Microalbuminuria has been associated with a cluster of metabolic and nonmetabolic risk factors, suggesting that it might indicate the presence of generalized microvascular damage in patients with essential hypertension. To explore whether microalbuminuria is associated with early target organ damage, two groups of essential hypertensive patients, with (n = 17) (HtAlb+) and without (n = 16) (HtAlb−) microalbuminuria, and a control group (C) of healthy normotensive subjects (n = 20) were studied. The study groups, selected among participants of a large epidemiologic trial, were carefully matched for several potentially confounding variables such as gender, age, duration of hypertension, and body mass index. Albumin excretion rate was evaluated by radioimmunoassay in three nonconsecutive timed overnight collections after 3 weeks of pharmacologic wash-out. Left ventricular mass was assessed by M-B-mode echocardiography, carotid wall thickness by a high resolution ultrasound scan, and renal vascular impedance by Doppler scan. Office as well as 24-h ambulatory pressure monitoring (Takeda TM-2420) were also evaluated. There was no difference between the two hypertensive groups for office and 24-h blood pressure levels except for a lower daytime/nighttime systolic blood pressure ratio in the group with microalbuminuria. Microalbuminuric patients showed signs of early organ damage as compared to normoalbuminuric patients and normal subjects, namely greater left ventricular mass indices (LVMI 167 ± 7 g/m² in HtAlb+; 139 ± 9 g/m² in HtAlb−; 118 ± 5 g/m² in C, P < .001) and increased wall thickness of common carotid arteries (intima plus media thickness 12.5 ± 0.2 mm in HtAlb+; 11.7 ± 0.3 mm in HtAlb−; 11.2 ± 0.2 mm in C, P < .001) as well as higher intrarenal vascular resistance (mean resistive index 0.62 ± 0.01 in HtAlb+; 0.59 ± 0.01 in HtAlb−; 0.59 ± 0.01 in C, P < .05). In conclusion, microalbuminuria is an early marker of diffuse target organ damage in essential hypertension and therefore can be useful to identify patients for whom more aggressive preventive strategies or additional treatment measures are advisable. Am J Hypertens 1998; 11:430–438 © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: Hypertension, microalbuminuria, left ventricular mass, carotid wall thickness, renal vascular impedance.
Abnormal urinary albumin excretion ranging from 30 to 300 mg/day, ie, microalbuminuria, is found in approximately 5% to 40% of patients with essential hypertension and has been shown to indicate increased risk for cardiovascular morbidity and mortality. Although the pathophysiologic mechanisms underlying the development of microalbuminuria remain to be clarified, several studies have shown that it is associated with a striking cluster of metabolic and nonmetabolic risk factors, such as increased blood pressure levels and altered 24-h blood pressure profiles, insulin resistance, blood pressure salt sensitivity, atherogenic serum lipid profile, systemic endothelial dysfunction, and increased activity of the renin-angiotensin system (RAS). While the above reported observations may per se account for the increased morbidity and mortality rates observed in hypertensive patients with microalbuminuria, they also suggest that increased urinary albumin excretion might reflect the presence of generalized vascular damage. In fact, it has been proposed that microalbuminuria signals, at least in part, the presence of abnormal systemic microvascular permeability, a phenomenon that occurs early in the development of atherosclerosis. If this hypothesis proves correct, microalbuminuria could therefore be regarded as an integrated cardiovascular risk factor and a marker of early, diffuse target organ damage.

The present investigation was initiated to evaluate whether microalbuminuria is associated with early target organ damage in essential hypertension by comparing two carefully matched groups of hypertensive patients with and without microalbuminuria and a group of healthy normotensive controls.

METHODS

Selection of Patients The MAGIC Study (Microalbuminuria: A Genoa Investigation on Complications) was initiated to evaluate the prevalence and clinical correlates of microalbuminuria in patients with essential hypertension as well as the effect of various antihypertensive treatments in patients with microalbuminuria. Details of the study were previously published. The prevalence of microalbuminuria in the cohort of patients studied (n = 787, 434 men and 353 women) was 6.7% (53 patients, 28 men, 25 women). Among these patients, fifteen (8 men and 7 women) were excluded from the present study because their serum creatinine was > 1.4 mg/dL (men) or > 1.1 mg/dL (women). Of the remaining 38 patients, 17 volunteered for this study and were defined as microalbuminurics (HtAlb−). A control group was established by selecting, among the entire cohort of patients participating in the MAGIC study, 16 hypertensive patients with normal albumin excretion (HtAlb−) matched for gender, age, body mass index, and known duration of hypertension. Twenty-one of the 33 hypertensive patients participating in the study had been previously treated for hypertension (10/16 in HtAlb− and 11/17 in HtAlb+). A group of 20 similarly matched healthy normotensive subjects, recruited from the staff of our hospital, was also studied (C). The study protocol was approved by the Ethical Committee of our institution and written or oral informed consent was obtained from each participant. Both groups of hypertensive patients (with and without microalbuminuria) and the normotensive control group underwent complete physical examination and routine biochemical analyses of blood and urine, including measurement of glomerular filtration rate and evaluation of the presence and extent of end organ damage. Hypertension was defined according to the criteria in the fifth report of the Joint National Committee (JNC V) as an average blood pressure ≥140/90 mm Hg on at least three different occasions or by the presence of antihypertensive treatment. Body mass index (BMI) was calculated using the formula: BMI = weight (in kilograms)/height (in meters) squared.

Twenty-four hour urinary collection was obtained from each subject on the day prior to the study to assess dietary sodium intake. All patients and controls were on a free, salt-unrestricted diet at the time of study. They had either never been treated for hypertension or had been taken off therapy at least 4 weeks prior to the study. Creatinine, blood urea nitrogen, electrolytes, uric acid, triglycerides, total and HDL cholesterol, and other standard chemistry evaluations were performed using serum according to routine methods. LDL cholesterol was calculated using Friedewald’s formula. Total and active plasma renin was measured by radioimmunoassay (Sanoﬁ Diagnosti­c Pasteur, Milano, Italy). Prorenin was calculated as the difference between total and active renin. Plasma and urine aldosterone were measured by radioimmu­noassay (Sorin Biomedica, Saluggia, Italy). Glomerular filtration rate was evaluated by plasma clearance of iothalamate as described elsewhere. The presence, type, and extent of hypertensive retinopathy were investigated by direct ophthalmoscopy in a darkened room and under pupil dilatation. Retinal lesions were classified according to the Keith-Wagener-Barker classification. Family history for hypertension and cardiovascular disease, the amount of physical activity, smoking habits and alcohol consumption were assessed by means of a standardized questionnaire.

Blood Pressure Measurements Blood pressure was measured on both arms according to the recommendations of the American Society of Hypertension with the patient in a sitting position after a 5 min rest and using a mercury sphygmomanometer (cuff size 12.5 × 40 cm). The systolic and diastolic blood pressures were read to the nearest 2 mm Hg. The disap-
pearance of Korotkoff’s sounds (phase V) was the criterion for diastolic blood pressure measurement. The lowest of three consecutive readings were recorded as the office blood pressure. No clinically significant difference between the two arms was found in any of the patients and therefore office measurements obtained from the nondominant arm (the left arm in all patients) were recorded. Each patient and control subject also underwent a 24-h ambulatory blood pressure recording (ABPM; Takeda TM-2420, Osaka, Japan). The efficiency and reliability of this ABPM device have been validated extensively in previous trials.33,34 Left arm readings were taken with a standard cuff over a 24 h period usually beginning between 8 and 9 AM. Measurements were taken every 20 min from 7 AM to 10 PM (daytime period) and every 30 min from 10 PM to 7 AM (nighttime period). ABPM was carried out during a working day and subjects were required to keep a diary of all daily activity, including whether, for any reason, they awakened at night. From the 24-h blood pressure profile we calculated average 24-h systolic and diastolic blood pressures, as well as average daytime and nighttime systolic and diastolic values.

**Albuminuria** All patients were instructed to provide three timed overnight urine collections on three nonconsecutive days after a 4 week period of pharmacologic wash-out, if any, in the presence of a negative urine culture. Whenever a positive urine culture was found, urine samples were discarded, appropriate antibacterial treatment instituted and urine collections for albuminuria repeated only after a second culture tested negative. Each urine collection was collected in a bottle appropriately labeled with specific instructions to record the beginning and the end of collection time to the nearest minute. All patients were instructed to submit urine collections to the Outpatient Clinic on the day of completion. Collection volume was measured to the nearest 5 mL in a graduated cylinder and urine was then stored in aliquots at −20°/−30°C until analysis. Diuresis was calculated by the volume and duration of each urine sample and expressed in milliliters/minute. Urinary albumin concentration was measured by a commercially available radioimmunoassay (Sclavo, Cinisello Balsamo, Italy). Albumin excretion rates were obtained by multiplying albumin concentration by the corresponding value of diuresis, and were expressed in micrograms/minute.35 Microalbuminuria was defined according to the International Consensus as albumin excretion rate (AER) in the 20 to 200 µg/min range in two out of three collections.36

The mean intraindividual day-to-day coefficient of variation was 33.5%, a value similar to that reported in the literature.36 The intra- and interassay variabilities of the method in our laboratory were 4.5% and 6.1% respectively.

**Echocardiography** All echocardiographic studies were performed using an Acuson (Mountain View, CA) XP-128 ultrasound machine. Echocardiograms were obtained at rest with patients supine in the left lateral position, using standard parasternal and apical views. The overall monodimensional left ventricular (LV) measurements and the bidimensional (apical four and two chamber) views were obtained according to the recommendations of the American Society of Echocardiography.37,38 All tracings were obtained and read by a single observer blinded to the clinical characteristics of the patients under observation. LV mass was derived from the formula described by Devereux and associates39,40 corrected for body surface area (LVMI), and expressed in units of grams/meter squared. No patients showed dysynergic areas that would invalidate the theoretical assumptions behind the cardiac mass calculations. Diagnostic criteria for LV hypertrophy using left ventricular mass index were ≥ 134 g/m² for men and ≥ 110 g/m² for women, representing the sex specific 97th percentiles of a previously published reference standard in a normal population.40

**Common Carotid Ultrasound Scan** The intima plus media thickness (IMT) of both carotid arteries was evaluated by high resolution ultrasound scan as described by Kawagishi et al.41 Carotid arteries were investigated in the longitudinal and the transverse projections by high resolution real-time ultrasonography using a 10-MHz in-line duplex Diasonic Spectra System (Esaote, Milan, Italy). The carotid artery was scanned at the level of the bifurcation and the common carotid artery (CCA). At each longitudinal projection, the far-wall IMT, as defined by Weldelhag et al.42 was measured at the distal end of the CCA, where the near and far walls lose their parallel configuration. Averages were calculated for each of the three measurements.

**Renal Ultrasound and Doppler Studies** Renal parenchymal echogenicity, renal volume, and mean resistive index (RI) were evaluated in a total of 34 kidneys in microalbuminuric and 32 in normoalbuminuric hypertensive patients and 40 kidneys in normotensive controls. Renal parenchymal echogenicity was classified on the basis of Hricak’s et al grading system.43 The renal volume was measured by use of the ellipsoid formula and corrected for body mass index.39,40 Microbubble contrast (SonoVue) was used for Doppler signals from the interlobar arteries by placing the sample volume at the edge of the medullary pyramids. The mean RI [(peak systolic velocity − end diastolic velocity)/peak systolic velocity] was calculated by using six measure-
TABLE 1. CLINICAL CHARACTERISTICS OF NORMOTENSIVE CONTROLS AND HYPERTENSIVE PATIENTS WITHOUT AND WITH MICROALBUMINURIA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>C</th>
<th>HtAlb−</th>
<th>HtAlb+</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>20</td>
<td>16</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>11/9</td>
<td>10/6</td>
<td>10/7</td>
<td>NS</td>
</tr>
<tr>
<td>AER (µg/min)</td>
<td>3.5*</td>
<td>4.9†</td>
<td>62.9‡</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.3 ± 1.3</td>
<td>49.2 ± 2</td>
<td>48.2 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 ± 0.4</td>
<td>26.9 ± 0.9</td>
<td>26.2 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>91 ± 0.8</td>
<td>120.8 ± 1.2</td>
<td>124.6 ± 2</td>
<td>&lt; .001#</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>—</td>
<td>4.0 ± 0.5</td>
<td>5.7 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>EH family history (+/−)</td>
<td>6/14</td>
<td>10/6</td>
<td>12/5</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting serum glucose (mg/dL)</td>
<td>89 ± 1.3</td>
<td>87.4 ± 2.7</td>
<td>85.5 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>4.9 ± 0.2</td>
<td>4.7 ± 0.4</td>
<td>5.5 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.91 ± 0.03</td>
<td>0.85 ± 0.04</td>
<td>0.86 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min/1.73 m²)</td>
<td>112 ± 3.4</td>
<td>113.9 ± 6.9</td>
<td>111.1 ± 5.9</td>
<td>NS</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>106.3 ± 4.9</td>
<td>107.2 ± 5.4</td>
<td>97.5 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>106.8 ± 13.9</td>
<td>104.6 ± 10.6</td>
<td>129.2 ± 9.4</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>194.6 ± 9.3</td>
<td>206.8 ± 13</td>
<td>226 ± 5.9</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>55.3 ± 1.7</td>
<td>52 ± 2.8</td>
<td>48.5 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>118.6 ± 12</td>
<td>131.7 ± 14</td>
<td>151.6 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Total renin (pg/mL)</td>
<td>31.5 ± 6.7</td>
<td>33.9 ± 5.2</td>
<td>79.5 ± 22.5</td>
<td>NS</td>
</tr>
<tr>
<td>Prorenin (pg/mL)</td>
<td>22.9 ± 6.3</td>
<td>25.7 ± 5.4</td>
<td>71.5 ± 21.3</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Active renin (pg/mL)</td>
<td>8.6 ± 0.9</td>
<td>8.8 ± 2.0</td>
<td>7.9 ± 9.04</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary aldosterone (pg/day)</td>
<td>15.4 ± 2.9</td>
<td>16.3 ± 3.8</td>
<td>17.6 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary Na (mEq/day)</td>
<td>156 ± 14</td>
<td>164 ± 22</td>
<td>147 ± 17</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Range 1 to 8.
† Range 2.1 to 9.8.
‡ Range 20 to 252.
# No difference between the two hypertensive groups.

P values were calculated by one way analysis of variance (ANOVA) or χ² test as appropriate.

Data are mean ± SEM, except for AER (median).

NS, not significant; BMI, body mass index; MBP, mean blood pressure; GFR, glomerular filtration rate. See text for other abbreviations.


dents (three from each of the two kidneys) taken for each patient. Ultrasound examination of the kidneys and pulsed Doppler analysis of the intrarenal arteries were performed using a Hitachi (Tokyo, Japan) AU 450 machine with a 3.5 MHz transducer working at 2.5 MHz for Doppler analysis.

Statistical Analysis All data are expressed as mean ± SEM. Differences between variables were assessed using the appropriate statistical test based on the underlying distribution of the variables. One-way analysis of variance (ANOVA) with multiple comparison posttest was used to analyze the data of the three study groups. Differences between prevalences were assessed by a χ² test or Fisher’s exact test as appropriate. To study the linear relationship between log AER and other continuous variables, Pearson correlation tests were used. Multiple regression analyses were performed to assess the independent contribution of several variables on albumin excretion rate as well as left ventricular mass, carotid wall thickness, and renal vascular resistance. All statistical analyses were performed using SAS (SAS Institute, Cary, NC) software.

RESULTS

As a consequence of selection procedures at entry, age, sex, smoking habits, known duration of disease (in hypertensive patients), and BMI were superimposable among the experimental groups (see Methods). Median albumin excretion rate was 3.5 µg/min (range: 1 to 8 µg/min) in controls, and 4.9 µg/min (2.1 to 9.8 µg/min) and 62.9 µg/min (20 to 252 µg/min) in non-microalbuminuric and microalbuminuric hypertensive patients, respectively (Table 1). Office systolic, diastolic, and mean blood pressure levels were higher in hypertensive patients as compared to controls, but were similar between normo- and microalbuminuric patients (Tables 1 and 2). There was no significant difference among the three groups in serum glucose, uric acid, lipid profile, and glomerular filtration rate (GFR). Hypertensive patients with microalbuminuria showed higher levels of prorenin even though dietary salt intake, as estimated by 24-h urine sodium excretion, was similar among the three study groups (Table 1). Office blood pressure readings, as well as readings from 24-h ambulatory blood pressure monitoring,
were similar between the two hypertensive groups, except for a lower systolic blood pressure (SBP) daytime/nighttime ratio in patients with microalbuminuria (Table 2).

Hypertensive patients with microalbuminuria showed early signs of target organ damage as compared to the other two groups. In fact, both the left ventricular mass index (167.3 ± 7 g/m², HtAlb+; 139 ± 9 g/m², HtAlb--; 118 ± 4.6 g/m², C; *P < .001 by ANOVA, Figure 1) and the posterior wall thickness (12.5 ± 0.2 mm, HtAlb+; 11.7 ± 0.3 mm, HtAlb--; 11.2 ± 0.2 mm, C, *P < .001 by ANOVA) were significantly greater in the former. Posttest analysis between the two hypertensive groups showed that patients with microalbuminuria had greater LVMI as compared to those without it (*P < .05). Furthermore microalbuminuric patients were more likely to show left ventricular hypertrophy as compared to normoalbuminuric hypertensives (16 of 17 in HtAlb+ versus 9 out of 16 in HtAlb--; odds ratio (OR) 12.4, 95% confidence interval (CI) 1.3 to 118, *P < .02). The mean thickness of the carotid artery wall (intima plus media layers) was significantly greater in hypertensive patients with microalbuminuria (0.93 ± 0.03 mm, range 0.65 to 1.25 mm) than in patients without microalbuminuria (0.75 ± 0.05, range 0.45 to 1.1 mm) or in normotensive healthy subjects (0.50 ± 0.03, range 0.3 to 0.7 mm; *P < .001 by ANOVA, Figure 2). Renal volume did not differ among the three study groups (102.2 ± 2.0 mL, HtAlb+; 103.1 ± 2.2 mL, HtAlb--; 105.4 ± 3.2 mL, C) while hypertensive patients with microalbuminuria showed higher renal vascular resistances, as indicated by mean resistive index, at Doppler examination of interlobar arteries (0.62 ± 0.01, HtAlb+; 0.59 ± 0.01, HtAlb--; 0.59 ± 0.01, C; #P < .05 by ANOVA). Finally, retinal vascular lesions (grade II) were more often observed at fundoscopic examination in hypertensive patients with microalbuminuria than in normoalbuminuric patients and in controls, although the difference did not reach statistical significance (9/17, 6/16, and 6/20, respectively, *P = .09 by χ² analysis).

### TABLE 2. OFFICE BLOOD PRESSURE AND 24-H AMBULATORY BLOOD PRESSURE IN HYPERTENSIVE PATIENTS WITHOUT (HTALB–) AND WITH (HTALB+) MICROALBUMINURIA

<table>
<thead>
<tr>
<th></th>
<th>HtAlb– (n = 16)</th>
<th>HtAlb+ (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office SBP (mm Hg)</td>
<td>156.8 ± 2.7</td>
<td>164.6 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Office DBP (mm Hg)</td>
<td>102.8 ± 1.2</td>
<td>104.6 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>24 h SBP (mm Hg)</td>
<td>143.0 ± 4.2</td>
<td>150.5 ± 6.9</td>
<td>NS</td>
</tr>
<tr>
<td>24 h DBP (mm Hg)</td>
<td>91.5 ± 2.8</td>
<td>90.8 ± 2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Daytime SBP (mm Hg)</td>
<td>148.4 ± 4.3</td>
<td>153.1 ± 7.2</td>
<td>NS</td>
</tr>
<tr>
<td>Daytime DBP (mm Hg)</td>
<td>94.1 ± 2.7</td>
<td>93.1 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Nighttime SBP (mm Hg)</td>
<td>127.6 ± 4.6</td>
<td>142.8 ± 7.5</td>
<td>NS</td>
</tr>
<tr>
<td>Nighttime DBP (mm Hg)</td>
<td>84.0 ± 3.9</td>
<td>85.9 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Daytime/nighttime SBP</td>
<td>1.17 ± 0.02</td>
<td>1.08 ± 0.03</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Daytime/nighttime DBP</td>
<td>1.13 ± 0.04</td>
<td>1.09 ± 0.02</td>
<td>NS</td>
</tr>
</tbody>
</table>

DBP, diastolic blood pressure; SBP, systolic blood pressure; see text for other abbreviations.

**FIGURE 1.** Left ventricular mass index (LVMI) in normotensive controls (C, n = 20) and in hypertensive patients without (HtAlb–, n = 16) and with (HtAlb+, n = 17) microalbuminuria. *P < .001 intergroup comparison; #P < .05 compared to HtAlb–.

**FIGURE 2.** Common carotid wall thickness (IMT) in normotensive controls (C, n = 20) and in hypertensive patients without (HtAlb–, n = 16) and with (HtAlb+, n = 17) microalbuminuria. #P < .001 intergroup comparison; **P < .01 compared to HtAlb–; *P < .001 compared to C.
Significant univariate correlations were found in hypertensive patients between log AER and nighttime SBP ($r = 0.455, P < .05$), carotid wall thickness ($r = 0.346, P < .05$), and Doppler resistive index at the renal level ($r = 0.431, P < .02$), while an inverse relationship was present between log AER and daytime/nighttime ratio of systolic blood pressure ($r = -0.525, P = .021$).

Multiple linear regression analysis showed that IMT and LVMI significantly influence albumin excretion rate and together account for about 30% of its variations (dependent variable: AER, $r = 0.575, r^2 = 0.331$, $F = 5.442, P < .02$; independent variables: IMT, $\beta = 0.43$, SE $\beta = 0.17$, $P = .02$; LVMI, $\beta = 0.40$, SE $\beta = 0.17$, $P = .03$).

Multiple logistic regression analysis showed that renal vascular resistances are significantly influenced by age ($\beta = 0.36$, SE $\beta = 0.12$, $P = .01$), family history for hypertension ($\beta = 0.36$, SE $\beta = 0.12$, $P = .01$), IMT ($\beta = 0.58$, SE $\beta = 0.13$, $P = .001$), and the presence of retinal vascular changes ($\beta = 0.28$, SE $\beta = 0.13$, $P = .04$). Altogether these variables explain about 60% of variations in renal vascular impedance ($r = 0.802, r^2 = 0.643, F = 10.812, P < .0004$).

**DISCUSSION**

The present study shows that microalbuminuria is associated with early end-organ damage, namely increased left ventricular mass index and carotid artery wall thickness in patients with essential hypertension. Left ventricular hypertrophy$^{1,45–47}$ and carotid atherosclerosis$^{48}$ have been previously reported in hypertensive patients with microalbuminuria, but this is the first time that both these abnormalities are described within the same group of patients. These findings are even more noteworthy when considering that the study groups were accurately matched for a number of potentially confounding variables, such as age, gender, duration of hypertension, and BMI. They were also similar in their lipid profiles and blood pressure levels, factors which are known to influence urinary albumin excretion and the development of end-organ damage.$^1$ Interestingly, multiple regression analysis indicates that albumin excretion rate is correlated with common carotid thickness and left ventricular mass index. Variations of these two markers of atherosclerotic vascular damage influence urine albumin excretion and together account for a significant part of the variations in urinary albumin excretion. Since the glomerulus is indeed a blood vessel, abnormal albumin leakage through the glomerular filter is indicative of blood vessel damage and, consequently, likely reflects injury elsewhere in the body. These results suggest that microalbuminuria signals the presence of early organ damage and can be considered a sensitive indicator of vascular remodeling in essential hypertension. Our findings are in agreement with earlier observations made by using less sensitive methods on larger populations.$^1$

In the present study, hypertensive patients with microalbuminuria were also characterized by higher mean resistive index from Doppler ultrasound evaluation of interlobar arteries, a technique which has proved to be an accurate, reproducible, and noninvasive way to evaluate renal blood flow characteristics.$^{49,50}$ Increased RI was previously reported in patients with moderate and severe hypertension, and has been shown to correlate with the duration and severity of the hypertensive state, suggesting the presence of increased vascular impedance, possibly due to intraparenchymal arteriosclerosis.$^{50}$ In the present study, a positive correlation was found between albumin excretion rate and renal vascular resistance ($P < .02$) in patients with hypertension. Furthermore, multiple regression analysis showed that age, family history for hypertension, common carotid wall thickness, and the presence of retinal vascular changes influence renal vascular resistance and together account for about 80% of its variations. These data suggest that increased renal arterial impedance may indicate the presence and extent of generalized vascular damage, which can be revealed at the renal level also by the presence of microalbuminuria.

The association of increased urinary albumin excretion and signs of target organ damage suggests that these abnormalities might be the result, at least in part, of the same pathogenetic mechanisms and could be the sign of diffuse atherosclerotic vascular changes. This is in agreement with data from several previously published large studies showing an association between microalbuminuria and a cluster of metabolic risk factors, such as insulin resistance,$^{18}$ atherogenic serum lipid profile,$^1$ and systemic endothelial dysfunction.$^{22}$

Besides diffuse atherosclerotic vascular damage, other factors, namely the severity of hypertension and abnormalities in the circadian pattern of blood pressure, are thought to play a role in the development of microalbuminuria. Several studies have shown that urinary albumin excretion rate strongly correlates with the level of office blood pressure and even more so with 24-h ambulatory blood pressure.$^{14–16}$ Although in the present study blood pressure levels were similar in normo- and microalbuminuric patients, the latter group showed a trend toward higher systolic blood pressure levels both when measured in the office and by ABPM, suggesting that a higher systolic blood pressure load may lead to increased urinary albumin excretion. Furthermore hypertensive patients with microalbuminuria showed a significantly lower SBP daytime/nighttime ratio (Table 2), indicating the lack of a physiologic blood pressure drop during the night, the so-called nondipping phe-
nomenon, which has previously been associated with increased urine albumin excretion and higher cardiovascular risk. In the present study, the albumin excretion rate was positively correlated with the nighttime systolic blood pressure levels and inversely correlated with the systolic blood pressure daytime/nighttime ratio in hypertensive patients \( r = 0.455, P < .05 \) and \( r = -0.5251, P < .02, \) respectively. Thus our data confirm, at least in part, previous studies indicating that in middle-aged hypertensive patients high blood pressure (especially systolic) maintained over time is a good indicator of the development of renal injury as well as other forms of target organ damage.

Other factors, such as renin-angiotensin system activity, might be implicated in the development of microalbuminuria and target organ damage. As a matter of fact a role for increased plasma renin activity in the pathogenesis of vascular damage is supported by a considerable amount of experimental and clinical proof. Furthermore, increased urine albumin excretion has been described in young hypertensive patients with hyperresponsiveness of the renin-angiotensin system. In the present study, under normal dietary salt intake, no difference was found among the study groups as for the circulating levels of active renin (Table I). However, it is noteworthy that, as compared to the two other study groups, patients with microalbuminuria showed higher levels of plasma prorenin, an abnormality that has previously been reported to precede and to predict the development of microvascular complications in patients with diabetes mellitus. Although the pathogenetic mechanism(s) linking higher prorenin levels and cardiovascular damage are at present unclear, it has been suggested that long-term exposure to increased circulating levels of prorenin may lead to vascular and glomerular damage possibly through hemodynamic changes mediated by an increase of regional formation of angiotensin II.

In conclusion, the pathogenesis of microalbuminuria in essential hypertension may be the result of multiple factors, such as the presence of atherosclerotic vascular disease, the height of blood pressure level or alterations in its circadian patterns, and the increased activity of circulating and possibly tissue renin-angiotensin system substances. Although the data presented here need to be interpreted with some caution due to the limited number of patients studied and the selection criteria, which probably explain the relatively high prevalence of left ventricular hypertrophy reported, the association between microalbuminuria and other signs of target organ damage lead us to believe that increased urinary albumin excretion is a specific and integrated marker of cardiovascular risk. Furthermore, these data provide evidence that microalbuminuria can be regarded as a useful and rather inexpensive clinical tool for the identification of patients at higher cardiovascular risk for whom more aggressive preventive strategies or additional treatment measures might be advisable.

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REFERENCES


