Factors Related to the Occurrence of Microalbuminuria During Antihypertensive Treatment in Essential Hypertension

Josep Redon, Eduardo Rovira, Amparo Miralles, Raul Julve, Jose M. Pascual

Abstract—The objective of the study was to assess the factors related to the occurrence of microalbuminuria during the follow-up of a young adult group with essential hypertension that had not been previously treated. Normo-albuminuric essential hypertensives, <50 years old, who had not been previously treated with antihypertensive drugs and who did not have diabetes mellitus were included. After the initial evaluation, patients were treated using only nonpharmacological measures (n=62), β-blockers (n=38), ACE inhibitors (n=64), calcium channel blockers (n=8), and several classes (n=15). Measurements were taken for office blood pressure, biochemical profile, and 24-hour urinary albumin excretion at the beginning of the study and were measured yearly during an average of 2.7±1.2 years of follow-up. Among the 187 patients included, 22 (11.7%) developed microalbuminuria (progressors, 4.4/100 patients/y). No differences were present between progressors and those who remained normo-albuminuric (nonprogressors) in terms of age, gender, body mass index, disease duration, blood pressure values, biochemical profile, familial history of diabetes or hypertension, smoking habits, or the presence of EKG leftventricular hypertrophy. The group with the lowest progression rate was the patients treated with ACE inhibitors(n=5; 2.9/100 patients/y), followed by the diet group (n=5; 3.3/100 patients/y) and the β-blockers group (n=5; 4.1/100 patients/y). When we excluded patients treated with calcium channel blockers or those who changed over time between different classes of treatment, no significant differences in the incidence of microalbuminuria were observed among the groups. Progressors showed higher slopes of fasting glucose (4.78±11.4 versus 0.50±6.8 mg/ y, P<0.02) and uric acid (0.58±0.93 versus 0.05±1.10 mg/y, P<0.03) compared with the slopes of nonprogressors. Both the slopes for glucose and systolic blood pressure over time were associated independently with the slope of the logarithm of urinary albumin excretion when adjusted for age, gender, and treatment groups. Cox proportional hazard model for progression of microalbuminuria showed that baseline urinary albumin excretion (risk ratio [RR]=1.06; confidence interval [CI] 95%, 1.01 to 1.11), slope for systolic blood pressure (RR=1.11; CI 95%, 1.03 to 1.20), and slope for glucose (RR=1.08; CI 95%, 1.03 to 1.14) were independently associated to the development of microalbuminuria. In conclusion, in a group of young adults with essential hypertension that had not been previously treated, the main factors influencing the occurrence of microalbuminuria during antihypertensive treatment were the values of microalbuminuria at baseline and the slopes for systolic blood pressure and fasting glucose. (Hypertension. 2002;39:794-798.)

Key Words: albuminuria ■ antihypertensive therapy

Microalbuminuria is now considered a marker of cardiovascular and renal risk in diabetic1 and nondiabetic elderly subjects.2 In hypertension, although the prevalence of microalbuminuria is variable and depends on the characteristics of the population studied, a clustering of cardiovascular risk factors has been observed in patients with microalbuminuria. Furthermore, recent data supports microalbuminuria as a prognostic marker for cardiovascular and/or renal risk.3–6

Assessment of urinary albumin excretion (UAEx) is increasing in a risk stratification strategy for hypertensive patients. Knowledge of the determinants of microalbuminuria seems to be important for a better understanding of the role of microalbuminuria assessment in the management of hypertension. Up to now, only cross-sectional studies have analyzed the factors related to the development of microalbuminuria. Our group7,8 and others9–11 have demonstrated that in essential hypertension, microalbuminuria was related to the levels of blood pressure (BP) values and to the presence of hyperinsulinemia as an expression of insulin resistance.12,13 Long-term surveys of microalbuminuria in essential hypertension are scanty,3,6,14,15 and information about the contribution of factors other than BP reduction in the changes of UAEx overtime is lacking. To add further information to the determinants of microalbuminuria in hypertensive subjects, the objective of the present prospective study was to assess the factors related to the occurrence of microalbuminuria...
during the follow-up of a group of never previously treated young adults with essential hypertension.

Patients and Methods

Selection of Study Participants and Design

Patients included in the study were selected from an outpatient clinic over the 5-year period from January 1992 through December 1996. All patients who fulfilled the inclusion criteria were invited to participate, and written consent was requested. The following were the inclusion criteria: (1) diastolic BP (DBP) in the range of high-normal to moderate essential hypertension, defined as being between 90 and 114 mm Hg (Korotkoff phase V, sitting position) for 3 or more subsequent visits at 1-month intervals in the absence of secondary hypertension; (2) age of 25 to 50 years; (3) World Health Organization grade I or II; (4) glomerular filtration rate >80 mL/min per 1.73 m²; and (5) hypertension that had not been previously treated. Patients with nephropathy, diabetes mellitus, urinary tract infection, fasting glucose in serum >120 mg/dL, or dipstick positive for albumin or glucose were excluded. The ethics committee of the hospitals approved the study, and all patients granted their consent in writing.

Of the 253 patients enrolled, the 187 who were initially normoalbuminuric were the object of this study. After enrollment and according to clinical criteria, the patients were placed on an nonpharmacological treatment consisting of moderate salt restriction, and a low-calorie diet if overweight, with or without a regimen of antihypertensive drugs based on β-blockers, ACE inhibitors, or calcium channel blockers. Hydrochlorothiazide was added when necessary to maintain the BP goal of <135/85 mm Hg. During the follow-up, UAE, renal function, and other clinical and analytical parameters were assessed on a yearly basis.

Procedures

BP was measured using a mercury sphygmomanometer with the patient in sitting position after 5 minutes of rest in a quiet environment, following the recommendations of the British Hypertension Society. Systolic BP (SBP) and DBP (Korotkoff phase I and phase V, respectively) were the average of 3 readings measured at 5-minute intervals.

Blood samples were obtained in the morning after a minimum of 8 hours fasting. Serum biochemical profiles were measured using an autoanalyzer system multianalyzer computer (SMAC). The glomerular filtration rate was estimated by the clearance of endogenous creatinine as expressed with reference to body surface (mL/min per 1.73 m²).

UAE for 2 separate 24-hour urine collections was measured using an immunonephelometric assay (Behring Institute). Aliquots of urine were taken from the 24-hour and nighttime collections, stored in glass tubes at 4°C, and analyzed 1 to 7 days after collection. The intra- and interassay variabilities of the method in our laboratory were 2% and 7%, respectively, and the normal values in a healthy normotensive population of the same age range and gender was 4.6±1.6 mg/24 hours. For each patient, the UAE was considered as the mean of values obtained in the 2 separate 24-hour urine collections. If a difference of values obtained between the 2 samples was ≥25% of the higher value, or a creatinine excretion over 24 hours was lower than expected for body size and gender, a third sample was requested; this led to an additional sample being collected in 5% of the patients. Microalbuminuria was defined as UAE 30 to 300 mg/24 hours in the 2 samples.

Statistical Analysis

Data on UAE were analyzed in 2 ways. First, they were categorized into normo-albuminuric and microalbuminuric groups, as previously defined. Second, a continuous variable with logarithmic transformation (logEUA) was used. We define progressors as patients who were initially normo-albuminuric and developed microalbuminuria during the follow-up; nonprogressors as those who remained normo-albuminuric. The changes of parameters during the follow-up were estimated as the individual-specific regression line slope values.

The differences between patients were sought by using Student’s t test for continuous variables and χ² test for discontinuous variables. The Pearson correlation coefficients were used to examine the linear relationship between slope of the logEUA and other regression line slope values. Multivariate regression analysis was performed to assess the factors related to the changes in UAE during the follow-up. The Cox proportional hazard model was used to assess the effect of the prognostic factor on development of microalbuminuria. Adjusted relative risk for the significant Cox model factors were calculated and expressed along with the 95% confidence interval (CI). For each variable, the values were expressed as mean±SD.

Results

One hundred eighty-seven normo-albuminuric subjects were followed during an average of 2.7±1.2 years. Twenty-two (11.7%) developed microalbuminuria (progressors), with an incidence of 4.4/100 patients/y. The hazard risk to develop microalbuminuria is in Figure 1.

The initial characteristics of the patients who remained normo-albuminuric and those who became microalbuminuric are shown in Table 1. No differences were observed in terms of age, gender distribution, body mass index, disease duration, BP, and biochemical profile. Only apolipoprotein A was significantly lower in the progressors compared with the nonprogressors. Likewise, no differences exist in the family histories of frequency of diabetes or hypertension, in smoking habits, or in the presence of EKG left ventricular hypertrophy. Only body mass index and UAE were slightly higher in the group of patients who became microalbuminuric, although they did not achieve statistical significance.

Sixty-two patients received an exclusively nonpharmacological treatment, 38 received β-blockers (atenolol, bisoprolol), 64 received ACE inhibitors (enalapril, lisinopril), and 8 received calcium channel blockers (slow-release nifedipine), whereas the other 15 changed their class of treatment over time for several reasons (eg, side-effects or uncontrolled BP). Of the 22 patients who developed microalbuminuria, the group with the lowest incidence was of the patients treated with ACE inhibitors (n=5; 2.9/100 patients/y), followed by the diet group (n=5; 3.3/100 patients/y) and the β-blocker group (n=5; 4.1/100 patients/y). When we excluded patients treated with calcium channel blockers or those who changed their class of treatment over time, no significant differences in
TABLE 1. General Characteristics of the Subjects Grouped by the Outcome During the Follow-Up

<table>
<thead>
<tr>
<th>Variables</th>
<th>Progressors (n=22)</th>
<th>Nonprogressors (n=165)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>38.7±8.4</td>
<td>39.0±8.2</td>
<td>NS</td>
</tr>
<tr>
<td>Gender</td>
<td>10/12</td>
<td>84/81</td>
<td></td>
</tr>
<tr>
<td>Body mass index, Kg/m²</td>
<td>29.7±4.2</td>
<td>28.0±4.6</td>
<td></td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>3.4±3.5</td>
<td>3.0±4.4</td>
<td></td>
</tr>
<tr>
<td>UAE, mg/24 h</td>
<td>13.9±9.6</td>
<td>10.4±7.4</td>
<td></td>
</tr>
<tr>
<td>Family diabetes</td>
<td>2 (9.1%)</td>
<td>25 (15.2%)</td>
<td></td>
</tr>
<tr>
<td>Family hypertension</td>
<td>8 (36.4%)</td>
<td>90 (54.5%)</td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>1 (4.5%)</td>
<td>17 (10.3%)</td>
<td></td>
</tr>
<tr>
<td>EKG left ventricular hypertrophy</td>
<td>2 (9.0%)</td>
<td>23 (13.9%)</td>
<td></td>
</tr>
<tr>
<td>Office blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>146.2±13.6</td>
<td>148.2±16.7</td>
<td>NS</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>95.0±7.1</td>
<td>94.8±7.7</td>
<td></td>
</tr>
<tr>
<td>Biochemical profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.4±0.6</td>
<td>5.5±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Urea, mmol/L</td>
<td>11.4±2.3</td>
<td>11.6±2.7</td>
<td></td>
</tr>
<tr>
<td>Uric acid, μmol/L</td>
<td>294.4±77.3</td>
<td>327.1±95.2</td>
<td></td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>92.8±15.9</td>
<td>90.2±17.7</td>
<td></td>
</tr>
<tr>
<td>Clearance Cr, mL/s</td>
<td>1.6±0.3</td>
<td>1.7±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Lipid profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-cholesterol, mmol/L</td>
<td>5.2±0.8</td>
<td>5.4±1.1</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.4±0.7</td>
<td>1.4±0.9</td>
<td></td>
</tr>
<tr>
<td>Apo A, g/L</td>
<td>1.4±0.2</td>
<td>&lt;0.05</td>
<td>1.5±0.3</td>
</tr>
<tr>
<td>Apo B, g/L</td>
<td>1.2±0.2</td>
<td>1.2±0.3</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%).

The average of the slope for the patient-specific regression lines for selected variables grouped by progression of microalbuminuria are shown in Figure 2. The progressor group showed higher slopes of fasting glucose (0.26±0.65 versus 0.03±0.37 mmol·L⁻¹·y⁻¹, P<0.02) and of uric acid (34.5±55.3 versus 3.0±65.4 μmol·L⁻¹·y⁻¹, P<0.03) compared with the slopes of nonprogressors. Although in these subjects, a less steep regression line for changes in SBP and DBP was observed, the values did not achieve statistical significance. Likewise, no differences were observed in the slope of plasma creatinine (0.44±9.7 versus 0.97±15.6 μmol·L⁻¹·y⁻¹). These results mean that in progressors, while UAE increases, uric acid and fasting glucose increase, too. Moreover, the reduction in BP is less for progressors than it is for nonprogressors.

Pearson’s correlation coefficients for the slope of the logUAE showed a significant correlation with the slope of SBP (r=0.134; P<0.03). Both the slopes for glucose and SBP over time were associated independently with the slope of the logUAE when multiple regression analysis adjusted for age, gender, and treatment groups was used (Table 2).

Finally, a Cox proportional hazard model for progression of microalbuminuria showed that baseline UAE (risk ratio [RR] = 1.06; CI 95%, 1.01 to 1.11), slope for SBP (RR = 1.11; CI 95%, 1.03 to 1.20), and slope for glucose (RR = 1.08; CI 95%, 1.03 to 1.14) were independently associated to the development of microalbuminuria when the type of antihypertensive treatments was taken into account (Table 3).

### Discussion

In the present study conducted in a group of young adults never previously treated with essential hypertension, the main factors influencing the occurrence of microalbuminuria during antihypertensive treatment were the values of microalbuminuria at baseline and the slopes of SBP and fasting glucose. Thus, it is important to achieve both the best BP control and the best metabolic control in glucose overtime to avoid microalbuminuria. Consequently, to prevent occurrence of microalbuminuria, BP needs to be lowered as much as possible, and the factors that impair glucose metabolism need to be controlled.

The characteristics of the patients included in the present study permitted the investigation of factors influencing the occurrence of microalbuminuria in essential hypertension and allowed us to avoid confounding factors. Patients with a significant disturbance of their carbohydrate metabolism (high baseline glucose levels or diabetes mellitus) were excluded. We also excluded patients with urologic or renal pathology produced by causes other than hypertension and

TABLE 2. Relationship of Selected Variables and UAE Slope by Multivariate Regression Analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>β</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline UAE</td>
<td>0.32</td>
<td>0.561</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Slope of glucose</td>
<td>0.24</td>
<td>0.381</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Slope of SBP</td>
<td>0.23</td>
<td>0.426</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Gender (female vs male)</td>
<td>1.13</td>
<td>2.512</td>
<td>0.511</td>
</tr>
</tbody>
</table>

The model includes age and kind of treatment.
renal failure. Patients who had never been treated with antihypertensive drugs were chosen to provide a better estimate of the impact of elevated BP on microalbuminuria and to avoid the possible treatment-induced changes in carbohydrate metabolism. To reduce day-to-day variability, UAE was measured in 2 separate 24-hour samples.

Another potential confounding factor, the type of the antihypertensive treatment that was used, merits special comment. Several studies have demonstrated that a reduction in BP values through the use of antihypertensive drugs was accompanied by a decrease in microalbuminuria in proportion to the reduction in BP.\(^{16}\) ACE inhibitors and antagonists of the angiotensin II type 1 receptor have shown additional beneficial effects on microalbuminuria, independent of BP reduction.\(^{16–18}\) In the majority of the patients who had received drugs as part of the antihypertensive treatment, 2 different kind of drugs, \(\beta\)-blockers and ACE inhibitors, were used. Because a different trend on the incidence rate of microalbuminuria has observed, we included the antihypertensive treatment as a dependent variable in the statistical analysis.

The factors related to the expression of microalbuminuria in hypertension have been the focus of several cross-sectional studies, including ours. BP level has been considered the most important factor related to microalbuminuria in essential hypertension.\(^{7,10,19}\) In addition, the overactivity of the renin-angiotensin system\(^{20}\) and hyperinsulinemia, as an expression of insulin resistance,\(^{12,13}\) has been linked to the development of microalbuminuria. Furthermore, the important of genetic factors has been emphasized in several studies, and the \(D\) allele of the polymorphism insertion/deletion (I/D) of the ACE gene, has been linked to a higher prevalence of microalbuminuria.\(^{21,22}\)

Although the study of microalbuminuria as a prognostic marker of cardiovascular or renal outcomes in hypertension has increased, long-term prospective studies on determinant factors of microalbuminuria are few.\(^{23,24}\) This is the first study that analyzes the state of the patient at baseline and the factors that affect microalbuminuria during follow-up. After the follow-up, we observed a 4.1 per 100 patient/year incidence rate of microalbuminuria for patients receiving antihypertensive treatment.

Baseline level of UAE was determinant of the occurrence of microalbuminuria in the multivariate regression analysis: the higher the baseline UAE, the higher the risk for developing microalbuminuria. Agewall et al\(^{24}\) studied 213 nondiabetic hypertensive patients without microalbuminuria after a 3-year follow-up, controlled biannually, using the level of UAE from a single measurement of overnight UAE.\(^{24}\) This study observed that patients who developed microalbuminuria had higher UAE at baseline compared with those who remained normo-albuminuric. Probably, the increase in baseline UAE is, at least in part, an expression of cardiovascular factors and end-organ damage even in values below the threshold to define microalbuminuria.\(^{25}\) The UAE changes during antihypertensive treatment are related in part to the presence of structural end-organ damage, and hypertensive patients with persistent but not reversible microalbuminuria under short intensive antihypertensive therapy have shown higher prevalence of end-organ damage.\(^{26}\)

In the present study, the incidence of microalbuminuria was related to the SBP achieved during antihypertensive treatment, in agreement with previous studies. In Agewall et al,\(^{24}\) patients who developed microalbuminuria, with an incidence rate similar to that of our study, had higher SBP. The changes in UAE values, however, were lower than those previously reported during short periods of observation\(^{16–18}\) when only the changes in BP values and the effect of the drug itself influenced the levels. Thus, BP control seems to be one of the main determinants in the increase of UAE overtime, although other factors are also implicated. A longer observation period, such as in the present study, allows for an analysis not only of the effect of the changes in BP but also of the impact of others factors on UAE.

The last factor that influences the occurrence of microalbuminuria was the slope of fasting glucose during the study: the more positive the slope, the higher the risk for developing microalbuminuria. Hypertensive subjects with microalbuminuria have shown higher values for fasting insulin and/or insulin area under the curve after glucose challenge, and hyperinsulinemia has been related to microalbuminuria.\(^{12,13,27}\) In diabetes mellitus, poor metabolic control is associated with an increased risk for developing microalbuminuria and nephropathy.\(^{28}\) The present study shows that in nondiabetic subjects, the metabolic control predicts progression to microalbuminuria. Whether or not these microalbuminuria subjects are therefore prone to develop type 2 diabetes is an attractive line of research.\(^{29}\)

In conclusion, UAE changes during antihypertensive treatment depend on the control of hemodynamic and metabolic factors. Whether or not the development of microalbuminuria is of prognostic significance in patients with essential hypertension remains to be demonstrated. Until more data becomes available, a control of the factors related to development of microalbuminuria seems to be a reasonable target during antihypertensive treatment.

References


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