines,[4] which is the accepted classification of any renal disease.

The available information about the prevalence of renal dysfunction in arterial hypertension arises chiefly from clinical trials enrolling elderly hypertensive subjects or patients with high or very high CV risk.[5–8] Little is known about the clinical correlates of the various stages of kidney disease in arterial hypertension, especially in patients without diabetes and free from CV complications.

We recently found that renal dysfunction is highly prevalent among non-diabetic middle-aged subjects with non-malignant arterial hypertension and without CV complications, participating to the REDHY (REnal Dysfunction in HYpertension) study.[9]

The aim of this study was to analyse, in the same wide group of hypertensive subjects, the clinical correlates of different degrees of renal dysfunction.

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Methods

The study population was selected from 2258 Caucasian hypertensive patients consecutively attending our hypertension centre. Most of them had been referred to our institution by their general practitioners for specialist advice.

Exclusion criteria:

- Age lower than 18 years and greater than 70 years
- Known diabetes or fasting glycaemia $\geqslant 126$ mg per 100 ml
- Grade II–III (World Health Organization classification) obesity (body mass index (BMI) $> 35\,kg/m^2$)
- Known renal, renovascular, malignant or endocrine hypertension
- Known proteinuria and haematuria
- Previous known nephritic diseases and hereditary renal diseases
- Heart failure
- Positive history or clinical signs of ischaemic heart disease
- Positive history or clinical signs of cerebrovascular diseases
- Major non-cardiovascular diseases
- Unreliable 24-h urine collection. (that is, creatinine excretion $< 10\,mg\,kg^{-1}$ for women and $< 15\,mg\,kg^{-1}$ for men was considered undercollection; a urinary creatinine ouptut $> 30\,mg\,kg^{-1}$ in men and $> 25\,mg\,kg^{-1}$ in women was considered as overcollection).[10]

Endocrine and renovascular hypertension was ruled out by clinical examination, and determination of serum electrolytes, plasma renin activity, plasma aldosterone, plasma catecholamines and where appropriate, by performing renal echography, echo-doppler of renal arteries and renoscintigraphy. Written informed consent was obtained from each subject and the study was approved by the local review board.

In all subjects, careful clinical history and physical examination were performed. Body weight, height and waist circumference were measured by a nurse and clinic blood pressure was recorded by a doctor, following the recommendations of the 2007 European Society of Hypertension/ European Society of Cardiology guidelines.[1] Clinic blood pressure was considered as the mean of three consecutive measurements obtained by a mercury sphygmomanometer, after 5 min of rest in sitting position. Blood samples were drawn to perform routine blood chemistry.

Measurements

Serum and urine creatinine concentrations were determined by the kinetic picrate method using an autoanalyser (Monarch 2000 autoanalyser; Instrumentation Laboratories, Lexington, MA, USA). The same analyser was used to determine the other routine biochemical parameters. The 24-h albumin excretion rate (AER) was assayed by radioimmunological analysis (Techno Genetics RIA Kit). In subjects with urinary tract infections, AER was determined only after appropriate antibacterial treatment. Urine collections were carried out on non-working days. The patients were advised to avoid excessive physical efforts on the day before and during the 24-h urine collections. Collections were postponed in female participants reporting menstruation or febrile illnesses at the time of collection.

The GFR was estimated (eGFR) by the abbreviated prediction equation of the Modification Diet in Renal Disease Study (MDRD):[11]

$186 \times \text{Serum creatinine (mg per 100 ml)}^{-1.154} \times \text{Age (years)}^{-0.203}$ ($\times 0.742$ for Women).

The ethnicity factor of the equation was not used because our study population was exclusively white.

Albuminuria was considered as 24-h AER $> 20\,\mu g\,min^{-1}$. Microalbuminuria and macroalbuminuria were defined as 24-h AER 20–199 $\mu g\,min^{-1}$ and $\geqslant 200\,\mu g\,min^{-1}$, respectively.

We used the classification proposed by the US NKF K/DOQI guidelines for CKD to define the stages of renal function impairment.[4] CKD stages were defined as follows: stage 1, eGFR greater than $90\,ml\,min^{-1}$ per $1.73\,m^2$ and 24-h AER $> 20\,\mu g\,min^{-1}$; stage 2, eGFR of 60 to $89\,ml\,min^{-1}$ per $1.73\,m^2$ and 24-h AER $> 20\,\mu g\,min^{-1}$; stage 3, eGFR of 30 to $59\,ml^{-1}min^{-1}$ per $1.73\,m^2$; stage 4, eGFR of 15 to $29\,ml\,min^{-1}$ per $1.73\,m^2$; stage 5, eGFR less than $15\,ml\,min^{-1}$ per $1.73\,m^2$.[4]

Statistics

A total of 402 subjects met the exclusion criteria. Therefore, the final analysis involved 1856 patients.

Continuous variables were given as mean ± s.d., except for AER, which, because of its skewed distribution, was expressed as the median and interquartile range. It was therefore log-transformed before starting the statistical tests.

We used one-way ANOVA for independent samples to evaluate differences in means. Comparisons of each stage of CKD with the group of subjects without CKD were performed, if the overall F-test was significant, by using the Holm post hoc test.

Proportional differences between groups were assessed by the χ^2-test, with Yates' correction.

The relationship between eGFR and AER was tested by the Pearson's correlation coefficients.

To investigate the independent correlates of each stage of CKD, multiple logistic regression analyses were performed by calculating odd ratios and their 95% confidence limits, after adjustment for age, systolic (SBP) and diastolic (DBP) blood pressures, waist circumference, serum uric acid (SUA), triglycerides, high-density lipoprotein (HDL) cholesterol, total cholesterol, duration of hypertension (included as continuous variables), gender, previous treatment

for hypertension, smoking habit (included as categorical variables). For this analysis, patients of stage 4 and stage 5 were pooled in a single group because the low number of subjects belonging to the stage 5.

In all multiple regression analyses, a backward stepwise procedure was used, with $\alpha = 0.15$ as the cut-off for entry or removal of variables, which is the default value of the SYSTAT statistical package.

The null hypothesis was rejected at a two-tailed $P \leqslant 0.05$.

The statistical analyses were performed using the SYSTAT DATA software package, version 5.2 (Systat, Evanston, IL, USA).

Results

The mean age of the 1856 patients enrolled in the study was 47 ± 14 years, 53% of whom were men. The median value and interquartile range of AER were 9 (5–18.5) $\mu g\,min^{-1}$. Microalbuminuria and macroalbuminuria were detected, respectively, in 22.7 and 0.7% of the entire population. The mean values of serum creatinine and estimated GFR were, respectively, 0.97 ± 0.58 mg per 100 ml and 89.7 ± 26 $ml\,min^{-1}$ per 1.73m^2. Only 5.2% of the overall population had simultaneously albuminuria and an estimated GFR less than 60 $ml\,min^{-1}$ per 1.73m^2. AER and eGFR were weakly ($r = -0.13$), but significantly ($P < 0.001$) inversely related.

The prevalence of the five stages of renal dysfunction is shown in Figure 1. The main clinical characteristics of the hypertensive patients with the different stages of CKD, compared to those without CKD, are given in Table 1.

Of the patients enrolled in the study, 70% were already pharmacologically treated for hypertension. The antihypertensive treatment of this subgroup was based on: ACE inhibitors (alone and in combination with a diuretic; 35%); AT1 blockers (alone and in combination with a diuretic; 25%),

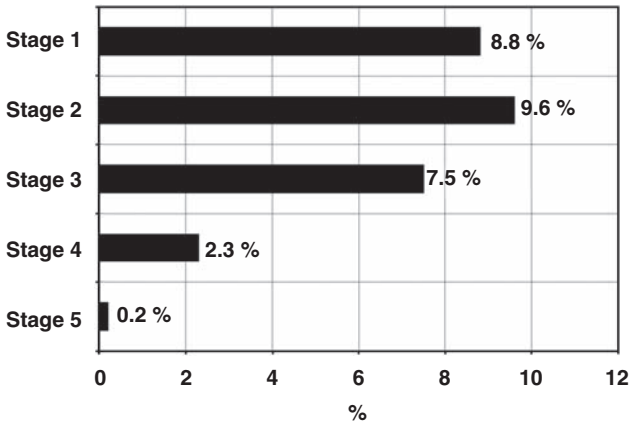

Figure 1 Distribution of the stages of renal dysfunction (NKF classification of chronic kidney disease (CKD)) in the study population.

Table 1 The main clinical characteristics of the patients with different degrees of renal dysfunction compared to those without kidney disease

	No CKD (n = 1329)	*CKD 1 (n = 164)*	*CKD 2 (n = 178)*	*CKD 3 (n = 139)*	*CKD 4 (n = 42)*	*CKD 5 (n = 4)*	*ANOVA or χ^2-test (P)*
Male gender (%)	51.7	61*	60.2*	54.3	42	50	0.019
Age (years)	45.9 ± 13.2	40.1/13.7*	48.1 ± 15.9	50.1 ± 12.4*	56.8 ± 14.5*	65.2 ± 12.6*	<0.001
Current smokers (%)	29.9	37.8	31	25.2	26.2	25	NS
Systolic blood pressure (mm Hg)	150.6 ± 19.7	154.3 ± 19.6*	157.1 ± 24*	156.1 ± 25.4*	159 ± 25.9*	143.1 ± 35.6	<0.001
Diastolic blood pressure (mm Hg)	91.1 ± 13.7	91.3 ± 13.2	93.8 ± 14.6*	91.6 ± 17.8	96.3 ± 20.3	83.3 ± 20.7	0.003
Duration of hypertension (years)	5.7 ± 6..2	6.3 ± 6.2	7.1 ± 7.6*	8.1 ± 8.4*	6.8 ± 7	7.8 ± 5.7	<0.001
Body mass index (kg/m^2)	27.6 ± 3.5	27.9 ± 3.9	28.4 ± 3.6*	27.5 ± 3.4	26.5 ± 3.6	27.1 ± 1.1	0.017
Waist circumference (cm)	94.1 ± 10.5	94.9 ± 11.7*	97 ± 8.8*	93.1 ± 11.4	89.9 ± 11.4*	93.7 ± 6.1	<0.001
Total cholesterol (mg per 100 ml)	205.4 ± 40.6	203.7 ± 45.2	212.9 ± 45.9*	205 ± 46.4	218.5 ± 60	187.2 ± 54.5	<0.001
HDL cholesterol (mg per 100 ml)	45.8 ± 10.2	45.4 ± 9.6	45 ± 12.5	43.9 ± 11.4	43 ± 12	38.4 ± 9.9	NS
Triglycerides (mg per 100 ml)	139.9 ± 78.1	139.4 ± 69.8	157.7 ± 78.7*	135.5 ± 64.6	179.2 ± 102.4*	120 ± 19.6	0.002
Glycaemia (mg per 100 ml)	92.8 ± 12.4	92.9 ± 11.9	94.4 ± 12.5	90.4 ± 14.2	93.7 ± 13.4	92.8 ± 21.5	NS
Serum uric acid (mg per 100 ml)	4.7 ± 1.4	4.8 ± 1.2	5.3 ± 1.3*	6.4 ± 1.7*	7 ± 2.3*	8.9 ± 2.1*	<0.001
Serum creatinine (mg per 100 ml)	0.85 ± 0.18	0.77 ± 0.14	0.99 ± 0.16	1.43 ± 0.32	2.56 ± 0.58	6.4 ± 2.2	<0.001
Estimated GFR ($ml\,min^{-1}$ per 1.73 m^2)	94.7 ± 21.7	110.7 ± 17.4	77.1 ± 7.7	49.7 ± 8.5	24.9 ± 3.6	9.2 ± 3.7	<0.001
Albumin excretion rate ($\mu g\,min^{-1}$)	6.9 (4.2–10.6)	41.5 (28.1–73.9)*	36.6 (26–58.6)*	11.2 (5.2–45.5)*	82.3 (41.7–129.7)*	34.8 (25.8–42.8)*	<0.001

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein.
*Significantly different from the 'No CKD' group.

β-blockers or α-β-blockers (alone and in combination with a diuretic; 11%), α-blockers (3%), calcium antagonists (12%), a combination of two or more of these drugs (14%). The distribution of the antihypertensive therapy and of the classes of BP-lowering drugs among the patients divided according to the level of renal function is reported in Table 2. Even if the prevalence of patients treated for hypertension was higher in the group of subjects belonging to stage 1 and stage 2 CKD, when compared to the group without kidney dysfunction, the percentage of subjects treated with ACE inhibitors or AT1-blockers or other classes of antihypertensive drugs did not differ significantly in the various groups.

A stepwise multiple logistic regression model (Table 3) in which each stage of CKD was considered as outcome variable and including as covariates age, SBP and DBP, waist circumference, SUA, triglycerides, HDL cholesterol, total cholesterol, duration of hypertension, gender, previous treatment for hypertension, smoking habit, revealed that SBP was independently associated with stage 1, stage 2 and stage 3 CKD, whereas waist circumference was positively related to stage 1 and stage 2 CKD and inversely associated with stage 3 and stages 4–5 CKD. The same analysis showed that SUA was an independent predictor of stage 3 and stages 4–5 CKD and age was negatively associated with stage 1 and positively related to stage 3 CKD. Previous pharmacological antihypertensive therapy was positively related to stage 1 and stage 2 CKD but these associations attain statistical significance only for stage 2 CKD (Table 3).

Discussion

This study showed that, in a population of non-diabetic hypertensive subjects without CV complications, the factors associated with milder forms of renal dysfunction are, in part, different from those associated with more advanced stages of kidney dysfunction.

Indeed, multiple logistic regression analysis disclosed that waist circumference, SBP and previous pharmacological therapy for hypertension were independent correlates of both stage 1 and stage 2 CKD, even if this latter association reached statistical significance only for stage 2 CKD. These findings are consistent with several previous studies showing that SBP and abdominal obesity are two important determinants of microalbuminuria,[12–16] a key component of the two first stages of the NKF classification of CKD.

The greater proportion of subjects, pharmacologically treated for high BP, we found in the group with stage 1 and stage 2 CKD when compared to the group without renal dysfunction is probably due to the longer duration of hypertension, the higher BP values and the greater BMI observed in the former

Table 2 Distribution of the antihypertensive therapy and of the classes of BP-lowering drugs among the patients divided according to the level of renal function

	No CKD (n = *1329*)	*CKD 1* (n = *164*)	*CKD 2* (n = *178*)	*CKD 3* (n = *139*)	*CKD 4* (n = *42*)	*CKD 5* (n = *4*)	χ^2-*test (P)*
Subjects pharmacologically treated for hypertension (%)	67.8	77*	80*	71	68.8	50	0.001
ACE inhibitors (%)	23.9	26.9	28.8	23	23.7	0	NS
AT1 blockers (%)	16.9	19.6	20.9	18	14.1	25	NS
β- and α-β-Blockers (%)	7.5	10.4	9	7.8	0	0	NS
Calcium antagonists (%)	8.2	7.3	9.5	8.5	16.7	0	NS
α-Blockers (%)	2	2.4	2.2	2.2	2.4	0	NS
Combination of two or more drugs (%)	9.3	10.4	9.6	11.5	11.9	25	NS

Abbreviations: CKD, chronic kidney disease; NS, not significant.
*Significantly different from the 'No CKD' group.

Table 3 Independent predictors of stage 1, stage 2, stage 3 and stages 4–5 CKD in the overall study population

Variable	*Estimate (s.e.)*	*Odds ratio*	*95% Confidence Interval*		P
			Lower	*Upper*	
Stage 1					
Age	−0.05 (0.014)	0.951	0.926	0.977	<0.001
Systolic blood pressure	0.016 (0.004)	1.014	1.003	1.025	0.009
Waist circumference	0.025 (0.012)	1.026	1.004	1.050	0.026
Pharmacological treatment for hypertension	0.78 (0.434)	2.18	0.932	5.102	0.072
Stage 2					
Systolic blood pressure	0.02 (0.006)	1.020	1.007	1.033	0.002
Waist circumference	0.032 (0.013)	1.029	1.009	1.052	0.004
Pharmacological treatment for hypertension	0.644 (0.281)	1.888	1.061	3.390	0.037
Stage 3					
Age	0.086 (0.017)	1.090	1.053	1.128	<0.001
Serum uric acid	0.538 (0.119)	1.713	1.358	2.162	<0.001
Waist circumference	−0.055 (0.021)	0.947	0.908	0.987	0.01
Systolic blood pressure	0.02 (0.009)	1.021	1.004	1.038	0.018
Stages 4–5					
Serum uric acid	1.026 (0.207)	2.79	1.859	4.188	<0.001
Waist circumference	−0.115 (0.043)	0.891	0.820	0.969	0.007

in comparison to the latter. It is likely that all these characteristics prompted the general practitioners to treat these patients with antihypertensive drugs more frequently than those without CKD.

The inverse association we found between age and stage 1 is likely attributable to the inclusion in this stage of subjects with normal estimated GFR, which is inversely related to age in the equation used to calculate it by the MDRD study formula.[11] Probably for the opposite reason we found a direct association between age and stage 3 CKD. This stage was also independently related to increased SUA and higher SBP values. Although SUA elevations have long been recognized as marker of renal disease, they are not usually considered to have a causal role in kidney dysfunction.[17] However, recent epidemiologic studies have identified SUA elevations as an independent risk factor for CKD.[17,18] On the other hand, it well known that the kidney may be both a cause and a victim of high BP and there is now a consensus that systolic, rather than diastolic, BP poses the greater risk for renal function deterioration.[19]

Besides these expected relationships of stage 3 with SUA and SBP elevations, we observed an inverse association between waist circumference and stage 3 and stage 4–5 CKD. This finding seems to be in contrast with recent evidence that highlighted the importance of obesity as risk factor for end-stage renal disease.[20–21] However, it is noteworthy that this evidence arises chiefly from longitudinal studies performed in the general population,[20–21] also including severely obese subjects. In our study, patients with BMI greater than 35 kg/m^2 were excluded to reduce the potential influence on the prevalence of kidney dysfunction of our population of the glomerulopathy related to an increased BMI and especially to severe degrees of obesity. Moreover, in some studies, conducted in hypertensive persons, lower levels of BMI were detected in subjects with decreased values of GFR, such as in our study[6,8,22] and more recently the Framingham Offspring Study showed that obesity was not associated *per se* with an independent risk to develop stage 3 CKD, after adjustment for known CV disease risk factors.[23] Observational investigations suggested that nutritional status deteriorates as GFR declines.[24,25] Therefore, undernutrition may contribute to explain the negative relationship we found between obesity and advanced stages of CKD. However, the cross-sectional design of this study does not allow us to establish the direction of causality relations between obesity and renal insufficiency. Some other aspects of our study need to be discussed.

Increased AER and reduced eGFR were only weakly related to each other ($r = 0.13$). This implies that these two markers of renal dysfunction identify, in part, different groups of patients in the hypertensive population. In fact, only 5.2% of patients had simultaneously albuminuria and a reduced eGFR. Moreover, the factors associated with stages 1–2 CKD were at least, in part, distinct from those related to stages 3–5 CKD. This observation suggests that milder forms of renal dysfunction and more advanced stages of kidney dysfunction have partially different pathogenetic mechanisms and may provide complementary infor-

mation regarding CV risk. Our findings are, in part, in line with recent observations obtained in hypertensive individuals[26,27] and in general population.[28–30] All these data support recent recommendations defining CKD[4] and stratifying subsequent risks based on both decreased GFR and albuminuria.[1–3]

To estimate the GFR we used the four-variable formula proposed by the MDRD study, a method that is now considered the best predictor of true GFR in clinical settings[4,31,32] and a reliable tool for determining impaired kidney function in several populations.[3,32] This formula has been recently questioned, because it may underestimate the true GFR in the normal-high range.[31] Consequently, the MDRD equation should be used with caution in patients with GFR $> 60\,ml\,min^{-1}$ per $1.73\,m^2$. Despite this limitation, it has been clearly documented that the GFR estimated by the MDRD formula is a powerful prognosticator for adverse CV outcomes.[6,8,20,28–30,33] Moreover, in the hypertensive population of the VALUE trial, the MDRD study equation was a better predictor of CV events than the creatinine clearance rate calculated by the Cockcroft–Gault formula.[8]

Study limitations

Our study should be interpreted within the context of its limitations.

The main limitation is the cross-sectional nature of our investigation that precluded assessment of the temporality of the observed associations and thus determination of causality.

Another possible weakness in our results could be represented by the influence of pharmacologic treatment, even if it was taken into account in the multivariate analyses. Moreover, the percentage of subjects treated with ACE inhibitors or AT1-blockers or other classes of antihypertensive drugs did not differ significantly in the various groups.

It is well known that there is a considerable intrapersonal variation of urinary albumin excretion.[4,13] Therefore, the measurement of only one value of AER may be another limitation of our study. However, as reported in the methods section, we adopted several precautions to reduce the variability of AER. We previously performed a study in 70 never-treated hypertensive subjects, which underwent two measurements of the 24-h AER at 1 week interval, using the same precautions employed in this study.[34] We found a Spearman's correlation coefficient for these two measurements of 0.75 ($P<0.0001$). Of those participants with microalbuminuria at the fist examination, 81% had microalbuminuria at the second evaluation.[34] Moreover, it is important to note that in several studies, in which a relationship between AER and CV prognosis was found, only one measurement was performed.[13]

In conclusion, in non-diabetic hypertensive patients without CV complications the factors associated with milder forms of renal dysfunction are, in part, different from those associated with more advanced stages of kidney dysfunction. This may suggest partially distinct pathogenetic mechanisms.

What is known about this topic

- The presence or absence of albumin in urine and the level of glomerular filtration rate allow patients to be allocated to one of the five stages of chronic kidney disease (CKD).
- CKD is highly prevalent in subjects with arterial hypertension, especially in elderly patients and in those with high or very high cardiovascular (CV) risk.

What the study adds

- In non-diabetic middle-aged hypertensive patients without CV complications the factors associated with the first stages of CKD are in part different from those related to the more advanced stages of renal dysfunction.
- Waist circumference is positively associated with stage 1 and stage 2 CKD and inversely associated with stage 3 and stages 4–5 CKD.
- Serum uric acid is positively related to stage 3 and stages 4–5 CKD, but not with stage 1 and stage 2 CKD.

Conflict of interest

The authors declare no conflict of interest.

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