Albuminuria and Transferrinuria in Essential Hypertension
Effects of Antihypertensive Therapy
Claudio Alli, Michele Lombardo, Daniela Zanni, Antonio Maria Agrati, Mario Cassani, and Simonetta Granata

The objectives of this study were to evaluate the effects of an ACE inhibitor (fosinopril) and a calcium antagonist (amlodipine) on the urinary albumin and transferrin excretion and their relationship to the blood pressure in essential hypertension. Twenty-four never-treated patients (mean age, 46.4 ± 8.9 years) with a diastolic blood pressure between 90 and 114 mm Hg and normal renal function, randomly received amlodipine or fosinopril and, if the diastolic blood pressure was not normalized, doxazosin was added to the therapy. Twenty-four-hour ambulatory blood pressure monitoring and 24-h urine collection for albumin and transferrin measurements were performed before and after 3 and 6 months of therapy. Diastolic blood pressure was normalized in 23 patients (96%). Before treatment, microalbuminuria was present in 50% of patients. In the amlodipine and fosinopril group, antihypertensive therapy significantly decreased blood pressure and, only in the fosinopril group, albuminuria. Transferrinuria did not change significantly in both groups. Fosinopril lowered albuminuria in all patients, whereas amlodipine only in half of patients. Albuminuria, but not transferrinuria, was significantly correlated to the ambulatory blood pressure. This correlation was more pronounced for systolic than for diastolic pressure. In essential hypertensive patients with normal renal function, a high prevalence of microalbuminuria can be observed. Albuminuria appears to correlate with ambulatory blood pressure, particularly with systolic pressure. Intrarenal hemodynamic changes seem to play a more important role than systemic blood pressure decrease in the reduction of albuminuria. Transferrinuria does not seem a useful marker to follow-up nondiabetic hypertensive patients with early signs of glomerular dysfunction. Am J Hypertens 1996; 9:1068-1076

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Microalbuminuria is defined as urinary albumin excretion (UAE) of 20 to 200 μg/min (ie, 30 to 300 mg/24 h) and has been shown to predict the onset of clinical proteinuria, chronic renal failure, and cardiovascular morbidity and death in diabetic patients. Some studies have also shown that microalbuminuria may be a predictor of cardiovascular morbidity and mortality in elderly patients and in the general population. The clinical and prognostic significance of microalbuminuria in essential hypertension remains to be ascertained. It is probable that this marker can have the same predictive value in hypertensive patients, even if, to date, no prospective study is available on this issue. In fact in patients with essential hypertension, microalbuminuria is associated with potentially pathogenic factors for cardiovascular compli-
cations, i.e., an impaired insulin sensitivity and altered lipid levels, and might be a marker of systemic endothelial dysfunction. The effect of the hypotensive treatment on microalbuminuria in normotensive and hypertensive diabetic patients is largely known; several investigators have reported that angiotensin converting enzyme (ACE) inhibitors can decrease UAE, whereas dihydropyridine calcium antagonists may or may not have an effect. Conversely, there are less data regarding the effect of hypotensive therapy on microalbuminuria in nondiabetic hypertensive patients.

Some studies have shown that determination of urinary transferrin excretion (UTE) is more sensitive than determination of UAE for early detection of glomerular impairment in diabetics. The molecular size and radius of albumin (66 kDa; 3.6 nm) is less than transferrin (77 kDa; 3.8 nm), whereas transferrin is much less anionic than albumin (the isoelectric point is 5.7 vs 4.9). The relative increase in UTE in diabetes might reflect changes in anionic charge or pore size in the glomerular basement membrane, increase in negative charge of albumin when glycated, or differential tubular excretion/reabsorption of albumin and transferrin. Our study was designed to evaluate prospectively the effects of an ACE inhibitor (fosinopril) and a dihydropyridine calcium antagonist (amlodipine) on UAE and UTE in a group of never-treated patients with essential hypertension and no sign of renal damage and the relationship of UAE and UTE to the blood pressure (BP).

METHODS
The study population consisted of 24 patients (23 men and 1 woman; mean age, 46.4 ± 8.9 years; range, 26 to 62 years) with essential hypertension. Patients with clinical or laboratory evidence of renal disease, obesity, or diabetes mellitus were excluded. No patient had ever taken any kind of antihypertensive drugs. Patients were included in the study if their diastolic BP was persistently between 90 and 114 mm Hg during three subsequent visits to the outpatient hypertensive clinic, 1 week apart, and if conventional semiquantitative test strips gave a negative result for proteinuria. During the baseline evaluation period, clinical history, physical examination, and laboratory profile were obtained. Blood pressure was measured with a standard mercury sphygmomanometer after the patients had been in a supine position for at least 5 min and in the standing position for 1 min. Three readings were made in a supine position and the average was used for analyses. Baseline BP value was defined as the average of the three measurements taken at the third visit. Before initial treatment the following instrumental examinations were carried out: 12-lead electrocardiogram, chest roentgenogram, and 24-h ambulatory BP monitoring. Furthermore, after fasting overnight for at least 12 h, all patients came to the outpatient clinic and blood samples were drawn for peripheral renin activity, aldosterone and atrial natriuretic peptide levels after subjects had rested 30 min in the supine position and routine biochemistry (complete blood count, serum urea nitrogen, creatinine, glycosylated hemoglobin, triglycerides, total and high density lipoprotein cholesterol, uric acid, sodium, potassium and urinalysis). Twenty-four-hour urine collections were obtained to measure the urinary excretion of creatinine, UAE, and UTE with the patients admitted to our department to assure a correct urine collection and to avoid physical activity altering the UAE. These instrumental and biochemical examinations, except chest roentgenogram, were repeated after 3 and 6 months of therapy. The eligible patients were kept on their habitual diet and randomly received an oral dose of either amlodipine (5 or 10 mg) or fosinopril (10 or 20 mg) once daily. The administration of the drugs was open-labeled. The goal of therapy was to lower the supine diastolic BP to less than 90 mm Hg. Follow-up visits took place every 2 weeks during the first month and every 4 weeks for the following 5 months. At each visit supine and standing BP as well as heart rate and weight were recorded. After 3 months if the BP was not normalized, doxazosin (2 or 4 mg once daily) was added to the therapy.

Ambulatory Blood Pressure Monitoring Twenty-four-hour BP monitoring was performed by a portable, noninvasive recorder (Medilog, Oxford Medical, England), validated according to the criteria of the American Association for Medical Instrumentation and of the British Hypertension Society. This monitor uses an algorithm that gates the Korotkoff sounds to the R-wave from the electrocardiogram, allowing validation of a good R-wave signal in all patients. Before patients left the clinic, microphone placement was evaluated for agreement between monitor-derived Korotkoff sounds and those auscultated by mercury sphygmomanometer through a T tube connector. Blood pressure readings were obtained automatically at 15-min intervals during waking hours and at 30-min intervals during sleep. All patients underwent ambulatory BP monitoring as outpatients during a working day. We used the criteria of Appel and colleagues to delete single BP readings.

The effects of the therapy on ambulatory BP values were analyzed as means for the entire 24-h period and its subsets of time (i.e., awake and asleep) and according to the method of White and co-workers. These investigators proposed cut-off values for abnormally elevated readings of 140/90 mm Hg for the waking period and 120/80 mm Hg for the sleeping period, on the basis of data in normotensive and hypertensive cohorts. We assessed the number of abnormally elevated BP values during the
TABLE 1. PATIENT CHARACTERISTICS AND BASELINE OFFICE BLOOD PRESSURE, SERUM UREA AND CREATININE LEVELS IN THE AMLODIPINE AND FOSINOPRIL GROUP

<table>
<thead>
<tr>
<th></th>
<th>Amlodipine (n = 12)</th>
<th>Fosinopril (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.6 ± 9.8</td>
<td>48.2 ± 7.9</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>12 M</td>
<td>11 M-1 F</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 ± 1.6</td>
<td>25.5 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.91 ± 0.11</td>
<td>1.83 ± 0.33</td>
<td></td>
</tr>
<tr>
<td>Supine SBP (mm Hg)</td>
<td>152 ± 13</td>
<td>150 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Supine DBP (mm Hg)</td>
<td>103 ± 6</td>
<td>104 ± 4</td>
<td></td>
</tr>
<tr>
<td>Standing SBP (mm Hg)</td>
<td>148 ± 17</td>
<td>141 ± 11</td>
<td></td>
</tr>
<tr>
<td>Standing DBP (mm Hg)</td>
<td>104 ± 8</td>
<td>102 ± 8</td>
<td></td>
</tr>
<tr>
<td>S-urea (mg/dL)</td>
<td>35 ± 0.7</td>
<td>32 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>S-creatinine (mg/dL)</td>
<td>1.08 ± 0.12</td>
<td>1.05 ± 0.13</td>
<td></td>
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</tbody>
</table>

Values are means ± SD.

M, male; F, female; BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; S, serum.

24-h period to calculate the percentage of elevated readings from the ambulatory BP data and this percentage of abnormally elevated BP values is called "BP load." White and coworkers found that BP load was equal or more than the average ambulatory BP value in predicting organ damage due to hypertension.

Analytic Procedures

Plasma renin activity, aldosterone, and atrial natriuretic peptide concentrations were estimated by radioimmunoassay techniques. UAE and UTE were determined by an immunonephelometric technique.

Statistical Analysis

Results are expressed as mean ± 1 SD for normally distributed data and also median for skewed data (UAE and UTE). Student's paired and unpaired t test for normally distributed data and Wilcoxon signed rank test as well as Mann-Whitney U test for skewed data were used to evaluate the difference between mean values. Analyses of variance both for normally distributed data and for skewed data (Friedman test) were also used to evaluate the changes of the values within the groups. Linear regression after logarithmic transformation for skewed data was used to determine whether correlations existed between variables. A stepwise multiple regression analysis was performed to examine the individual contribution of different parameters (age, body mass index, 24-h systolic and diastolic BP, creatinine clearance, plasma aldosterone, and renin activity) on the logarithm of UAE. The same analysis was repeated using waking or sleeping systolic and diastolic BP instead of 24-h BP. Significance was established at the level of P < .05 (two-tailed analysis).

FIGURE 1. Mean ± SD 24-h, waking and sleeping blood pressure in the amiodipine (left) and fosinopril (right) group at baseline and after 3 and 6 months of therapy. *P < .01 for change from baseline.
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ALBUMINURIA AND TRANSFERRINURIA IN HYPERTENSION

RESULTS

Effects of Amlodipine and Fosinopril  Baseline patient characteristics in the groups of patients receiving amlodipine (group A) and fosinopril (group F) are shown in Table 1. No significant difference was observed. All patients took the maximal dose of either amlodipine or fosinopril; in each group, 3 patients (25%) required the addition of doxazosin (4 mg daily) to the initial regimen. Diastolic BP values were normalized in all patients of both groups, except one in the group F. A significant reduction in office supine and standing BP was already evident in both groups at 2 weeks, whereas heart rate was not significantly affected during the study.

Data from ambulatory BP monitoring in groups A and F are shown in Figure 1. No significant difference between baseline BP measurements in the two groups was observed. Ambulatory BP was significantly decreased by amlodipine and fosinopril by the third month, as well as 24-h BP load, although the decrease in group A was a little greater than that in group F (Figure 2). The same results were obtained in both groups when using the analysis of variance \((P < .001)\). No significant change in weight was observed in the two groups at 3 and 6 months.

Before treatment, UAE and creatinine clearance values were higher in group A, even if not significantly. After drug therapy, UAE significantly decreased in group F, whereas in group A a nonsignificant reduction at the third month and an increase at the sixth month was observed (Table 2). At baseline microalbuminuria was present in 7 (58%) of group A patients and in 5 (42%) of group F patients, whereas at the end of the study in 8 (67%) and in 1 (8%) of groups A and F, respectively (Figure 3). Fosinopril lowered UAE in all patients, whereas amlodipine decreased UAE in 6 patients and increased it in the other half of patients at the end of the study (Figure 3). Creatinine clearance decreased in group A and increased in group F at 3 months and returned to the initial values in both groups at 6 months (Table 2). UTE showed a nonsignificant trend toward a reduction in both groups; it was more evident in group F (Table 2). Similar results were obtained when using the analysis of variance; a significant change in UAE was observed only in group F \((P < .001)\).

No significant change in routine biochemical values was found. Aldosterone significantly decreased in group F and increased in group A, whereas renin activity significantly increased in group F and remained constant to the end of the study in group A (Table 2). No change in the atrial natriuretic peptide values in both groups was observed. Only aldosterone in group F significantly changed with the analysis of variance \((P < .05)\).

Correlations A significant positive correlation was found between UAE and UTE before treatment \((r = 0.55, P < .01)\), but not at 3 and 6 months of therapy. No significant relationship between creatinine clearance and UAE or UTE was observed at baseline and during the study period.

At baseline UAE, but not UTE, correlated with 24-h, waking, and sleeping systolic BP \((r = 0.56, r = 0.55, P < .01, r = 0.45, P < .05, P < .05, r = 0.45, P < .05\), respectively) and with 24-h systolic and diastolic BP load \((r = 0.61, P < .001, r = 0.61, P < .001, r = 0.45, P < .05, r = 0.45, P < .05\), respectively). These correlations were not confirmed at 3 and 6 months. No relationship between UAE or UTE and office BP as well as the indices of BP variability (24-h, awake and asleep BP standard deviations and the ratio of awake to asleep BP) was observed. If the differences between baseline and 3 or
TABLE 2. CREATININE CLEARANCE, URINARY ALBUMIN AND TRANSFERRIN EXCRETION, PLASMA ALDOSTERONE, RENIN ACTIVITY AND ATRIAL NATRIURETIC PEPTIDE IN THE AMLODIPINE AND FOSINOPRIL GROUPS AT BASELINE AND AFTER TREATMENT

<table>
<thead>
<tr>
<th></th>
<th>Amlodipine</th>
<th>P Value</th>
<th>Fosinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 12)</td>
<td></td>
<td>(n = 12)</td>
</tr>
<tr>
<td>CrCl (mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>105.8 ± 16.7</td>
<td>&lt; .005</td>
<td>85.6 ± 13.5</td>
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<tr>
<td>3 months</td>
<td>94.4 ± 17.3 *</td>
<td>NS</td>
<td>90.2 ± 26.2</td>
</tr>
<tr>
<td>6 months</td>
<td>101.5 ± 24.3</td>
<td>&lt; .03</td>
<td>83.5 ± 9.1</td>
</tr>
<tr>
<td>UAE (mg/24 h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>75.5 ± 106.3 (37.6)</td>
<td>NS</td>
<td>49.8 ± 49.4 (25.6)</td>
</tr>
<tr>
<td>3 months</td>
<td>31.1 ± 23 (27.5)</td>
<td>NS</td>
<td>25.2 ± 29.4 (15)</td>
</tr>
<tr>
<td>6 months</td>
<td>47 ± 41.9 (37.5)</td>
<td>&lt; .01</td>
<td>17.9 ± 15.4 (13.9)</td>
</tr>
<tr>
<td>UTE (ng/24 h)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>35.9 ± 42.6 (27)</td>
<td>NS</td>
<td>35.4 ± 24 (34)</td>
</tr>
<tr>
<td>3 months</td>
<td>30.7 ± 16.9 (32)</td>
<td>NS</td>
<td>26.8 ± 16.6 (27)</td>
</tr>
<tr>
<td>6 months</td>
<td>28.7 ± 13.3 (30)</td>
<td>NS</td>
<td>25.5 ± 10.2 (23.7)</td>
</tr>
<tr>
<td>PA (ng/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20.9 ± 10.3</td>
<td>NS</td>
<td>21.1 ± 11.4</td>
</tr>
<tr>
<td>3 months</td>
<td>27.4 ± 11 *</td>
<td>&lt; .002</td>
<td>14.1 ± 6.1 *</td>
</tr>
<tr>
<td>6 months</td>
<td>32.1 ± 9.6 *</td>
<td>&lt; .001</td>
<td>14.4 ± 7.8 *</td>
</tr>
<tr>
<td>PRA (ng/mL/h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.17 ± 1.49</td>
<td>NS</td>
<td>0.92 ± 0.99</td>
</tr>
<tr>
<td>3 months</td>
<td>1.29 ± 1.25</td>
<td>&lt; .05</td>
<td>3.21 ± 2.62 *</td>
</tr>
<tr>
<td>6 months</td>
<td>1.07 ± 0.94</td>
<td>NS</td>
<td>3.02 ± 3.35 *</td>
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<tr>
<td>ANP (pg/mL)</td>
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<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>53 ± 36</td>
<td>NS</td>
<td>49 ± 16</td>
</tr>
<tr>
<td>3 months</td>
<td>56 ± 35</td>
<td>NS</td>
<td>46 ± 20</td>
</tr>
<tr>
<td>6 months</td>
<td>57 ± 24</td>
<td>NS</td>
<td>49 ± 27</td>
</tr>
</tbody>
</table>

Values are means ± SD. UAE and UTE values in parentheses are median values. CrCl, creatinine clearance; UAE, urinary albumin excretion; UTE, urinary transferrin excretion; PA, plasma aldosterone; PRA, plasma renin activity; ANP, atrial natriuretic peptide.

* P < .05 and † P < .01 for change from baseline. Statistical analyses for UAE and UTE were performed by nonparametric techniques using Wilcoxon signed rank test and Mann-Whitney U test.

6 months values of BP, UAE, and UTE were considered, there was a better correlation between BP and UAE, but not with UTE (Table 3).

No significant relationship between UAE or UTE and plasma hormones was observed, except for between UAE and aldosterone and only at baseline (r = 0.61, P < .001).

In the multiple regression analysis, UAE was significantly associated only with aldosterone (regression coefficient and 95% confidence limits: 0.023, 0.011–0.034, P = .0004) and with 24-h as well as waking and sleeping BP (0.019, 0.008–0.030, P = .002, 0.018, 0.007–0.029, P < .003, and 0.014, 0.003–0.025, P < .02, respectively) and only at baseline.

FIGURE 3. Individual values of urinary albumin excretion in the amloidipine (left) and fosinopril (right) group at baseline and at the end of the study.
untreated patients, the degree of BP well controlled, patients (25%) in group A, but this did not lead to withdrawal from therapy. No other adverse reactions in both groups were observed or referred.

**DISCUSSION**

The true prevalence of microalbuminuria in essential hypertension is not well known; it has been shown to occur in 14% to 40% of hypertensive patients and the different prevalence in these studies might be related to different selection criteria (ie, age, race, the severity of hypertension, the enrollment of treated or untreated patients, the degree of BP well controlled, the coexistence of renal insufficiency). In our study, microalbuminuria was present in 50% of patients with never-treated essential hypertension and no sign of renal damage. This prevalence is based on the analysis of a single 24-h urine collection and could be criticized. In fact, it is generally agreed that UAE is very variable and, according to some investigators, the definition of microalbuminuria should be based on the median UAE in at least three urine samples collected over several months. However, the following considerations should be taken into account. First, whether a patient’s risk status is influenced by the degree of variation of UAE around a risk level or the classification of risk is improved by multiple collections awaits testing in prospective studies. Second, nearly all epidemiologic studies showing that microalbuminuria is an independent predictor of cardiovascular morbidity and mortality in diabetic and nondiabetic subjects, performed a single urine collection to determine UAE values used in the correlations are the differences between baseline and third or sixth month values. UAE, urinary albumin excretion; SBP, systolic blood pressure; DBP, diastolic blood pressure.

### TABLE 3. CORRELATION COEFFICIENTS BETWEEN URINARY ALBUMIN EXCRETION AND AMBULATORY BLOOD PRESSURE

<table>
<thead>
<tr>
<th>UAE and value</th>
<th>Baseline Minus 3 Months*</th>
<th>Baseline Minus 6 Months*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24-h SBP</td>
<td>24-h DBP</td>
</tr>
<tr>
<td></td>
<td>0.44 &lt;.&lt;05</td>
<td>0.56 &lt;.01</td>
</tr>
<tr>
<td></td>
<td>0.49 &lt;.05</td>
<td>0.51 &lt;.01</td>
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<tr>
<td></td>
<td>0.45 &lt;.05</td>
<td>0.49 &lt;.05</td>
</tr>
<tr>
<td></td>
<td>0.54 &lt;.01</td>
<td>0.42 &lt;.05</td>
</tr>
</tbody>
</table>

* Urinary albumin excretion and ambulatory blood pressure values used in the correlations are the differences between baseline and third or sixth month values. UAE, urinary albumin excretion; SBP, systolic blood pressure; DBP, diastolic blood pressure.

**Side Effects** Peripheral edema was present in 3 of 12 patients (25%) in group A, but this did not lead to withdrawal from therapy. No other adverse reactions in both groups were observed or referred.

**Effects of Amlodipine and Fosinopril on Urinary Albumin Excretion** Before treatment, patients in group F were characterized by a significantly lower creatinine clearance value and by a lower, but not significant value of BP than patients in group A. It is improbable that lower creatinine clearance values in group F could reflect a higher degree of renal vascular damage due to hypertension, both because these values were in the normal range and because baseline UAE value and prevalence of microalbuminuria were lower in group F than in group A. After drug therapy, BP significantly decreased in both groups, even if a little more in group A, whereas only group F showed a significant reduction in UAE. Moreover, fosinopril lowered UAE in all patients, whereas amlodipine did so only in half of the patients. Our findings are in agreement with previous animal and human studies on essential hypertension showing a preferential effect of ACE inhibitors, versus other hypertensive drugs, in reducing elevated levels of UAE. Conversely, other investigators reported a similar effect on microalbuminuria of calcium antagonists and ACE inhibitors. A metagression analysis assessing the relative effect of different antihypertensive agents on proteinuria and renal function in diabetic patients concluded that any drug that reduces BP also decreases proteinuria. Nevertheless, it was evident from this study that unlike other antihypertensive agents, ACE inhibitors can reduce proteinuria and preserve renal function independently of changes in systemic BP. In fact, several studies on diabetic patients have shown that microalbuminuria can also be reduced in normotensive subjects. Although the pathophysiologic mechanisms involved in proteinuria in diabetes and in essential hypertension may be different, recently in another meta-analysis, Maki and coworkers showed that long-term beneficial effects of hypertensive agents on proteinuria and glomerular filtration rate are proportional to BP reductions and similar in diabetic and nondiabetic patients with renal disease and, moreover, that ACE inhibitors have additional beneficial effects on proteinuria independently of BP reductions. Therefore, it is probable that other factors, besides systemic BP, can play a role in the development of microalbuminuria. The different effects of calcium antagonists and ACE inhibitors on microalbuminuria in essential hypertension observed in our, as well as in other studies may be attributable to different hemodynamic intrarenal effects of these two classes of antihypertensive agents and are similar to those re-
ported in diabetes mellitus. Experimental data suggest that high intraglomerular capillary pressure may play an important role in glomerular injury. The ACE inhibitors reduce glomerular capillary pressure by dilating efferent more than afferent glomerular arterioles and probably by relaxing mesangial cells and increasing the ultrafiltration coefficient. Reduction in intraglomerular pressures would reduce macromolecular traffic through the mesangium and prevent endothelial injury. Moreover, it has also been reported that these agents can reduce glomerular permeability. Conversely, because calcium antagonists preferentially dilate the afferent arteriole, it has been proposed that these drugs should theoretically favor an increase in glomerular capillary pressure. In fact, Buzio and coworkers have reported that in essential hypertensive patients single doses of nifedipine, preceding a protein load, raised both glomerular filtration rate and renal plasma flow and increased urinary protein excretion rate, whereas captopril did not. Finally, the favorable effects of ACE inhibitors on microalbuminuria are likely also attributable to nonhemodynamic mechanisms due to inhibition of the renin-angiotensin-aldosterone system, such as a reduction in mesangial proliferation by suppressing angiotensin II and a vascular protective effect at the endothelial level by sparing potassium. In confirmation of this last issue, in our study fosinopril significantly decreased aldosterone, whereas amlodipine increased it and, before treatment, a positive correlation between UAE and aldosterone was observed.

Effects of Amlodipine and Fosinopril on Urinary Transferrin Excretion UTE did not significantly change during the study in both groups, whereas a significant decrease in UAE, at least in group F, was observed by the third month. Blood pressure was already significantly reduced after 2 weeks of therapy in both groups. Bianchi and coworkers reported a significant reduction in BP and UAE after 4 weeks of ACE inhibitor therapy. Therefore, we might conclude that UAE is sensitive to short-term changes in systemic BP, whereas UTE does not seem to be influenced by afterload reduction and it appears less sensitive than UAE for early detection of glomerular dysfunction in essential hypertension. In fact, in our study the UTE of patients with microalbuminuria was remarkably less than in diabetic patients, but similar to healthy subjects reported by Martin and coworkers. The different results observed in diabetes patients might be explained by changes in anionic charge of the glomerular basement membrane with nonenzymatic glycosylation or by the fact that, when glycated, albumin becomes much more anionic and thus more repelled by the glomerular polyanion basement membrane than transferrin. In confirmation of our findings, Konen and coworkers observed that UTE was less elevated than UAE in hypertensive patients without diabetes.

Relationship Between Urinary Transferrin and Albumin Excretion and Blood Pressure No correlation between UTE and BP was observed, whereas UAE was significantly and positively correlated to ambulatory BP, both as mean and BP load, but not to office BP. Some investigators reported a significant correlation between office BP and UAE, but others did not. A weak, even if significant, correlation with office BP (from r = 0.23 to r = 0.34) was observed by Hoegholm and coworkers, whereas the same and other investigators found a significantly stronger correlation between UAE and ambulatory BP. In this study as well as in another study a more pronounced correlation for systolic than for diastolic BP was found.

In conclusion, in these patients with never-treated essential hypertension and without signs of renal function impairment, a high prevalence of microalbuminuria has been observed. Antihypertensive therapy, particularly with an ACE inhibitor agent, shows to have a favorable effect on UAE. This finding might suggest that intrarenal hemodynamic changes can play a more important role than systemic BP decrease. A significant correlation has been found between UAE and BP with ambulatory, but not with office measurements, and it was more pronounced for systolic than for diastolic BP. UTE does not seem as useful a marker to follow-up essential hypertensive patients with early signs of glomerular dysfunction.

The clinical implications of these observations on the initial changes of renal function in essential hypertension remain to be ascertained.

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