Prognosis in Essential Hypertensive Patients

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Abstract. The existence of a significant percentage of treated hypertensive patients presenting a diminished renal function has been recently described. Mild renal function abnormalities are recognized as powerful predictors of cardiovascular morbidity and mortality. However, longitudinal data demonstrating this association are lacking. The objectives of this study have been analysis of the evolution of GFR, assessed as creatinine clearance (CrCl), during long-term follow-up of hypertensive patients and evaluation of the impact of the development of chronic kidney disease (CKD) on cardiovascular prognosis. A historical cohort of 281 patients attending our Hypertension Unit was selected according to the following criteria: essential hypertension, more than 5 yr of follow-up, and normal GFR at baseline (CrCl > 90 ml/min per 1.73 m²). Patients had an average follow-up of 13.2 ± 4.8 yr. Forty-one patients (14.6%) developed CKD (CrCl < 60 ml/min per 1.73 m²) attributed to hypertensive nephrosclerosis. Initial serum creatinine, age, systolic BP at baseline, and average total cholesterol during follow-up were independent predictors of CKD development. Forty-nine (17.4%) of 281 patients presented a cardiovascular event during follow-up: 17 patients (40.6%) who developed CKD and 32 patients (13.3%) with preserved renal function (log rank test P < 0.001). After adjustment in a Cox multivariate analysis, age, development of CKD during follow-up, and male gender were independent predictors of the appearance of cardiovascular events. In essential hypertensive patients with normal renal function at baseline, the development of CKD during the follow-up is strongly and independently related with poor cardiovascular prognosis.

The relation between elevated BP and end-stage renal disease (ESRD) is well established (1). In fact, high levels of treated BP are positively and significantly related to early decline in kidney function among hypertensive men (2), and hypertensive nephrosclerosis is recognized as a major cause of ESRD (3,4). The prevalence of chronic kidney disease (CKD) in essential hypertension has been considered to be low (<2%) on the basis of serum creatinine concentration as the index to estimate renal function (5,6). However, other evidences indicate that renal prognosis is not so benign in hypertensive patients (4,7–9) and that CKD is more prevalent than previously expected in treated essential hypertension (10 –12). Evaluation of renal function in long-term treated hypertensive patients has two main difficulties: first, the slow rate of progression to ESRD of nephrosclerosis, requiring very long follow-ups to investigate the evolution of renal function (4); second, the low discriminatory capacity of serum creatinine levels as an indicator of the renal filtration capacity and its changes with time (13,14). GFR is the best measure of overall renal function in health and disease (14). In clinical practice, measurement of creatinine clearance with 24-h urine collection is considered as an adequate estimate of GFR. This parameter can also be estimated from serum creatinine levels by using prediction equations (Cockroft-Gault or Modification of Renal Disease [MDRD] equations) that take age, sex, race, and body weight into account (15,16), although it has been described that the MDRD equation consistently underestimates GFR, whereas the Cockroft-Gault equation overestimates measured GFR in people with normal renal function (17). Independent of the etiology, the presence of CKD is a strong predictor of cardiovascular disease (18). In fact, JNC-7 recognizes an estimated GFR below 60 ml/min as a major cardiovascular risk factor (19). Unfortunately, no prospective therapeutic trials aimed at reducing the cardiovascular burden in people with CKD are available (18).

All these facts prompted us to analyze the development of CKD secondary to hypertensive nephrosclerosis in patients referred to our center. Our aims were to establish the incidence of CKD attributable to hypertension-related benign nephrosclerosis in the long-term follow-up of a cohort of essential hypertensive patients with normal renal function at baseline and to analyze the impact of the development of CKD on cardiovascular prognosis.

Materials and Methods

Study Design

This was an observational, long-term follow-up study of a historical cohort of essential hypertensive patients with normal renal function at baseline attending our Hypertension Unit, intended to establish the incidence of CKD attributable to hypertension-related nephroscler-
rosis and to analyze the influence of known factors conditioning renal damage and their impact on cardiovascular outcome.

Patients
We selected patients aged between 18 and 75 yr, with any grade of essential hypertension, normal renal function at baseline (defined as a creatinine clearance > 90 ml/min per 1.73 m²), and at least 5 yr of follow-up in our computerized data system. We excluded patients with malignant hypertension, suspected or diagnosed secondary hypertension, renal insufficiency, proteinuria (defined as >300 mg/24 h) or urinary sediment alterations, urologic diseases, chronic administration of antinflammatory drugs, and uncontrolled diabetes mellitus (defined as an average fasting plasma glucose > 200 mg/dl [11.1 mmol/L]).

Follow-Up
Complete medical history and physical examination were performed at entry. Data about presence of previous diabetes, smoking, dyslipidemia (defined as a total cholesterol levels > 200 mg/dl), and hyperuricemia were collected. According to our usual protocol, patients were followed at 3-mo intervals for BP measurement and medication adjustment to achieve the recommended BP goals (<140/ <90 mmHg). These BP goals were uniform during follow-up. Blood samples and 24-h urine collection were obtained at least twice a year to measure serum creatinine, glucose, total cholesterol, HDL and LDL cholesterol, triglycerides, serum uric acid, sodium, and potassium, as well as for the calculation of creatinine clearance and 24-h proteinuria, natriuresis, and kaliuresis. BP was measured using a mercury sphygmomanometer after 5 min in a seated position, using an adequate cuff. Serum and urine creatinine concentrations were determined by the routine Jaffe reaction.

Outcome Variables
The primary end point was defined as a reduction of creatinine clearance below 60 ml/min per 1.73 m² in two consecutive measurements during follow-up. Due to the fact that the MDRD equation underestimates GFR and the Cockroft-Gault equation overestimates measured GFR in people with normal renal function (17), we selected creatinine clearance measured with 24-h urine collection to define renal end point. Secondary variables included mean serum glucose, HDL, LDL, and total cholesterol, triglycerides, and systolic and diastolic BP. These mean values were calculated as the average of successive determinations during follow-up for each patient. Baseline serum creatinine values were divided into quartiles to facilitate the analysis.

According to the appearance of renal events, patients were classified in two groups: renal event-free group (F group) or those who developed CKD (C group).

Appearance of cardiovascular events (acute myocardial infarction, angina, congestive heart failure, stroke, and/or cardiovascular death) was considered as a secondary variable. Acute myocardial infarction was defined as an ischemic pain of myocardial origin, persisting at least 30 min, with electrocardiographic changes (persistent ST-segment elevation of ≥0.1 mv or new pathologic Q waves, each in at least two contiguous leads) and total CK levels higher than two times the upper limit of normal. Angina was defined as typical myocardial ischemic pain with electrocardiographic ischemic changes (horizontal or downsloping ST-segment depression of at lest 0.1 mv measured 80 msec from the J point and returning to normal within approximately 1 h), confirmed by angiography (obstructive lesion of at least 70% diameter stenosis) or exercise or pharmacologic challenge nuclear study. Chronic heart failure was defined by two or more of the following features: dyspnea on exertion in the absence of new pulmonary disease, bilateral pedal edema, paroxysmal nocturnal dyspnea, orthopnea, pulmonary rales, pulmonary edema or radiographic evidence of pulmonary congestion, cardiomegaly (cardiac thoracic ratio ≥ 0.55), left ventricular ejection fraction ≤ 40%, left ventricular fractional shortening < 0.25, or S 3 gallop on auscultation. Stroke was defined as an acute focal neurologic dysfunction of vascular origin with rapid onset of signs and symptoms and lasting more than 24 h. CV death was defined as natural death due to cardiac causes, heralded by abrupt loss of consciousness within 1 h of the onset of acute symptoms.

Statistical Analyses
Results are expressed as mean and SD or 95% CI as indicated. Statistical analyses were performed with the SPSS version 10.0. The significance of the differences in categorical and continuous variables among groups was examined by means of the Pearson χ² test and t test, respectively. All tests were two-tailed; P < 0.05 was considered statistically significant. A survival analysis was performed to evaluate the percentage of patients who developed CKD, both in the whole group and classifying the patients by quartiles according their baseline serum creatinine levels.

Kaplan-Meier survival analyses were performed, with log-rank as significance test for differences, to evaluate the impact of angiotensin-converting enzyme inhibitor (ACEI) administration and diabetic status on renal function. The same survival analysis was performed to evaluate the appearance of cardiovascular events and its possible relationship with renal function and ACEI administration. Cox regression analysis was performed, incorporating most important predictors of renal outcome (age, gender, weight, body mass index, baseline systolic and diastolic BP, baseline serum creatinine, diabetes, smoking status, and follow-up mean values of systolic and diastolic BP and serum HDL, LDL, and total cholesterol, triglycerides, glucose, and uric acid) to recognize independent predictors of CKD development. The same analysis was performed to assess the independent predictors of cardiovascular events, including CKD development during follow-up. A backward elimination method was used to exclude variables for the initial model.

Results
Baseline Characteristics
Two hundred eighty-one patients with baseline mean age of 46.9 ± 4.8 yr (range, 18 to 74 yr; 58% female) were included in the study. Mean follow-up was 13.2 ± 4.8 yr (13.1 ± 4.3 yr in group F, n = 240; 13.3 ± 4.9 yr in group C, n = 41, P = NS). Table 1 contains baseline characteristics of the whole group and of F and C subgroups. Age and systolic and diastolic BP values were higher at baseline in the C group than in the F group (53.1 ± 5.7 versus 45.7 ± 3.9 yr, P < 0.01; 181.5 ± 31 versus 161.8 ± 24 mmHg, P < 0.03; and 111.6 ± 17 versus 101.8 ± 14 mmHg, P < 0.01). Baseline serum creatinine and serum uric acid were significantly higher in group C compared with F group (serum creatinine 93.7 ± 17.7 versus 82.2 ± 17.7 μmol/L, P < 0.01; serum uric acid 386.6 ± 101.1 versus 345.0 ± 95.2 μmol/L, P < 0.01). Creatinine clearance calculated with 24-h urine sample showed a nonsignificant difference between F and C groups.
Follow-Up

During follow-up, mean systolic BP values remained significantly higher in the C group compared with F group (152 ± 11 mmHg versus 146 ± 12 mmHg, P < 0.05), albeit patients in group C received more antihypertensive drugs than those in group F (2.2 ± 0.8 versus 1.8 ± 0.9 drugs, P < 0.01) (Table 1).

Mean total cholesterol values during follow-up were significantly more elevated in group C than in group F (6.18 ± 0.70 versus 5.72 ± 0.88 mmol/L, P < 0.05).

Evolution of Renal Function

Forty-one patients (14.6%) experienced the renal event defined as primary end point. The mean time to event was 12.5 ± 5.2 yr. Patients included in the highest quartile of baseline serum creatinine showed the worst renal function prognosis (Figure 1). Considering the whole group, the prognosis of renal function did not differ between patients receiving or not an ACEI (Figure 2A), nor between diabetic and nondiabetic patients, although a better trend can be seen in nondiabetic patients (Figure 2B). The analysis of the influence of ACEI administration on renal function was performed with the group divided into nondiabetic and diabetic patients (Figure 2, C and D).

Table 1. Baseline characteristics, concomitant risk factors, and mean values during follow-up

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Total Group</th>
<th>Free Renal Event Patients</th>
<th>CKD Development Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>281</td>
<td>240 (85.4)</td>
<td>41 (14.6)</td>
</tr>
<tr>
<td>age, yr</td>
<td>46.9 ± 4.8</td>
<td>45.7 ± 3.9</td>
<td>53.1 ± 5.7</td>
</tr>
<tr>
<td>female (%)</td>
<td>58.0</td>
<td>58.3</td>
<td>56.7</td>
</tr>
<tr>
<td>follow-up, yr</td>
<td>13.2 ± 4.8</td>
<td>13.1 ± 4.3</td>
<td>13.3 ± 4.9</td>
</tr>
<tr>
<td>weight, kg</td>
<td>73.3 ± 12.4</td>
<td>73.3 ± 12.6</td>
<td>73.7 ± 11.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.1 ± 4.3</td>
<td>28.0 ± 4.2</td>
<td>29.7 ± 4.4</td>
</tr>
<tr>
<td>systolic BP, mmHg</td>
<td>165 ± 27</td>
<td>161.8 ± 24</td>
<td>181.5 ± 31</td>
</tr>
<tr>
<td>diastolic BP, mmHg</td>
<td>103 ± 15</td>
<td>101.8 ± 14</td>
<td>111.6 ± 17</td>
</tr>
<tr>
<td>serum creatinine, µmol/L</td>
<td>84.0 ± 17.7</td>
<td>82.2 ± 17.7</td>
<td>93.7 ± 17.7</td>
</tr>
<tr>
<td>creatinine clearance, ml/min per 1.73 m²</td>
<td>104 ± 18</td>
<td>105 ± 18</td>
<td>98 ± 19</td>
</tr>
<tr>
<td>serum uric acid, µmol/L</td>
<td>351.0 ± 95.2</td>
<td>345.0 ± 95.2</td>
<td>386.6 ± 95.2</td>
</tr>
<tr>
<td>total cholesterol, mmol/L</td>
<td>5.66 ± 1.39</td>
<td>5.61 ± 1.37</td>
<td>5.90 ± 1.27</td>
</tr>
</tbody>
</table>

Concomitant risk factors

| smoking (%)               | 14.1        | 13.0                     | 17.0                    |
| type 2 diabetes (%)       | 26.6        | 24.5                     | 38.0                    |
| baseline (%)              | 11.0        | 10.8                     | 16.9                    |
| new onset diabetes (%)    | 15.6        | 13.7                     | 21.1                    |
| dyslipidemia (%)          | 17.4        | 17.0                     | 19.0                    |

Mean values during follow-up

| systolic BP, mmHg         | 147 ± 12    | 146 ± 12                 | 152 ± 11b               |
| diastolic BP, mmHg        | 89 ± 6      | 89 ± 6                   | 90 ± 6                  |
| drugs, n                 | 1.9 ± 0.9   | 1.8 ± 0.9                | 2.2 ± 0.8c              |
| ACEI (%)                 | 45.4        | 47.3                     | 34.1                    |
| total cholesterol, mmol/L | 5.79 ± 0.88 | 5.71 ± 0.88             | 6.18 ± 0.70b            |

* Values are mean ± SD. CKD, chronic kidney disease; BMI, body mass index.
* b P < 0.05 with respect to free renal event patients.
* c P < 0.01 with respect to free renal event patients.

Follow-Up

Evolution of Renal Function

Figure 1. Risk of chronic kidney disease (CKD) development according baseline serum creatinine distribution. 1st quartile (□); Scr: <1 mg/dl for male, <0.7 mg/dl for female. 2nd quartile (○); Scr: 1.0 to 1.1 mg/dl for male, 0.7 to 0.9 mg/dl for female. 3rd quartile (×); Scr: 1.1 to 1.2 mg/dl for male, 0.9 to 1.0 mg/dl for female. 4th quartile (●); Scr: >1.2 mg/dl for male, >1.0 mg/dl for female.
In patients with type 2 diabetes (n = 75), the inclusion of an ACEI (n = 41) in their antihypertensive therapy facilitated a significantly better renal prognosis when compared with other therapies (calcium channel blockers, beta-blockers, and diuretics) (log rank test P < 0.05) (Figure 2D). Cox regression analysis showed that baseline serum creatinine, baseline systolic BP, age, and mean values of total cholesterol during follow-up are independent predictors for developing of CKD (Table 2). The analysis of slopes of serum glucose during follow-up showed a nonsignificant trend for higher values in patients developing CKD (84.4 μmol/L per yr) compared with those preserving renal function (63.3 μmol/L per yr, P = 0.485).

Cardiovascular Events

Forty-nine (17.4%) of 281 patients presented a cardiovascular event (16 acute myocardial infarction, 9 angina, 8 congestive heart failure, 16 stroke) during follow-up: 17 patients (40.6%) who developed CKD and 32 patients (13.3%) with preserved renal function (log rank test P < 0.001) (Figure 3A). Among patients receiving an ACEI (n = 128), 16 (12.5%) presented a cardiovascular event compared with 33 (21.6%) of 153 patients receiving other antihypertensive drugs (log rank test P < 0.05) (Figure 3B). After adjustment in a Cox multi-

Table 2. Cox regression analysis: independent predictors for developing of chronic kidney disease

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio</th>
<th>CI 95%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline serum creatinine</td>
<td>6.33</td>
<td>(1.69 to 29.9)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Baseline systolic BP</td>
<td>1.21</td>
<td>(1.08 to 1.34)</td>
<td>0.0031</td>
</tr>
<tr>
<td>Age</td>
<td>1.48</td>
<td>(1.10 to 1.87)</td>
<td>0.0328</td>
</tr>
<tr>
<td>Mean total cholesterol in follow-up</td>
<td>1.25</td>
<td>(1.09 to 1.34)</td>
<td>0.0170</td>
</tr>
</tbody>
</table>

* Hazard ratios for baseline serum creatinine, baseline systolic BP, age, and mean total cholesterol in follow-up are 0.1 mg/dl, 10 mmHg, 10 yr, and 10 mg/dl increases, respectively.

Variables excluded for the initial model were as follows: gender, weight, BMI, baseline diastolic BP, diabetes, smoking status, and follow-up mean values of systolic and diastolic BP and serum HDL and LDL cholesterol, triglycerides, glucose, and uric acid.
variate analysis, age, development of CKD during follow-up, and male gender were independent predictors of the appearance of cardiovascular events (Table 3).

Discussion

There is very little information in the literature about the development of CKD in hypertensive patients. In 500 untreated hypertensive patients followed until death, Perera (20) described that proteinuria was present in 42% and chronic renal failure in 18%. Growing evidence indicates that renal prognosis is not so good in either hypertensive patients or the general population (4,7–12). The Heart Outcomes Prevention Evaluation (HOPE) study showed a prevalence of CKD of 10.4% according to serum creatinine values \( \geq 1.4 \text{ mg/dl} \) (21). We have recently described that 7.6% of patients referred to our hypertension unit have a decreased renal function according to serum creatinine levels, and one of every four patients has a decreased creatinine clearance (12). The prevalence of CKD in the community could be even higher according to the values of estimated creatinine clearance seen in the Third National Health and Nutrition Examination Survey (NHANES III) (7,22).

Perneger et al. (9) published an integrated analysis of data from several population studies showing a crude annual incidence of hypercreatininemia in hypertensive patients of 4.61 per 1000 subjects. Adjusting for gender and race, annual rates of hypercreatininemia were 4.06, 1.84, 8.41, and 4.96 per 1000 subjects in white men, white women, African-American men, and African-American women, respectively (9). On average, these results suggest that 1 in 13 hypertensive patients progresses to hypercreatininemia every year (9). Nevertheless, this study assessed renal function according to serum creatinine level, a poor indicator of GFR (13,14). Ronstad et al. (10) showed a deterioration of renal function in a 15% of treated hypertensive patients also according serum creatinine levels. A similar percentage is observed in our study (14.6%), but according to creatinine clearance, a more sensitive parameter. Furthermore, in our study the mean follow-up was long enough (13.2 ± 4.8 yr) to ensure a large enough number of renal events.

Our results show that development of CKD, estimated as a creatinine clearance below 60 ml/min per 1.73 m\(^2\) in hypertensive patients with baseline normal renal function is a not infrequent finding along follow-up: 14.6 per 1000 patients included developed CKD during more than 13 yr of mean follow-up. This finding means an annual rate of 1.11 per 100 patients and it represents more than two times the incidence of hypercreatininemia described by Perneger et al. in white men (9). Cox regression analysis showed that baseline serum creatinine level is the strongest predictor of CKD development. Every increase of 0.1 mg/dl in serum creatinine level increases the risk of CKD by six times. Cox regression analysis showed that baseline serum creatinine level is the strongest predictor of CKD development.

Table 3. Cox regression analysis: independent predictors for the appearance of cardiovascular events

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>CI 95%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06</td>
<td>(1.02 to 1.09)</td>
</tr>
<tr>
<td>CKD development</td>
<td>2.53</td>
<td>(1.32 to 4.81)</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.06</td>
<td>(1.09 to 3.89)</td>
</tr>
</tbody>
</table>

* Hazard ratio for age is for 1-yr increase. Variables excluded for the initial model were as follows: weight, BMI, baseline diastolic BP, diabetes, smoking status, follow-up mean values of systolic and diastolic BP and serum HDL and LDL cholesterol, triglycerides, glucose, and uric acid.

Figure 3. (A) Cardiovascular prognosis between patients developing chronic kidney disease (CKD) and those with preserved renal function. (B) Cardiovascular prognosis between patients receiving angiotensin-converting enzyme inhibitors and those receiving other antihypertensive therapies.
predictive capacity. This finding was true even in normal range of serum creatinine levels (Figure 1). Other independent predictors were the age and systolic BP at the beginning of follow-up and serum total cholesterol level. Serum glucose was not an independent predictor, albeit the analysis of the slope of its evolution with time exhibited a trend for higher values in those developing renal failure (84.4 versus 63.3 μmol/L per yr; \( P = 0.485 \)). In a cross-sectional study intended to define the clinical characteristics of hypertensive patients (\( n = 1625 \)) with metabolic syndrome, we found that glucose metabolism disturbance was related with a diminished creatinine clearance and higher urinary albumin excretion (23).

The relevance of CKD as a predictor of cardiovascular risk has received ample review recently (24). In hypertensive patients, the presence of a diminished estimated GFR (<60 ml/min per 1.73 m\(^2\)), microalbuminuria, small elevations in serum creatinine or proteinuria have been recognized by recently published Hypertension Management Guidelines (19,25) as major cardiovascular risk factors. Recent data from the ARIC (Atherosclerosis Risk on Communities) study have shown that the level of GFR is an independent risk factor for atherosclerotic CV disease (26). The HOORN study showed that mild to moderate loss of renal function is strongly associated with an increased risk of CV mortality (27). Nevertheless, data about the relationship between the development of CKD and cardiovascular risk are lacking (18). Our study shows that hypertensive patients who developed CKD presented a rate of cardiovascular events 2.5 times higher than those with preserved renal function.

Very recently, ACEI have shown beneficial effects on the progression of hypertensive nephrosclerosis in the presence of renal damage (28,29). Considering either the whole group or the nondiabetic patients, we have not found differences between ACEI-treated and not treated patients in CKD development. This is not the case in type 2 diabetic patients treated with ACEI, in whom our results show a better prognosis of renal function than was seen in patients treated with other antihypertensives. This finding is in agreement with previous evidences about favorable effects of ACEI on prevention of CKD in type 2 diabetes (30).

Among patients receiving an ACEI, the appearance of cardiovascular events was significantly lower than in patients treated with other antihypertensive drugs. These results are in agreement with HOPE (31) and EUROPA (EUAuropean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) (32) studies, showing the cardiovascular benefits of ACEI in high CV risk patients.

Our study has limitations related to its retrospective character and to the absence of a randomized distribution of therapies. Moreover, our data must be analyzed in the light of the level of BP control that was poor for the actual standards of BP goal (19,25). A more strict BP control might have enhanced renal protection and the effect of ACEI in essential hypertension. It is also true that we analyzed referred patients with high CV risk, and extrapolation of these results to the general population has to be made with caution. However, the presence of CKD will have always the same predictor capacity.

In conclusion, our data indicate that a relevant percentage of patients with arterial hypertension develop CKD, defined as a fall in creatinine clearance to values below 60 ml/min per 1.73 m\(^2\). This evolution is not prevented by ACEI treatment in essential hypertensive patients, albeit this therapy prevents renal damage when type 2 diabetes is present. The development of CKD is strongly and independently related with poor cardiovascular prognosis.

References