ORIGINAL ARTICLE

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Prevalence and significance of mild renal dysfunction in a group of hypertensive patients followed-up in Hypertension Units

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ABSTRACT

Aim: The European Clinical Guidelines for Hypertension have stated that slight elevation of serum creatinine concentration (1.2-1.4 mg/dl in women; 1.3-1.5 mg/dl in men) should be considered in hypertensive patients as renal target organ damage. This study seeks to assess the prevalence of the renal target organ damage defined by this recommendation and its correlation with renal failure severity as measured by estimated glomerular filtration.

Patients and Methods: 3163 hypertensive patients followed-up in Hypertension Units were evaluated. Serum creatinine was analysed and glomerular filtration rate estimated using the abbreviated Modification of Diet in Renal Disease formulation and Cockcroft-Gault Formula. Patients were classified using the K/DOQI Guidelines categories.

Results: 257 (55.3% males) hypertensive patients showed renal target organ damage (8.12%). Mean age was 66.7±13.3 years. Mean serum creatinine was 1.29±0.10 mg/dl. Averaged and Cockcroft-Gault Formula was 52.8±6.0 ml/min/1.73 m2 and mean creatinine clearance was 56.4±184 ml/min. Men have higher serum creatinine concentration (p<0.001) but also higher glomerular filtration rate (p<0.001). Creatinine clearance calculated using Cockcroft-Gault Formula was the same in males and females before adjusting for body surface area, but it was different after correcting for this parameter (p=0.012). Twenty-nine men and 17 women were in Stage II of chronic kidney disease and the remainder (114 men, 79.8%; and 97 women, 85.1%) were in Stage III. Renal target organ damage was less frequent in women aged less than 55 years (men 19.8%, women 14.0%, p=0.037).

Conclusions: Renal target organ damage defined as small serum creatinine increases is common among hypertensive patients followed-up in Hypertension Units. Estimated glomerular filtration rate revealed a worse renal function than suspected from serum creatinine, meaning strict management is needed.

Key-Words:
Hypertension; renal dysfunction; target organ disease.

INTRODUCTION

Chronic renal failure is an important risk factor not only for premature atherosclerosis but also for

its rapid progression, as the risk of cardiovascular and peripheral vascular disease is associated with the metabolic abnormalities involved in uraemia[1]. In recent years, a large body of information has confirmed that as soon as renal function exhibits even minor dysfunction, a rise in cardiovascular risk occurs with a continuous relationship between decreasing renal function, leading to end-stage renal disease and increasing cardiovascular risk[2,3].

It is currently known that the accepted range of normality for serum creatinine includes a high number of patients with mild and even moderate renal failure and as such it has been recommended to calculate glomerular filtration rate (GRF) in clinical practice to avoid errors caused by hidden chronic kidney disease. Review of the literature showed a paucity of data on the lower limit of a normal GFR in elderly populations. Therefore, older individuals with low GFR should be assessed for other markers of chronic kidney disease including proteinuria and hypertension[4].

Regarding this latter sign the European Society of Cardiology-European Hypertension Society Clinical Guidelines have recently stated that slight elevation of serum creatinine concentration in hypertensive patients (either 107-124 µmol/l, 1.2-1.4 mg/dl in women or 115-133 µmol/l, 1.3-1.5 mg/dl in men) should be taken as a sign of target organ damage (TOD), and higher creatinine concentrations regarded as an associated clinical condition to arterial hypertension[5,6]. These Guidelines have refined the classical normal definition of creatinine to use in better classification of hypertensive patients for cardiovascular risk stratification and for defining renal subclinical (target organ) disease. The prevalence of this kind of TOD has not been evaluated.

In this study we sought to evaluate the prevalence and significance of mild serum creatinine increases (following the European Clinical Guidelines definition of renal TOD) in hypertensive patients followed-up in Hypertension Units.

PATIENTS AND METHODS

Five Hypertension Units, which work in adjacent geographical areas, took part in this study; four from Spain (Badajoz, Caceres, Plasencia and Zafra from the region of Extremadura) and one from Portugal (Elvas, from the neighbouring region of the Alentejo). The clinical files of 3163 hypertensive outpatients followed-up in these hospitals' Hypertension Units were evaluated. 16.2% were diabetic. Patients were selected for the study in line with the European Society of Cardiology-European Hypertension Society Clinical Guidelines criteria of renal TOD (slight elevation of serum creatinine concentration 1.2-1.4 mg/dl in female patients or 1.3-1.5 mg/dl in males)[5].

Height and weight, gender, age and serum creatinine of selected patients were registered. GFR was estimated through the abbreviated Modification of Diet in Renal Disease (MDRD) formulation, which gives the results as ml/min/1.73 m^2 body surface area[7]. Creatinine clearance was also estimated by the Cockcroft-Gault Formulation (CGF), which is expressed as ml/min[8], corrected for gender and then normalised to 1.73 m^2 of body surface area. All recruited patients were Caucasian.

To categorise the severity of renal dysfunction the patients were classified into five stages following the K/DOQI Guidelines[5] categories: I: GFR higher than 90 ml/min; II: GFR from 60 to 89 ml/min; III: GFR from 30 to 59 ml/min; IV: GFR from 15 to 29 ml/min; and V: ‹15 ml/min using the GFR calculated by MDRD formulation.

Results are expressed as mean±1 standard deviation. Continuous values were compared using the non-paired Student T test. The chi-squared test was used to compare discrete data. All statistical tests were two-sided. Pearson coefficients were used to assess linear correlation. *P* values lower than 0.05 were considered as significant. Analysis was developed with the statistical package SPSS for Windows 13.0.

RESULTS

257 evaluated hypertensive patients out of the overall sample showed renal TOD (8.12%), 143 males (55.3%) and 114 females (44.7%), mean age of overall sample 66.7±13.3 years, mean serum creatinine 1.29±0.10 mg/dl. The average MDRD estimated GFR was 52.8±6.0 ml/min/1.73 m2 and mean CGF calculated creatinine clearance was 56.4±184 ml/min.

Table I

General statistics

	Overall	Men	Women	Significance
Age (years)	66.7±13.3	65.5±13.7	68.2±12.7	0<0.001
Creatinine	1.29±0.10	1.35±0.06	1.22±0.08	0.113
GFR (MDRD)	54.0±6.32	56.6±4.19	50.6±6.94	<0.001
CCr (Cockroft-Gault)	56.3±18.2	57.9±19.3	54.4±16.7	0.162
CCr/1.73 m2SC	73.1±20.3	76.3±20.9	69.3±19.7	0.012
Waist	105.2±9.72	106.6±8.9	103.4±10.6	0.261
Weight	79.5±14.1	81.6±3.1	76.9±14.9	0.014
BMI	31.1±5.27	29.6±4.23	32.9±6.08	<0.001

CCr: Creatinine clearance (ml/min). GFR in ml/min. Waist in cm. Weight in kg. BMI in kg/m^2.

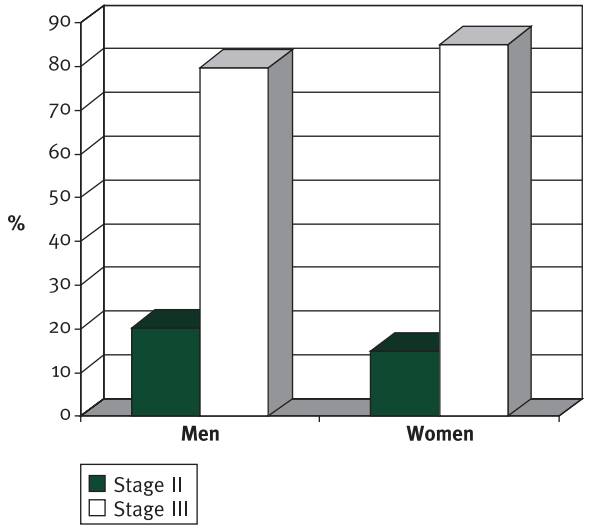

Figure 1

The figure plots the percentage of patients in each K/DOQI stage of chronic kidney disease by gender. The difference is not significant.

Table II

Patient distribution by age

Age (years)	Overall	Men	Women	Significance
<55	51	35	16	0.037
55-64	38	20	18	NS
64-75	87	42	43	NS
>75	81	44	37	NS

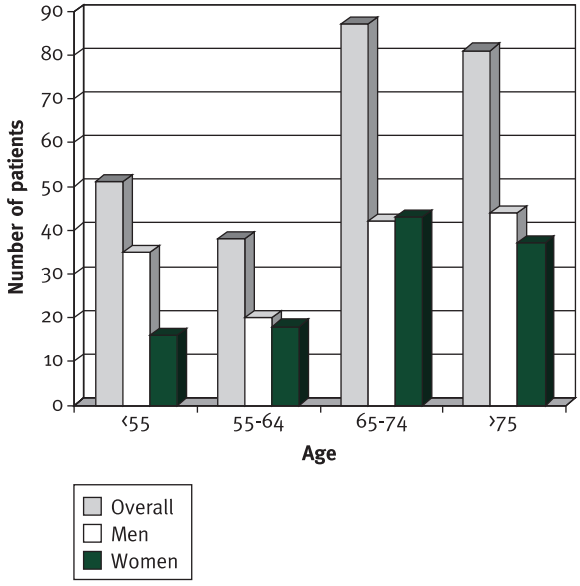

Figure 2

Number of patients split by age groups and gender. Renal TOD was more frequent in women aged less than 55 years old.

Separate data for men and women are given in Table I. Men had higher serum creatinine concentration (p<0.001) but also higher GFR as calculated by MDRD formulation (p<0.001). There was no difference between creatinine clearance calculated using CGF between males and females before adjusting for body surface area, but it was significantly different after correcting for this parameter (p=0.012). Weight and body mass index (BMI) of women were significantly lower (weight, p=0.014; BMI, p<0.001). On the other hand, abdominal girth was not significantly different by gender.

Splitting the overall sample into K/DOQI categories showed no patient was in Stage I chronic kidney disease; 29 men (20.2%) and 17 women (14.9%) were in Stage II and the remainder (114 men, 79.8% and 97 women, 85.1%) were in Stage III, with this difference non-significant (Fig. 1).

Renal TOD was less frequent in women aged less than 55 years (men 19.8%, women 14.0%, p=0.037, chi-squared test). There were no statistically significant differences for other age groups (Table II and Fig. 2).

28.4% of patients were diabetic, meaning diabetes mellitus was associated to a higher risk of presenting slight increase in serum creatinine (p=0.0023, chi-squared test). The characteristics of the diabetic group are shown in Table III. 64.7% were women, with this difference non-significant. Diabetic patients were older and had greater weight and BMI.

Table III

Overall report

	Non diabetic	Diabetic	Significance
Age (years).	60.4±13.7	71.4±9.16	‹0.001
Creatinine	1.28±0.11	1.26±0.12	0.428
GFR (MDRD)	54.5±5.65	51.0±5.27	0.003
CCr (Cockroft-Gault)	68.1±19.3	62.2±14.2	0.134
CCr/1.73 m2SC	75.1±20.3	68.9±11.3	0.086
Waist	104.5±9.8	107.1±9.8	0.429
Weight	78.1±14.6	85.9±12.5	‹0.001
BMI	30.1±6.37	33.6±5.51	‹0.001

CCr: Creatinine clearance (ml/min). GFR in ml/min. Waist in cm. Weight in kg. BMI in kg/m^2.

DISCUSSION

Data from the National Kidney Foundation suggest that the prevalence of end-stage renal failure (0.1% of the US adult population) is low but earlier stages of CKD affect a high percentage of the general population (10.8% of the US adult population) including patients with normal GFR and risk factors for CKD such are diabetes or hypertension[5]. Accelerated and malignant hypertension have long been known to be linked with an increased risk of renal failure, and clinical trials studying patients with this diagnosis have demonstrated that antihypertensive drug therapy prolongs survival and slows the progression of renal disease[9,10,11]. The risk of renal failure associated with less severe hypertension is graded and continuous throughout the distribution of blood-pressure readings above the optimal level, making the kidney considered a target organ for hypertension and a higher prevalence of CKD among hypertensive patients expected. Currently European Clinical Guidelines state three different criteria to define renal TOD[5]: 1) Slight increase in plasma creatinine: M: 115-133 mmol/l (1.3-1.5 mg/dl); W: 107-124 mmol/l (1.2-1.4 mg/dl); 2) Low estimated GFR (‹60 ml/min/1.73 m2) or creatinine clearance (‹60 ml/min); or 3) Presence of microalbuminuria 30-300 mg/24 h or albumin-creatinine ratio: ≥22 (M); or ≥31 (W) mg/g creatinine. Several studies have estimated the frequency of the two latter criteria in the general population[12,13], but the prevalence of first definition category among hypertensive patients (definition introduced by 2003 European Clinical Guidelines[14]) has not been evaluated until now and our results suggest that a high percentage of hypertensive patients may have renal TOD using this criterion.

This observation may have some biases. Microalbuminuric patients have not been evaluated, so that the percentage of patients presenting renal TOD should be higher than estimated only by creatinine increment. On the other hand, since we evaluated patients followed-up in Hypertensive Units, the number of affected patients would be higher due to the increased severity of hypertension in patients referred to this kind of unit. Broader samples obtained from overall hypertensive population followed-up in the primary care setting are needed to correctly answer these questions.

The new definition of renal TOD was arrived at in the background of associated cardiovascular risk and it is related to cumulated experience showing an increased cardiovascular risk within this range of serum creatinine concentrations. The Hypertension Detection and Follow-up Program trial was the first to show that the presence of elevated serum creatinine values (›1.7 mg/dl) at baseline was a very potent predictor for all-cause mortality within 5-8 years[15]. Data from the Hypertension Optimal Treatment (HOT) study indicated an elevated cardiovascular risk in hypertensive patients with serum creatinine above 1.3 mg/dl)[16,17]. In the same way, the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) Study showed that the cardiovascular event rate increased progressively from the first to the fourth gender-specific quartiles of creatinine distribution (1.5, 2.3, 2.3, and 3.5 per 100 patient-years respectively). The observed excess risk was 1.30 for a 0.23-mg/dL increase in creatinine concentration[18]. This means that almost a tenth of patients followed-up in hospital-based Hypertension Units may be at high cardiovascular risk due to small increments in serum creatinine concentration and adequate medical treatment should be implemented to reduce this increased risk, specifically straight blood pressure and lipids control with lower treatment targets[2,3].

The most common measure used to assess overall kidney function is the serum creatinine concentration. Interpretation of this index may be complicated, as it is inversely proportional to the GFR and varies between individuals based on differences in age, gender and muscle mass. Furthermore, serum creatinine concentration is affected by factors other than GFR, such as tubular secretion, generation and extrarenal excretion of creatinine[19]. These well-known variations may explain the higher prevalence of renal TOD among younger male patients (or, conversely, the lower prevalence among younger female patients) whose muscle mass

is higher than age-adjusted female subjects. The cardiovascular significance of this difference is currently unknown and may deserve some future attention.

Since using serum creatinine concentrations to determine an absolute level of kidney function, including distinguishing normal from abnormal function in the individual patient, may be difficult, the K/DOQI guidelines recommended estimation of GFR by using prediction equations based on serum creatinine determinations such as the abbreviated MDRD formulation used in this study[20]. The K/DOQI guidelines advise that chronic kidney disease can be defined and appropriately managed by a staging approach that relies on estimating the severity of kidney damage based on the degree of proteinuria and impaired kidney function, this latter assessed as a decrease in the glomerular filtration rate. These guidelines define fives stages of chronic renal disease from I (glomerular filtration rate >90 ml/min) to V (<15 ml/min). A GFR ≤60 mL/min/1.73 m^2 has been selected as the cut-off value for definition of chronic renal failure because it represents a reduction by more than half of the normal value GFR in young men and women, and this level of GFR is associated with the onset of laboratory abnormalities characteristic of kidney failure, including increased prevalence and severity of several CVD risk factors[5]. Using this classification most patients with renal TOD (slight increments of serum creatinine within the currently accepted reference range) have indeed moderate renal failure (stage III from 30 to 60 ml/min of GRF). Consequently, this group of patients should be considered as truly chronic kidney disease patients and treated as this situation deserves; the renal TOD definition is a helpful approach to identifying this kind of patient without needing GFR calculation.

As a final conclusion it can be remarked that renal TOD defined by slight increments of serum creatinine concentration is not uncommon among hypertensive patients followed-up in Hypertension Units. Estimated GRF of these patients reveals a worse renal function than suspected from serum creatinine and increases the need for strict control of cardiovascular risk factors and renal protection in this patient group. Diabetic patients might be at a higher risk of showing slight increases in serum creatinine. Wider studies in overall hypertensive populations followed-up in the primary care setting are needed to correctly quantify the true prevalence of this complication.

Conflict of interest statement. None declared.

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