Long-Term Impact of Systolic Blood Pressure and Glycemia on the Development of Microalbuminuria in Essential Hypertension

Jose Maria Pascual, Enrique Rodilla, Carmen Gonzalez, Santiago Pérez-Hoyos, Josep Redon

Abstract—The objective was to assess the temporal impact of factors related to the development of microalbuminuria during the follow-up of young adult normoalbuminurics with high-normal blood pressure or at stage 1 of essential hypertension. Prospective follow-up was conducted on 245 normoalbumuric hypertensive subjects (mean age 40.9 years; 134 men; blood pressure 139.7/88.6 mm Hg; body mass index 28.5 kg/m²) never treated previously with antihypertensive drugs, with yearly urinary albumin excretion measurements, until the development of microalbuminuria. After enrollment, patients were placed on usual care including nonpharmacological treatment or with an antihypertensive drug regime to achieve a blood pressure of <135/85 mm Hg. Thirty subjects (12.2%) developed microalbuminuria after a mean follow-up of 29.9 months (range 12 to 144 months), 2.5 per 100 patients per year. Baseline urinary albumin excretion (hazard ratio, 1.07;  P=0.006) and systolic blood pressure during the follow-up (hazard ratio, 1.03;  P=0.008) were independent factors related to the follow-up urinary albumin excretion in a Cox proportional hazard model. A significant increase in the risk of developing microalbuminuria for urinary albumin excretion at baseline >15 mg per 24-hour systolic blood pressure >139 mm Hg and a positive trend in fasting glucose were observed in the univariate analyses. However, in the multivariate analysis, only the baseline urinary albumin excretion and the trend of fasting glucose were independently related to the risk of developing microalbuminuria. In mild hypertensives, the development of microalbuminuria was linked to insufficient blood pressure control and to a progressive increment of glucose values. (Hypertension. 2005;45:1125-1130.)

Key Words: hypertension, essential ■ blood pressure ■ glucose ■ microalbuminuria

During the last few years, microalbuminuria has become a prognostic marker for cardiovascular or renal risk in diabetic and nondiabetic subjects. Although determinants of subtle increases in urinary albumin excretion (UAE) and its progression remain poorly understood, microalbuminuria assessment is now recommended in a risk stratification strategy for hypertension management. Moreover, the potential of microalbuminuria as an intermediate end point during antihypertensive treatment is still unclear, although evidence is appearing. A better understanding of what determines the development of microalbuminuria in hypertensives will help formulate a more rational allocation of microalbuminuria at the time of risk stratification as well as during treatment.

Factors related to the presence of microalbuminuria in essential hypertension have been analyzed in cross-sectional studies. Microalbuminuria has been related to blood pressure (BP) values and to hyperinsulinemia as an expression of insulin resistance. Obesity, smoking, and genetics have also been implicated as determinants of microalbuminuria in some of the studies.

Follow-up studies of microalbuminuria in essential hypertensives are rare, and information about the contribution of factors other than BP reduction on the changes of UAE over time is lacking. Thus, the objective of the present study was to assess the long-term impact of factors related to the development of microalbuminuria during follow-up for a group of young adult normoalbuminurics with essential hypertension who had never received antihypertensive treatment.

Patients and Methods

Selection of Study Participants and Design

Subjects, all white, were recruited from the hypertension outpatient clinic of the Hospital General of Sagunto (Sagunto, Spain) from January 1988 to December 2000. Patients were selected if their systolic BP (SBP) or diastolic BP (DBP) was in the high-normal to mild-essential hypertensive range, defined as being between 130 and 159 mm Hg or 85 and 100 mm Hg, respectively, in each of 3 visits at 1-month intervals and in the absence of secondary hypertension. None showed signs of renal damage on entering the study. Two strict entry criteria were that UAE had to be in the normal range and that no antihypertensive therapy had ever been received. Patients diag-
nosed with nephropathy, diabetes mellitus, urinary tract infection, fasting glucose in serum >6.7 mmol/L or urine dipstick positive for albumin or glucose were excluded. The study was approved by the Committee for the Protection of Human Subjects of the Sagunto Hospital, and all participants gave informed written consent.

A prospective follow-up with UAE measurements every year was performed until the development of microalbuminuria, at which time the patients were dropped from the study. The remaining patients were observed for up to 13 years. After enrollment, patients were placed on usual care treatment, which included a nonpharmacological treatment consisting of moderate salt restriction and a low-calorie diet, if overweight, with or without a regime of antihypertensive drugs based on β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers. Hydrochlorothiazide (and/or other drugs) was added if necessary to maintain the BP goal of <135/85 mm Hg at any time during the follow-up.

### Procedures

BP was measured using a mercury sphygmomanometer following the recommendations of the British Hypertension Society. SBP and DBP were the average of 3 readings measured at 5-minute intervals. Blood samples were obtained in the morning after a minimum of 8 hours of fasting. Serum biochemical profiles were measured using a multiple-channel autoanalyzer. Plasma glucose was assayed by the glucose oxidase method (Beckman Glucose Analyzer; Beckman Instruments). Total cholesterol and triglycerides were measured by an enzymatic method (Roche Diagnostics). 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 was measured in 2 separate 24-hour urine collections using a nephelometric immunoassay (Behring Institute). Aliquots of urine were taken, stored in glass tubes at 4°C, and analyzed 1 to 7 days after collection. For each patient, the UAE was considered as the mean value obtained in the 2 separate 24-hour urine collections. Microalbuminuria was defined as UAE ranging between 30 and 299 mg per 24 hours, as confirmed by 2 consecutive measurements <1 week apart.

### Statistical Analysis

Differences in parameters of interest between groups were sought by the U Mann–Whitney. The Wilcoxon rank-sum test was used with the repeated measurements. Baseline values of selected parameters were considered fixed covariates. BP, plasma glucose, and the sign of the slope of plasma glucose change were considered time-dependent covariates. The probability of developing microalbuminuria was analyzed using Kaplan–Meier survival analysis. Cox regression analysis with baseline and time-dependent covariates was used to assess the effect of the prognostic factors on the development of microalbuminuria. Adjusted relative risk for the significant Cox model factors was calculated and expressed along with 95% confidence interval (CI). Stata27 was used to carry out analysis. Statistical significance was assumed if P<0.05 (2-tailed).

### Results

#### General Characteristics at Entry Into the Study

From a total of 525 patients screened, 245 were included in the study. A total of 135 were excluded because their UAE was >30 mg per 24 hours: 32 because of baseline glucose >6.7 mmol/L, 82 because SBP >160 mm Hg or DBP >100 mm Hg, and the remainder for other reasons. The general characteristics of the study population are shown in Table 1. The sample had a mean age of 40.9 years (39.7 to 42.1 95% CI). UAE was in the normal range in all patients. Arterial BP, measured in the office, was SBP 139.7 mm Hg (95% CI, 138.2 to 141.2 mm Hg) and DBP 88.6 mm Hg (95% CI, 87.4 to 89.9 mm Hg). The percentage of subjects with electrocardiographic–left ventricular hypertrophy (Cornell criteria) was 25.4%. Thus, this group is representative of a middle-aged population with mild hypertension.

In 30 subjects (12.2%), UAE increased to the microalbuminuric range, from 13.1±7.7 mg to 44.2±18.2 mg per 24 hours (P<0.001) after a mean follow-up of 29.9 months (range 12 to 144 months). Half of these patients became microalbuminuric after 22.2 months of follow-up, and 75% had developed it by 35 months. The rate of conversion was 2.5 per 100 patients per year.

A total of 215 subjects (87.8%) did not develop microalbuminuria after a mean follow-up of 61.7 months (range 12 to 174 months). In these patients, UAE did not increase, even within the normoalbuminuric range (from 9.4±6.2 mg to 9.0±9.7 mg per 24 hours). The 30 subjects who developed microalbuminuria are henceforth referred to as progressors, and the remaining 215 subjects who did not are referred to as nonprogressors.

**TABLE 1. General Characteristics of the Study Population (n=245)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.9</td>
<td>39.7–42.1</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>134/111</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.5</td>
<td>27.9–29.1</td>
</tr>
<tr>
<td>Hypertension, family history (%)</td>
<td>81.6</td>
<td>75.6–87.5</td>
</tr>
<tr>
<td>Diabetes, family history (%)</td>
<td>18.0</td>
<td>12.9–23.0</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>22.8</td>
<td>16.7–28.9</td>
</tr>
<tr>
<td>Office measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>139.7</td>
<td>138.2–141.2</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>88.6</td>
<td>87.4–89.9</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>79.4</td>
<td>77.2–84.5</td>
</tr>
<tr>
<td>Biochemical and lipid profiles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.4</td>
<td>5.3–5.4</td>
</tr>
<tr>
<td>Uric acid (μmol/L)</td>
<td>324</td>
<td>312–336</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>89.3</td>
<td>87.5–91.1</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.4</td>
<td>5.2–5.5</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.4</td>
<td>1.3–1.5</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>94.3</td>
<td>90.1–98.5</td>
</tr>
<tr>
<td>UAE (mg/24 hours)</td>
<td>9.9</td>
<td>9.1–10.7</td>
</tr>
<tr>
<td>EKG-LVH (%)</td>
<td>25.4</td>
<td>18.5–32.4</td>
</tr>
</tbody>
</table>

LVH indicates left ventricular hypertrophy (Cornell criteria).

**General Characteristics of the Progressors and Nonprogressors**

The 2 groups, progressors and nonprogressors, were similar in age (41.3±9.2 years and 40.9±4.9 years, respectively) and sex distribution (53% and 55% men, respectively). Likewise, no differences were observed in terms of family history of hypertension (81% and 82%) or diabetes (17% and 18%), respectively.

At the beginning of the study (Table 2), there were no significant differences between progressors and nonprogressors in body mass index or either SBP or DBP taken in the office. Nor were there any differences in fasting glucose, uric acid, creatinine, total cholesterol, triglycerides, and creatinine clearance values, or in the frequency of EKG-left ventricular...
hypertrophy. However, the UAE at baseline was significantly higher in progressors than in nonprogressors ($P=0.01$).

The evolution of selected parameters in each group is also depicted in Table 2. In progressors and nonprogressors, the body mass index, uric acid, creatinine, creatinine clearance, total cholesterol, and triglycerides remained essentially unchanged. During the follow-up, SBP and DBP decreased significantly in progressor and nonprogressor groups, and no significant differences in the extent of SBP ($P=0.82$) and DBP ($P=0.38$) reduction were observed between groups.

Likewise, no differences in the use of statins were observed between groups: 14% for progressors and 13% for nonprogressors.

### Factors Influencing the Occurrence of Microalbuminuria
Cox regression analysis with baseline and time-dependent covariates was performed to analyze their relationship with the UAE at follow-up. Baseline UAE (hazard ratio [HR], 1.07; $P=0.006$) and SBP during the follow-up (HR, 1.03; $P=0.008$) were independent factors related to UAE. However, fasting glucose levels during the follow-up were not significantly related to UAE (HR, 0.99; $P=0.71$). Because the type of drugs used in the treatment of hypertension has

### TABLE 2. Evolution of Selected Parameters in Progressors and Nonprogressors

<table>
<thead>
<tr>
<th>Variables</th>
<th>Progressors (n=30)</th>
<th>Nonprogressors (n=215)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Follow-Up</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.9±4.4</td>
<td>31.5±9.3</td>
</tr>
<tr>
<td>Office measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>141.9±12.9</td>
<td>137.2±10.1</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>89.4±9.6</td>
<td>82.3±8.5</td>
</tr>
<tr>
<td>Biochemical and lipid profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.31±0.40</td>
<td>5.73±1.39</td>
</tr>
<tr>
<td>Uric acid (μmol/L)</td>
<td>302.0±78.8</td>
<td>311.2±51.6</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>94.0±22.1</td>
<td>89.3±23.9</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.23±1.20</td>
<td>5.27±0.90</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.34±0.63</td>
<td>1.29±0.53</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>86.9±26.2</td>
<td>93.0±37.8</td>
</tr>
<tr>
<td>UAE (mg/24 hours)</td>
<td>13.1±7.7*</td>
<td>44.2±18.2†</td>
</tr>
<tr>
<td>No. of drugs (average)</td>
<td>0.5±0.6†</td>
<td>1.8±1.3†</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD. *Significant differences between groups upon initial examination; †significant differences between groups upon last examination; ‡numbers of drugs used during the first year of follow-up.
undergone change over time, the type of drugs has not been included in the analysis.

Each of these related factors was categorized: UAE \(<15\) mg per 24 hours and \(\geq 15\) mg per 24 hours; SBP \(<130\) mm Hg, the limit for defining normal pressure,\(^{11}\) between 130 and 139 mm Hg and \(\geq 139\) mm Hg; and negative or 0 and positive slope of plasma glucose changes. The number of patients, the percentage of subjects who developed microalbuminuria, and the univariate and multivariate HR for each of the established categories on the development of microalbuminuria are shown in Table 3. A significant increase in the risk to develop microalbuminuria for UAE baseline \(>15\) mg per 24 hours, SBP \(>139\) mm Hg, and positive trend in fasting glucose were observed in the univariate analyses (Figure, a through c). In the multivariate analysis, the baseline UAE and the trend of fasting glucose were independently related to the risk of developing microalbuminuria. The SBP values, although they tended to increase the risk, did not achieve statistical significance.

Furthermore, the 52 subjects who achieved SBP \(<130\) mm Hg and DBP \(<80\) mm Hg during the entire follow-up had a 3.61\% (1.3 to 15.3 95\% CI) lower risk of developing microalbuminuria than did the remaining patients.

**Discussion**

The present study assessed the development of microalbuminuria in a segment of population not analyzed previously, those with a low cardiovascular risk and untreated mild hypertension at the beginning of the follow-up period. The results demonstrate that the persistence of higher-than-normal SBP precedes the development of microalbuminuria. Additionally, an upward trend in fasting glucose values seems to be present in those subjects who develop microalbuminuria. Thus, the potential for developing microalbuminuria, a marker of endothelial dysfunction\(^{28}\) and of increased cardiovascular risk in hypertension,\(^{5}\) appears very low in subjects who achieve strict normal BP or in those who maintain stable fasting glucose values.

The findings of the present study are in keeping with the hypothesis of previous cross-sectional studies that BP is the main determinant of microalbuminuria in normotensive and hypertensive nondiabetic subjects as well as in diabetics. The normotensive arm of the Appropriate Blood Pressure Control in Diabetes (ABCD) study in type 2 diabetes also demonstrates that patients with an intensive DBP control program (128/75 mm Hg) had a lower risk of developing microalbuminuria than those with a moderate therapy (137/81 mm Hg).\(^{30}\) The impact of BP values on the presence of microalbuminuria is further reinforced with data from studies using 24-hour ambulatory BP monitoring. Reduction in the physiological nocturnal BP fall and the persistence of elevated BP during night were associated with high UAE rates.\(^{30}\) Furthermore, a progressive increase in SBP during sleep has been related to the development of microalbuminuria in normotensive type 1 diabetics.\(^{31}\)

Therefore, the present study has defined the temporal relationship between BP and microalbuminuria in essential hypertension. Examining to what extent microalbuminuria reflects cardiovascular or kidney damage, one can conclude that the more effective the SBP controls, the lower the risk of developing microalbuminuria. Consequently, the maintenance of high BP may have a key pathogenic role in the development of microalbuminuria.

Besides the impact of BP values on the risk of developing microalbuminuria, a second set of factors potentially influencing microalbuminuria in essential hypertension are insulin resistance\(^{15}\) and hyperinsulinemia.\(^{19}\) The pathogenic role of insulin resistance in microalbuminuria is further supported by noting that microalbuminuria is more prevalent among type 2 diabetics than in matched nondiabetic subjects\(^{32}\) and that microalbuminuria increases the risk of developing type 2 diabetes.
of glucose tolerance. Thus, even in a hypertensive population, increased risk occurs in a graded fashion across the spectrum normal levels also increased the risk, suggesting that the integrated fasting glucose levels were strongly associated with the risk of developing microalbuminuria in the general population. The increased risk was not limited to diabetic levels of fasting glucose, and subtle elevations in apparently normal levels also increased the risk, suggesting that the increased risk occurs in a graded fashion across the spectrum of glucose tolerance. Thus, even in a hypertensive population, in which BP values play a major role in the development of microalbuminuria, glucose metabolism is also an important determinant to be considered.

The impact of antihypertensive treatment merits further comment. Although the study was not designed to search for differences among antihypertensive agents, it is necessary to consider whether or not treatment modifies the interpretation of the observed data. It is noteworthy to mention that regardless of the antihypertensive drug class used, the development rate of microalbuminuria was apparently similar if BP values were reduced enough. This is in agreement with the Framingham Offspring Study, in which BP values were reduced enough to lower UAE thresholds than the 30 mg per 24 hours required to be defined increased risk in people with hypertension. The present study demonstrated that those subjects with an initial UAE level in the high range of normality, >15 mg per 24 hours, had an increased risk of progressing toward microalbuminuria. Whether the high UAE, even in the normoalbuminuric range, is indicative of a longer previous hypertensive period or a predisposition to develop organ damage needs to be assessed in further studies. Whatever the case, appropriate intervention may reduce the progressive increment of UAE and, therefore, cardiovascular and renal risk.

Perspectives
The present study offers valuable information toward a better understanding of the development of microalbuminuria, an already well-established marker of cardiovascular and renal damage. In mild hypertensives, development of microalbuminuria is linked to insufficient BP control and to a progressive increment of glucose values. Therefore, the existence of either or both risk factors may warrant an intervention that could be initiated at a stage earlier than the microalbuminuric phase of the disease. Moreover, defining the risk of microalbuminuria at an early stage would be ideal for guiding therapies geared to the prevention of progression. Whether or not prompt intervention to avoid the development of microalbuminuria may result in better protection against hypertension-induced organ damage needs to be assessed in prospective studies.

References
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Hypertension. 2005;45:1125-1130; originally published online May 16, 2005; doi: 10.1161/01.HYP.0000167151.52825.11

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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