How relevant and frequent is the presence of mild renal insufficiency in essential hypertension?.

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Abstract
Recent analyses of the influence of renal function on the cardiovascular outcome in essential hypertensive patients have confirmed the relevance of the kidney in cardiovascular prognosis since the initial stages of renal failure. The evaluation of renal function in clinical practice is based mainly on the finding of changes in serum creatinine, but the estimation of creatinine clearance or its determination after 24-hour urine collection is not usually performed.

The objective of this study was to analyze the prevalence of mild chronic renal insufficiency (MCRI), through the determination of creatinine clearance, in patients with essential hypertension, to reinforce the need to consider this parameter in daily clinical practice.

We analyzed clinical and biochemical data from 2686 essential hypertensive patients referred to our unit from 1979 to 1999. MCRI was defined as serum creatinine $\geq 1.5$ mg/dl in men and $\geq 1.4$ mg/dl in women, creatinine clearance estimated by the Cockroft-Gault formula or through 24-hour urine collection <60 ml/min.

A prevalence of MCRI was found in 7.6% according to serum creatinine levels. This prevalence raised to 22.3% and 21.5% when the diagnostic criteria for MCRI was the estimation of 24 hour creatinine clearance in urine or its estimation using the Cockroft-Gault formula, respectively. According creatinine clearance values, patients with MCRI were characterized by older age, elevated systolic BP, higher serum total cholesterol, LDL cholesterol, and tryglicerides, lower levels of HDL cholesterol, higher serum uric acid, fasting serum glucose, serum potassium, and higher levels of urinary albumin excretion.

In summary, MCRI is more prevalent that previously thought in essential hypertension, particularly if estimated creatinine clearance is considered. The finding of an altered renal function is associated to a significant increase in cardiovascular risk. This fact reinforces the need to pay attention to any of the manifestations of renal damage observed in the usual clinical assessment of any hypertensive patient.

Introduction
The kidney and hypertension are closely related. A defective capacity to cope with the sodium content of the diet appears to account for the initial increase in blood pressure (BP), and various primary renal abnormalities may be at the renal origin of hereditary hypertension [1].

On the other hand, primary and secondary forms of renal disease are accompanied by a progressive elevation in BP values, and most patients with end-stage renal disease (ESRD) have hypertension [2].

Recent analyses of the influence of renal function on the cardiovascular outcome in trials performed in patients with essential hypertension [3,4,5], have confirmed the relevance of the kidney in cardiovascular prognosis since the initial stages of renal failure.

The diagnosis of a deranged renal function in clinical practice is based mainly on the finding of changes in serum creatinine, and/or the detection of an elevated urinary excretion of albumin below (microalbuminuria) or above (macroalbuminuria) the usual laboratory methods to detect proteinuria. An increase in serum creatinine above normal values, or the presence of proteinuria or microalbuminuria could constitute the most potent predictors for the future development of cardiovascular death in essential hypertension. The clinical relevance of these findings is reinforced by its simplicity in clinical practice. Evaluation of glomerular filtration rate through estimation of creatinine clearance [6] or its determination after 24-hour urine collection is not usually performed in clinical practice. However it has been shown to be a useful predictor of cardiovascular risk when
values are below 60-70 ml/min [3,5].

The objective of this study was to analyze the prevalence of mild chronic renal insufficiency, through the determination of creatinine clearance, in patients with essential hypertension followed in a hospital located hypertension unit, to reinforce the need to consider this parameter in daily clinical practice.

Material and methods

Study Design

This was a cross sectional study, aimed to describe the prevalence of chronic renal insufficiency in a population of hypertensive patients, and to define the clinical characteristics of hypertensive patients presenting with a diminished (<60 ml/min) value of creatinine clearance.

Definitions

We have used three parameters to appraise renal function: the concentration of serum creatinine, the estimation of serum creatinine clearance through the Cockroft and Gault formula [6], and a direct estimation of creatinine clearance through the simultaneous measurement of serum and 24-hour urinary excretion of creatinine. The definition of the presence of renal insufficiency was made according to the following criteria: Serum creatinine $\geq 1.5$ mg/dl in men and $\geq 1.4$ mg/dl in women [7,8], creatinine clearance estimated by means of the Cockroft-Gault formula or through 24-hour urine collection inferior to 60 ml/min [3,5].

Patients

Patients included in this study were being followed at the Hypertension Unit of our hospital. This Unit is exclusively dedicated to the treatment of hypertension and gives assistance to a geographic area with a population of 645166 persons [9]. All patients had been diagnosed as having essential hypertension and had been followed for at least one year in our unit.

Selection Process

In a period between 1979 and 1999, a total of 4232 patients were referred to our center for the study of hypertension. After the usual clinical assessment, 3922 patients were diagnosed of essential hypertension. The analysis included here corresponds to 2686 patients. The clinical and biochemical characteristics of this group of patients are reflected in Table 1.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>N</th>
<th>Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>1157</td>
<td>57.92</td>
<td>14.45</td>
</tr>
<tr>
<td>Females</td>
<td>1529</td>
<td>56.93</td>
<td>12.14</td>
</tr>
</tbody>
</table>

Table 1: Clinical and renal function of the global group included for the study on the prevalence of mild renal insufficiency in patients with essential hypertension.

Results

Figure 1 reflects the results of our study on the prevalence of MCRI in essential hypertension; renal function was appraised following three methods of measurement. A prevalence of MCRI was found in 7.6% according
to serum creatinine levels. However this prevalence is raised to 22.3% and 21.5% when the diagnostic criteria for MCRI was the estimation of 24 hour creatinine clearance in urine or its estimation using the Cockroft-Gault formula. Table 2 shows the clinical and biochemical characteristics that differentiate the group of hypertensive patients with MCRI of those patients with a normal renal function according to the diagnostic method used. According creatinine clearance values, patients with a diminished renal function were characterized by older age (65±13 vs 56±14 years, p<0.01), elevated systolic BP (163±25 vs 155±23 mmHg, p<0.01), higher serum total cholesterol (232±46 vs 221±42 mg/dl, p<0.01), LDL cholesterol (152±39 vs 147±37 mg/dl, p<0.01), and triglycerides (139±78 vs 132±71 mg/dl, p<0.05), lower levels of HDL cholesterol (51±13 vs 53±14 mg/dl, p<0.01), higher serum uric acid (6.3±2.0 vs 5.8±1.7 mg/dl, p<0.01), fasting serum glucose (116±41 vs 108±30 mg/dl, p<0.01), serum potassium (4.4±0.5 vs 4.2±0.4 mEq/l, p<0.01), and higher levels of urinary albumin excretion (0.14±0.66 vs 0.05±0.47 g/24h).

Discussion
In the last decade, nephrosclerosis has been recognized as a very frequent cause of ESRD [10,11]. This finding led to conclude that renal involvement in hypertension had to be prevalent and that better degrees of renal protection must be obtained in patients with hypertension. These statements were in apparent disagreement with the data published in the very few series of patients in which renal function was analyzed.

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**Table 2** Clinical characteristics of a group of 2686 patients followed for more than one year in our Hypertension Unit, at the Hospital 12 de Octubre in Madrid.

<table>
<thead>
<tr>
<th></th>
<th>Normal Creatinine Clearance</th>
<th>Cockroft-Gault</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76±14</td>
<td>76±13</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>156±23</td>
<td>156±23</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>96±13</td>
<td>96±18</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>223±43</td>
<td>223±44</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>132±72</td>
<td>132±73</td>
</tr>
<tr>
<td>HDL-Cholesterol (mg/dl)</td>
<td>52±13</td>
<td>52±14</td>
</tr>
<tr>
<td>LDL-Cholesterol (mg/dl)</td>
<td>147±30</td>
<td>147±30</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>57±1,6</td>
<td>57±1,7</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>109±33</td>
<td>110±36</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>4,2±0,4</td>
<td>4,2±0,4</td>
</tr>
<tr>
<td>Proteinuria (g/24h)</td>
<td>0,05±0,4</td>
<td>0,05±0,4</td>
</tr>
</tbody>
</table>


Figura 1: Prevalence of mild renal insufficiency in the population of hypertensive patients followed in our Hypertension Unit. Figures represent percentages.
with adequate criteria for blood pressure control [12,13] in which less than 2% of patients presented MCRI, diagnosed by the presence of elevated serum creatinine values. In fact, in the population participating in the Framingham Heart Study, the existence of a relevant prevalence (8.7% in males and 8.0% in females) of mild renal insufficiency, based on serum creatinine values [7], has been described. The prevalence of a mild decrease in renal function in the community could be even higher according to the values of estimated creatinine clearance seen in the NHANES III Survey [14]. Interestingly, in the Framingham population the presence of mild renal insufficiency did not depend on the existence, in this group of patients, of a higher prevalence of hypertension [7]. However, the prevalence of left ventricular hypertrophy was 3-4 times higher for similar blood pressure levels in patients with renal insufficiency when compared to those with a normal renal function. This indicates that like in diabetes, the cardiovascular and renal system of these subjects could be particularly sensitive to very small blood pressure elevations. On the other hand, the existence of a mild decrease in renal function can contribute to a progressive rise in blood pressure through the different mechanisms involved in the development of hypertension in renal disease.

According to serum creatinine levels, our results show that 7.6% of patients referred to our hypertension unit have a decreased renal function, and one of every five patients has a decreased creatinine clearance. These patients have a high or very high cardiovascular risk profile as a result of elevated BP, associated risk factors, or both, according to recently published guidelines [15,16]. The prevalence of MCRI in our unit according to serum creatinine values is superior to that seen in the HOT study [3], but lower to that observed in the HOPE study [5] that included patients with a very elevated level of global cardiovascular risk. These data indicate that the higher the level of cardiovascular risk, the higher will be the prevalence of MCRI in the hypertensive population.

On the other hand, it is also well known that serum creatinine levels are poor indicators of the renal filtration capacity and that the measurement of glomerular filtration rate (GFR) is a much more reliable index. Unfortunately, an accurate methodology to adequately estimate GFR is rarely available in clinical practice. This has led to the utilization of different formulas to estimate creatinine clearance [6,7], to further evaluate the presence of MCRI in essential hypertension. In the HOT study, using the Cockcroft and Gault formula and a cut-off point of 60 ml/min, a prevalence of MCRI of 12.3% was found [3]. It went up to a 35% in the HOPE study [5]. This is agreement with the clear relationship among global cardiovascular risk and MCRI. Considering serum creatinine levels as diagnostic test of MCRI, the prevalence of MCRI could be lower in general hypertensive population, but it is necessary to reinforce the need to estimate creatinine clearance for renal function evaluation, to avoid the misclassification of hypertensive patients with MCRI as patients with normal renal function.

The presence of hypercreatininemia (above 1.7 mg/dl) at baseline was found to be a very potent predictor for 5 and 8 year all cause mortality in the Hypertension Detection and Follow-up Program trial [17]. Data from the HOT [3] and HOPE [5] studies have confirmed those findings and reinforce the relevance of finding mild elevations in serum creatinine to stratify the global cardiovascular risk of hypertensive patients. In the HOT study [3] study we also investigated the prognostic value of the finding of a diminished creatinine clearance, as estimated by the Cockroft and Gault formula, and it was found that values below 60 ml/min were accompanied by a significantly higher cardiovascular risk. Similar results have been found in the analysis of the data from the HOPE study [5]. In Table 2, the clinical characteristics of the group of patients with essential hypertension with MCRI in our unit are compared with those of patients with preserved renal function: most associated risk factors present significantly elevated values when MCRI is present. These findings agree with those observed in those subjects of the general population presenting MCRI [7,18].

The relevance of proteinuria for cardiovascular prognosis in the community was described in the Framingham Heart Study [19]. The presence of proteinuria in essential hypertension oscillates among 4 and 16% in different series of treated hypertensive patients and it is associated with a much higher prevalence of cardiovascular events and death [20]. The very recently published INSIGHT study (International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment) [4] compared the capacity of a long-acting dihydropyridine and a diuretic to diminish cardiovascular events and death in patients with essential hypertension who had at least one associated risk factor. In this study, proteinuria was considered for the first time as an associated risk factor and the analysis of the predictive power of the different risk factors revealed that proteinuria was the most powerful, even more than the existence of previous myocardial infarction or diabetes [4].

The increase in cardiovascular risk accompanying the existence of chronic renal failure since its mildest stages has led with the consideration that the identification of predictors of the future development of renal damage in hypertension would be of great clinical value. In this sense, it has been described that black males with elevated blood glucose and systolic blood pressure have an increased risk of developing impaired renal function [18,21]. There is also greater damage in the renal vessels of hypertensive patients presenting hyperuricemia in the presence of a normal glomerular filtration rate [22]. The elevated prevalence of hyperuricemia in previously untreated hypertensive population makes this finding of interest, because
elevated levels of uric acid are a characteristic of the denominated X syndrome [22,23], characterized by the presence of insulin resistance and hyperinsulinism that contributes to a significant increase of cardiovascular morbidity and mortality. In our experience [18], nephrosclerosis is associated to higher initial levels of both systolic and diastolic blood pressure, a predominant male gender, higher initial levels of serum uric acid and triglycerides, and lower levels of HDL-cholesterol. A multivariate logistic regression analysis identified systolic and diastolic blood pressure, as well as serum uric acid and triglycerides as independent predictors for the development of nephrosclerosis [18].

In summary, the presence of a diminished renal function is more prevalent that previously thought in essential hypertension. This is particularly so if estimated creatinine clearance is considered routinely in the evaluation of all hypertensive patients. The finding of an altered renal function is associated to a significant increase in cardiovascular risk. This fact reinforces the need to pay attention to any of the manifestations of renal damage observed in the usual clinical assessment of any hypertensive patient.

References

Name and Surname: 
Country: Argentina
E-Mail address: @

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