Microalbuminuria in Essential Hypertension
Reduction by Different Antihypertensive Drugs

Christiane M. Erley, Uwe Haefele, Nils Heyne, Norbert Braun, and Teut Risler

The effects of four different antihypertensive drugs (the Ca$^{2+}$-channel blocker felodipine, the β-blocker metoprolol, the angiotensin converting enzyme inhibitor ramipril, and the α-blocking agent doxazosin) on microalbuminuria and renal hemodynamics were evaluated in a double-blind, crossover study in 17 patients (10 women, seven men, aged 39±14 years) with mild-to-moderate essential arterial hypertension and microalbuminuria. Patients were studied after a 2-week placebo phase preceded by 2 weeks off all medication and after 12 weeks of treatment with each drug. Between each drug treatment, there was another 14-day placebo washout period. At the end of the study, we performed two additional 2-week placebo periods. After each placebo and treatment period, we measured albumin excretion during a 3-day collecting period. Renal hemodynamics were assessed by clearance techniques (inulin and p-aminohippurate clearance) at the end of the first and last placebo periods and after each treatment period. All drugs reduced mean arterial pressure and microalbuminuria to a similar and statistically significant extent (mean arterial pressure: placebo phase, 116±5 mm Hg; felodipine, 101±4 mm Hg; metoprolol, 101±5 mm Hg; ramipril, 101±4 mm Hg; doxazosin, 102±5 mm Hg; urinary albumin excretion: placebo phase, 46±50 mg/day; felodipine, 18±23 mg/day; metoprolol, 14±12 mg/day; ramipril, 16±16 mg/day; doxazosin, 14±14 mg/day). Mean arterial pressure levels and urinary albumin excretion returned to baseline after the last placebo period (110±6 mm Hg and 40±46 mg/day, respectively). Glomerular filtration rate and renal plasma flow were not significantly changed by any drug and were normal in all patients. Renal vascular resistance and filtration fraction were lowest during angiotensin converting enzyme inhibition, but these differences did not reach statistical significance. In conclusion, all types of antihypertensive drugs under investigation reduced microalbuminuria in patients with mild-to-moderate arterial hypertension and without an elevation in filtration fraction. In the case of essential arterial hypertension, reduction of blood pressure seems to be an important factor for treatment of albuminuria.

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KEY WORDS • hypertension, essential • antihypertensive agents • hemodynamics, renal • microalbuminuria

Microalbuminuria in essential hypertension is associated with increased mortality,1-3 and proteinuria seems to be an independent risk factor for cardiovascular and cerebrovascular disease.4 The increased urinary albumin excretion (UAE) in arterial hypertension may be induced by several factors, such as renal hemodynamic changes, permselectivity changes of the glomerular filter, and structural arteriolar and glomerular changes due to nephrosclerosis. Albuminuria at low levels detected by radioimmunoassay methods as well as clinically apparent proteinuria (e.g., as detected by dipstick) are related to the level of arterial blood pressure.5-8 High blood pressure can be reduced by a variety of antihypertensive agents. Because most of them show different actions regarding kidney function, the question rises as to whether there are differences concerning the reduction of microalbuminuria.

To answer this question we performed a double-blind, placebo-controlled, crossover study in 17 patients with mild-to-moderate hypertension and microalbuminuria regarding the reduction of UAE and changes in renal hemodynamics under four different antihypertensive drugs (β-blocker, angiotensin converting enzyme inhibitor, Ca$^{2+}$-channel blocker, and α-blocker).

Methods

Patients

Seventeen patients (10 women, seven men) with mild-to-moderate hypertension were enrolled in this study (mean age, 39±14 years). Informed consent was obtained and the study was approved by the Institutional Review Board and local Ethics Committee. All patients had a normal renal function and microalbuminuria >20 mg/day (range, 20-300 mg/day). Adults from the outpatient center conforming with the following criteria were included: blood pressure levels > 140/95 mm Hg at the end of the placebo period, microalbuminuria of 20-300 mg/day on 3 consecutive days, absence of any other underlying renal or cardiac disease, exclusion of secondary forms of hypertension, exclusion of diabetes mellitus, blood pressure values < 130/85 mm Hg under medication, and age >18 and <65 years. Nine...
patients had been treated with antihypertensive drugs before entering the study. All drugs were discontinued 2 weeks before the study began, and concomitant medication was not allowed during the study period. Patients were allowed to continue their normal diet.

**Study Protocol**

All patients were followed on an outpatient basis. To obtain stable data, we measured blood pressure at least three times at study entry. After a 14-day placebo period, patients were initially investigated clinically, and blood samples for laboratory assays were drawn. At this time, patients had been without medication for 4 weeks. During the following 12 weeks, patients received the first drug (either felodipine, metoprolol, ramipril, or doxazosin) in a double-blinded fashion followed by another thorough examination. Before entering the next treatment phase, patients received placebo medication for 14 days. Subsequently, another 12-week period of medication ensued (Figure 1). The 17 patients were divided into four groups, and drugs were administered according to a Latin square design.

During the entire study period, blood pressure measurements were obtained every morning before drug intake by the patients themselves and during each hospital visit. The drug dosage was adjusted to lower blood pressure to normotensive levels in each patient (<130/85 mm Hg). Additionally, each patient underwent a 24-hour blood pressure measurement (Spacelabs 90202, Spacelabs Inc., Redmond, Wash.) at the end of each placebo period and after dosage adjustment to obtain comparable measurements. Mean daily dosage after adjustment for each drug was 8 mg felodipine, 85.5 mg metoprolol, 5 mg ramipril, and 2 mg doxazosin.

In general, all patients underwent 24-hour blood pressure recordings in a time range from 4 to 6 weeks after commencement of dosage adjustment and at the end of the placebo period. This was done to make sure that blood pressure levels were within the normal range after the adjustment period of 4 weeks. Subsequent blood pressure values were obtained from the patient's self-measurements, which were done before drug intake each day in the morning. We calculated the mean values of these measurements from the last 8 weeks of every treatment phase and the mean values of the last week of the placebo period.

Microalbuminuria was assessed after a 3-day collection period starting at the 11th day of placebo intake and after 53 days of antihypertensive medication. The values of microalbuminuria in Table 1 and Figures 2 and 3 were obtained from these 3-day collection periods and are given as mean±SD. The differences between the collecting days were <10%. During outpatient follow-up, drugs were administered after blood pressure recording and blood sampling had been finished and 4 hours before clearance measurements were started. Blood was also drawn for measurement of hormone activities (renin, aldosterone, antidiuretic hormone, and atrial stimulating factor). Glomerular filtration rate and renal blood flow were determined with the patients in a supine position the day before the first administration of drug and after 12 weeks of treatment. Additionally, microalbuminuria and blood pressure were assessed 4 weeks after the last treatment.

**Methods**

Arterial blood pressure was measured with a standard mercury sphygmomanometer. Measurements were performed in triplicate after 10 minutes of rest in a supine position. Glomerular filtration rate and renal plasma flow were measured by means of a constant infusion through P6 are placebo periods 1-6. Thin arrows indicate investigation of urinary albumin excretion and blood pressure. Thick arrows represent investigation of urinary albumin excretion, hormone levels, renal hemodynamics, and blood pressure.

**Table 1. Blood Pressure, Microalbuminuria, β-2-Microglobulinuria, and Sodium Excretion During Medication With Four Different Antihypertensive Drugs**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MAP (mm Hg)</th>
<th>UAE (mg/day)</th>
<th>β2 excretion (mmol/day)</th>
<th>Na excretion (mmol/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>116±5</td>
<td>56±50</td>
<td>150±199</td>
<td>200±93</td>
</tr>
<tr>
<td>Felodipine</td>
<td>101±4*</td>
<td>18±23*</td>
<td>208±297</td>
<td>163±82</td>
</tr>
<tr>
<td>Placebo phase 2</td>
<td>108±7</td>
<td>24±20</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>101±5*</td>
<td>14±12*</td>
<td>115±128</td>
<td>171±45</td>
</tr>
<tr>
<td>Placebo phase 3</td>
<td>107±6</td>
<td>19±18</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Ramipril</td>
<td>101±4*</td>
<td>16±16*</td>
<td>114±165</td>
<td>159±62</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>102±5*</td>
<td>14±14*</td>
<td>114±213</td>
<td>187±83</td>
</tr>
<tr>
<td>Placebo phase 5</td>
<td>106±7</td>
<td>22±22</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Placebo phase 6</td>
<td>110±6</td>
<td>40±46</td>
<td>142±211</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure; UAE, urinary albumin excretion; n.d., not determined. Values are mean±SD. UAE values in parentheses are median values.

*p<0.05 compared with baseline.
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Figure 2. Plots show excretion of albumin during the study. There were four different periods of drug intake. Each symbol represents a patient. Patients received drugs in the following order: group 1, felodipine, metoprolol, doxazosin, ramipril; group 2, metoprolol, ramipril, felodipine, doxazosin; group 3, ramipril, doxazosin, metoprolol, felodipine; group 4, doxazosin, felodipine, ramipril, metoprolol. P, placebo.

Figure 3. Bar graph shows urinary albumin excretion (UAE) and mean arterial pressure (MAP) during treatment with each of the four antihypertensive drugs and at the beginning and end of the study. *p<0.05 compared with placebo.

technique of inulin and p-aminohippurate (PAH) after an initial loading dose starting at 8:30 AM. Inulin and PAH clearance (C_in and C_PAH) parameters were calculated as urine concentration divided by plasma concentration multiplied by urine volume in milliliters per minute and were corrected for standard body surface area (1.73 m²). Filtration fraction was calculated as C_in/C_PAH and was expressed as a percentage of C_PAH. Renal blood flow was calculated from C_PAH by using the peripheral venous hematocrit. Renal vascular resistance was calculated as mean arterial pressure/renal blood flow x 80.

Serum and urinary potassium, sodium, calcium, creatinine, uric acid, and albumin were measured by routine laboratory methods (Autoanalyzer, Hitachi, Japan). The peripheral venous hematocrit was determined with a microhematocrit technique. Renin activities, aldosterone, and antidiuretic hormone, and ANP were measured by radioimmunoassays (renin activities: Serono Diagnostics, Freiburg, FRG; aldosterone and vasopressin: Biermann Corp., Bad Nauheim, FRG). Urinary albumin values and β₂-microglobulinuria (Behring Corp., Marburg, FRG) were measured by an enzyme-linked immunosorbent assay.

All data are expressed as mean±SD. The Wilcoxon test was used to compare values at the end of the first and last placebo periods. The Friedman test was used to evaluate additional parameters. The correlation between drug-induced changes of mean arterial pressure, glomerular filtration rate, filtration fraction, and reduction of microalbuminuria was analyzed by Spearman’s method with calculation of the rank coefficient value (r).

Results

Routine laboratory parameters, e.g., serum values of sodium, uric acid, creatinine, urea nitrogen, and hemoglobin, as well as liver parameters and protein levels, did not change over the study period. Serum potassium was lowest under felodipine (3.96±0.32 mmol/L) and highest under metoprolol (4.16±0.21 mmol/L). This difference reached statistical significance (p<0.05). Cholesterol levels were in the normal range in all patients and did not change significantly because of drug treatment (placebo, 5.2±1.4 mmol/L; felodipine, 5.2±1.4 mmol/L; metoprolol, 5.1±1.0 mmol/L; ramipril, 5.0±1.3 mmol/L; and doxazosin, 4.9±0.8 mmol/L).

Arterial blood pressure decreased significantly (p<0.01 for all four drugs) under medication (Table 1, Figures 2 and 3) and increased in the placebo phases. During the short washout periods between the treatment phases, blood pressure did not completely reach baseline levels (Table 1, Figure 2).

Microalbuminuria, expressed as UAE, changed the same way as the blood pressure did. UAE values decreased significantly (p<0.05) under antihypertensive treatment in all cases (Table 1, Figures 2 and 3).
Reduction of UAE was associated with a reduction of mean arterial pressure in the majority of patients (rank coefficient range, 0.29–0.98; mean r=0.65). Placebo values between the treatment periods showed an increase of UAE but did not reach baseline levels (Table 1, Figure 2). At the end of the last placebo phase, UAE was in the same range as at the study beginning (Table 1, Figures 2 and 3). The extent of UAE reduction was comparable for all drugs (Figure 3). β-Microalbuminuria, a marker of tubular dysfunction, was not significantly altered during any treatment (Table 1).

We could not demonstrate any significant changes in renal hemodynamics (see Table 2). No patient showed an elevation in filtration fraction at the time of investigation (Table 2).

Hormone levels for renin activity, aldosterone, and vasopressin are depicted in Table 3. Renin activity was significantly suppressed by metoprolol and enhanced by ramipril (Table 3).

**Discussion**

Microalbuminuria occurs in approximately 30% of hypertensive patients,10,11 and some authors have found an even higher prevalence.6,12,13 In patients with mild-to-moderate hypertension, the degree of microalbuminuria varies considerably, from 0% to >40%. There is some evidence for an association of microalbuminuria with an increased cardiovascular and total mortality.1-3

In most articles, microalbuminuria has been defined according to Mogensen as UAE of 30–300 mg/day.15 These values mostly apply to diabetic patients. Since the development of a special enzyme-linked immunosorbent assay for screening of microalbuminuria, our investigations revealed that, despite physical exercise, the UAE rate did not exceed 20 mg/day in the group of normotensive individuals.9,16 This has been substantiated by other authors.17,18 We included patients with a UAE of 20–300 mg/day to be able to study patients with only mildly elevated blood pressure who required only one antihypertensive drug to achieve normotension.

The increased UAE in arterial hypertension may be induced by several factors, such as renal hemodynamic changes, permselectivity changes of the glomerular filter, and structural arteriolar and glomerular changes due to nephrosclerosis. It may even serve as an indicator for an elevation of systemic blood pressure.9 No specific pathological changes can be detected in most of the patients with essential hypertension and microalbuminuria.19-21

There is also no obvious evidence for a relation between microalbuminuria and specific changes in renal hemodynamics, which have been noticed in patients with mild-to-moderate arterial hypertension.8,22-24 Furthermore, it is still not known whether microalbuminuria predicts development of proteinuria and a decline in renal function in essential hypertension, as seems to be the case in diabetes mellitus.25 The relation between microalbuminuria and an increased cardiovascular morbidity1-3,9,20 must be viewed with regard to a dependence of microalbuminuria on the magnitude of arterial blood pressure.7,13,17,27,28 Lowering blood pressure by different antihypertensive agents has been shown to be able to reduce urinary protein excretion and UAE in patients with essential hypertension.6,29-32 As in diabetes mellitus, some investigators showed favorable results with angiotensin converting enzyme inhibitors6,30-35 and Ca2+-channel blockers.36,37 However, other reports could not confirm any difference between these agents compared with β-blockers or thiazides.5,6,25,31,36 The favorable effects of angiotensin converting enzyme inhibitors are believed to be related to their special action on renal hemodynamics, especially to reduction in filtration pressure.39

In our prospective, double-blind, controlled study, we could not demonstrate any significant difference between a β-blocker (metoprolol), a Ca2+-channel blocker (felodipine), an angiotensin converting enzyme inhibitor (ramipril), and an α-blocker (doxazosin) regarding reduction of UAE (Figure 3). When looking separately at patients with UAE less than and greater than 30 mg/day, the statistical results concerning the reduction of UAE under the four different antihypertensive drugs did not change. The reduction of blood pressure was comparable in all patients because of dose adjustment (Table 1, Figure 3). We could not detect a significant change of renal hemodynamics and function (Table 2), although filtration fraction and renal vascular resistance were lowered during angiotensin converting enzyme inhibition and increased in the case of β-blockade. However, these changes did not reach statistical significance. It is of interest that our patient population showed no increase in filtration fraction. UAE was reduced during treatment

**Table 2. Renal Hemodynamics During Medication With Four Different Antihypertensive Drugs**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>GFR [(ml/min)/1.73 m²]</th>
<th>RPF [(ml/min)/1.73 m²]</th>
<th>FF (%)</th>
<th>RVR [(dyn · cm⁻² · sec⁻¹)/1.73 m²]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>112±17</td>
<td>554±84</td>
<td>20.3±2</td>
<td>18.8±3.1</td>
</tr>
<tr>
<td>Felodipine</td>
<td>114±28</td>
<td>526±119</td>
<td>21.6±5</td>
<td>17.5±4.3</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>111±29</td>
<td>517±134</td>
<td>21.8±3</td>
<td>18.4±5.1</td>
</tr>
<tr>
<td>Ramipril</td>
<td>116±21</td>
<td>545±110</td>
<td>20.5±3</td>
<td>17.2±3.9</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>111±19</td>
<td>521±114</td>
<td>22.3±4</td>
<td>18.0±3.8</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate; RPF, renal plasma flow; FF, filtration fraction; RVR, renal vascular resistance. Values are mean±SD.

**Table 3. Hormone Values During Medication With Four Different Antihypertensive Drugs**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Renin (ng/L · sec)</th>
<th>Aldosterone (pmol/L)</th>
<th>Vasopressin (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.29±0.24</td>
<td>300±161</td>
<td>1.34±0.58</td>
</tr>
<tr>
<td>Felodipine</td>
<td>0.39±0.45</td>
<td>350±169</td>
<td>1.42±0.48</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>0.14±0.14*</td>
<td>283±153</td>
<td>1.25±0.72</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.01±0.81*</td>
<td>239±214*</td>
<td>1.25±0.64</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>0.37±0.29</td>
<td>402±250</td>
<td>1.17±0.55</td>
</tr>
</tbody>
</table>

Values are mean±SD. *p<0.05 compared with baseline.
and increased in the placebo phases. Because UAE levels and mean arterial pressure during the placebo phases did not reach baseline levels, there seems to be some overlap of drug action (Figure 2). The extension of the placebo phase to 4 weeks at the end of the study resulted in a return to UAE and mean arterial pressure baseline levels. This provides evidence that the data obtained at the end of each 3-month period of drug therapy are reliable effects of medication.

Our observation is in contrast to studies in diabetic patients. In diabetes mellitus, microalbuminuria seems to be an early marker of renal involvement with corresponding histological changes of the glomerular capillary basement membrane. Here, drugs such as angiotensin converting enzyme inhibitors and Ca<sup>2+</sup>-channel blockers showed favorable effects regarding the reduction of microalbuminuria. These advantages are believed to be related to influences on the glomerular capillary basement membrane, thrombocyte aggregation, and lowering of the pathologically elevated filtration fraction in diabetes patients. A significant reduction of renal blood flow and an increase of vascular resistance in patients with hypertension is mostly seen in elderly patients and patients with severe hypertension, high renin levels, a long duration of hypertension, or insufficient blood pressure control. This may be due to an increase in resistance of the efferent glomerular arterioles. It is not surprising that we did not observe significant changes of renal hemodynamics, because our patients were only mildly hypertensive, mostly younger than 50 years, and had been treated with antihypertensive drugs in the past. However, this seems to reflect the majority of hypertensive patients physicians have to deal with. Hence, we believe this study to be of clinical importance. Our results indicate that mild arterial hypertension with an elevated UAE without an elevation of filtration fraction does not occur in patients with essential hypertension and without signs of renal function impairment. This can be accomplished regardless of the type of drug used and independent of the action on renal hemodynamics.

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References

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