Is Microalbuminuria a Marker of Early Intrarenal Vascular Dysfunction in Essential Hypertension?

Albert Mimran, Jean Ribstein, Guilhem DuCaillar

Abstract The relation between basal intrarenal hemodynamics and the renal response to acute inhibition of angiotensin-converting enzyme by captopril and albuminuria was assessed in 106 lean patients with essential hypertension without detectable proteinuria. It was observed that the microalbuminuric group (24.5% of the total population) was characterized by a higher systemic arterial pressure, a lower level of high-density lipoprotein cholesterol, and similar mean values of age, duration of hypertension, glomerular filtration rate, renal plasma flow, filtration fraction, and plasma renin activity when compared with normoalbuminuric subjects. In response to captopril, a significant renal vasodilatation without a change in glomerular filtration rate or a fall in filtration fraction was observed in normoalbuminuric patients only. In contrast, the renal vasodilator response was abolished in microalbuminuric subjects, together with blunting of the rise in plasma renin activity associated with captopril. This occurred despite similar indexes of activity of the endogenous renin-angiotensin system. It is suggested that microalbuminuria may be a marker of early functional or fixed intrarenal vascular dysfunction in never-treated lean patients with essential hypertension. (Hypertension. 1994;23(part 2):1018-1021.)

Key Words • hemodynamics • hypertension, essential • albuminuria

Microalbuminuria (urinary excretion of albumin lower than 200 μg/min) was proposed as a reliable predictor of the development of overt (proteinuric) nephropathy in patients with insulin-dependent diabetes1 and of cardiovascular morbidity and mortality in diabetic2,3 and nondiabetic4 populations. The mechanisms and significance of microalbuminuria observed in some patients with essential hypertension are not clearly elucidated because of the lack of simultaneous assessment of the relation between albuminuria and intrarenal hemodynamics and long-term follow-up studies. In the present studies, an attempt was made to evaluate the systemic and renal determinants of microalbuminuria in a population of never-treated patients with mild to moderate hypertension of rather short duration. In addition, the renal response to acute blockade of angiotensin-converting enzyme was assessed to detect contrasting effects in microalbuminuric (MA+) and normoalbuminuric (MA−) patients. Only lean patients were included to eliminate the possible exacerbating influence of overweight in association with high blood pressure on the urinary excretion of albumin.5

Methods

Patients

One hundred six lean patients (34 women and 72 men) with mild to moderate essential hypertension were included in this study. Age range was 16 to 64 years, and body mass index was lower than 26 kg/m² in women and 27 kg/m² in men. All subjects had never received antihypertensive medication before participating in the studies. Women on oral contraceptives as well as patients with albustix-positive proteinuria were excluded. Informed consent was obtained from all subjects before beginning the studies.

Protocol

Studies were performed between 8 AM and 1 PM. After an overnight fast, patients came to the ward with two consecutive 24-hour urine collections for the determination of levels of creatinine, electrolytes, uric acid, and ura, and urinary albumin excretion (UAE). Throughout the study, with the subject in the supine position, arterial pressure and heart rate were monitored every 3 minutes with a Dynapal 845 XT (Critikon). After a 30-minute period of rest, blood was collected for the determination of levels of creatinine, electrolytes, uric acid, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Glomerular filtration rate (GFR) and effective renal plasma flow (RPF) were estimated by the constant infusion technique, using 99mTc-diethylenetriaminepentaacetic acid and 131I-sodium ortho-iodohippurate, respectively, in subjects maintained on water diuresis.6 After an equilibrium period of 90 minutes, three 20- to 30-minute control clearances were obtained (urine collected by spontaneous voiding). A 30-mg dose of captopril was then given orally, and the urine collected within 30 to 45 minutes was discarded. Thereafter, two 20- to 30-minute clearance determinations were obtained. After completion of renal function studies, left ventricular mass was estimated by two-dimensional echocardiography.7

Analytical Methods

Clearances obtained during the precaptopril and postcaptopril periods were averaged and proportioned to 1.73 m² of body surface area, and renal resistance was calculated as the ratio of mean arterial pressure to renal blood flow (RPF/1−hematocrit). Plasma renin activity, plasma aldosterone concentration, and urinary albumin were estimated by radioimmunoassay techniques.

Statistical Analysis

Data are presented as mean and SEM unless stated. Statistical analysis was carried out using paired or unpaired t tests.
Demographic, Clinical, Renal, and Hormonal Characteristics of Patients With or Without Microalbuminuria

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Microalbuminuria Absent (MA−)</th>
<th>Microalbuminuria Present (MA+)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>80</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>41±1</td>
<td>43±2</td>
<td>NS</td>
</tr>
<tr>
<td>Sex ratio (women/men)</td>
<td>27/53</td>
<td>7/19</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.4±0.3</td>
<td>24.1±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic arterial pressure, mm Hg</td>
<td>157±1</td>
<td>163±3</td>
<td>.05</td>
</tr>
<tr>
<td>Diastolic arterial pressure, mm Hg</td>
<td>97±1</td>
<td>101±2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>117±1</td>
<td>121±2</td>
<td>.05</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.05±0.02</td>
<td>1.02±0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Serum uric acid, mg/dL</td>
<td>4.7±0.1</td>
<td>4.9±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>216±4</td>
<td>225±9</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>56±2</td>
<td>47±3</td>
<td>.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>104±6</td>
<td>129±14</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m²</td>
<td>112±4</td>
<td>115±8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Renal function

- Glomerular filtration rate, mL/min per 1.73 m²: 103±2 vs 108±4, NS
- Effective renal plasma flow, mL/min per 1.73 m²: 446±9 vs 471±18, NS
- Filtration fraction, %: 23.5±0.4 vs 23.3±0.8, NS
- Urinary sodium, mmol/24 h: 153±7 vs 155±15, NS
- Urinary urea, mmol/24 h: 364±15 vs 434±29, .05
- Urinary albumin excretion, µg/min: 7±1 vs 37±5, .001
- Plasma renin activity, ng/mL per hour: 1.53±0.14 vs 1.34±0.18, NS
- Plasma aldosterone, ng/dL: 14.0±0.7 vs 15.2±1.3, NS

Data are expressed as mean±SEM. HDL indicates high-density lipoprotein.

Results

Characteristics of the Entire Population

In this group of never-treated patients with mild to moderate hypertension of rather short duration, albuminuria ranged between 0.4 and 106 µg/min; 26 of 106 patients (24.5% of the population) had microalbuminuria defined as UAE higher than 14 µg/min. This cutoff value was chosen after measurement of UAE in 59 lean normal subjects (aged 14 to 60 years) in whom a median UAE value of 4 µg/min (5±3 µg/min, mean±SD) was obtained.

The logarithm of UAE was positively correlated with systolic and mean arterial pressure ($r$ values of .32 and .25, respectively, $P<.01$) and urinary urea excretion ($r=28$, $P<.006$). No correlation between UAE and baseline parameters of renal function or left ventricular mass index was observed. Interestingly, a negative correlation with HDL cholesterol level was found ($r=-.34$, $P<.0007$).

Characteristics of Microalbuminuric and Normoalbuminuric Patients

Baseline

The two groups were similar in age, body mass index, sex repartition, and estimated duration of hypertension (26±4 and 25±5 months for MA− and MA+, respectively). The prevalence of a smoking history was higher in the MA+ (42%) than in the MA− (29%) group; however, it did not reach statistical significance ($P<.10$).

As summarized in the Table, higher mean values of systolic and mean arterial pressure as well as urinary excretion of urea (an index of protein intake) were found in the MA+ group. No difference in renal function and hemodynamics as well as hormonal parameters (plasma renin activity and plasma aldosterone concentration) between the two groups was observed. HDL cholesterol but not total serum cholesterol was lower in the MA+ group.

Renal Response to Acute Administration of Captopril

As shown in the Figure, the two groups were similar with respect to the response to captopril of mean arterial pressure (−6.3±3% and −5.8±1% in MA− and MA+, respectively) and plasma aldosterone concentration (−24±3% and −25±4% in MA− and MA+, respectively). In contrast, the renal vasodilator response to captopril was significantly blunted in MA+ patients (2.9±2.1% versus 11.3±1.5%, $P<.005$ for RPF), whereas GFR was unaltered in both groups. Calculated filtration fraction was unchanged in MA+ patients (2.2±1.2%) and decreased by 5.4±1% in the MA− group ($P<.05$). Moreover, the increase in plasma renin activity associated with captopril was blunted ($P<.005$) in the MA+ group (33±13%) when compared with the normoalbuminuric group (100±19%).
groups, and filtration fraction was not altered. If the presence of an elevated GFR and filtration fraction truly indicates the existence of an increase in intraglomerular pressure, by analogy to animal models of renal injury, the present studies yielded negative results. However, the present findings do not exclude the possibility of elevated GFR and glomerular pressure at the single nephron level, if the microalbuminuric patients correspond to those subjects with a lower number of glomeruli.12

The significance of microalbuminuria in essential hypertension remains to be established. Whether such an abnormality is an indicator of early renal damage or a predictor of the future development of progressive renal functional impairment remains to be determined. In patients with insulin-dependent diabetes, microalbuminuria was emphasized as the most important predictor of the later development of overt (albustix-positive) nephropathy and ultimately renal insufficiency.1 In addition, the use of angiotensin-converting enzyme inhibitors in contrast to placebo in normotensive microalbuminuric diabetic patients was successful in preventing the progression from incipient to overt nephropathy.13 In a recent study, a similar observation was made in normotensive non-insulin-dependent diabetic patients.14

The possibility that microalbuminuria is associated with an impaired renal functional reserve assessed by the GFR response to an acute infusion of amino acids was explored by Losito et al.15 It was observed that one third of 34 patients (most of whom were microalbuminuric) with mild to moderate essential hypertension displayed an abolished response of creatinine clearance (a rather unreliable marker of GFR) to this maneuver. In our studies, protein intake (as assessed by urinary excretion of urea) was higher in microalbuminuric when compared with normoalbuminuric patients. Because GFR was similar in both groups, it could be argued that such patients had an impaired renal response to chronic elevation in protein intake, thus suggesting that microalbuminuria may represent an early sign of renal inability to adapt to chronic changes in protein intake.

The finding of an abolished vasodilator response to acute inhibition of angiotensin-converting enzyme in microalbuminuric patients, in contrast to normoalbuminuric patients and normal subjects (A.M., unpublished observation), raises several questions. The inability of captopril to dilate the renal vasculature was observed despite the existence of a similar degree of endogenous activity of the renin-angiotensin system, as suggested by identical baseline plasma renin activity as well as a similar fall in mean arterial pressure and decline in plasma aldosterone concentration in response to captopril. This indicates that the renal vasculature of microalbuminuric patients may have lost responsiveness to endogenous angiotensin II, in contrast to systemic resistance vessels and adrenals. Interestingly, the rise in plasma renin activity in response to interruption by captopril of the negative feedback loop between angiotensin II and renin secretion and/or the fall in renal perfusion pressure was markedly blunted in microalbuminuric patients. Such an abnormality suggests that in these patients juxtaglomerular cells may be poorly responsive to endogenous angiotensin II or that renal baroreceptor mechanisms are altered as a consequence of intrarenal damage probably located at the afferent glomerular level, a known target of hypertension.16 Whether such a lack of renal responsiveness to interruption of the renin-angiotensin system is the consequence of a fixed inability of intrarenal vessels to dilate, a failure to produce vasodilator kinins in response to

Discussion
In the present studies conducted in a rather large number of never-treated lean patients with essential hypertension, it was observed that arterial pressure was the main determinant of UAE. No relation with renal function, RPF, and filtration fraction was observed, thus suggesting that an intrarenal hemodynamic imbalance (mainly an increase in filtration fraction, the sole available indicator of intraglomerular pressure in human studies) is not a major factor in the occurrence of microalbuminuria. Interestingly, the existence of microalbuminuria was associated with a lower level of HDL cholesterol and a higher urinary excretion of urea (a parameter that indicates that dietary protein intake was higher in these patients). In fact, the most original finding was that the renal vasodilator response to captopril associated with a fall in filtration fraction was abolished in microalbuminuric patients with identical plasma renin activity (mainly an increase in filtration fraction, the sole available indicator of intraglomerular pressure in human studies) is not a major factor in the occurrence of microalbuminuria.

In our population, the prevalence of microalbuminuria (cutoff value of 14 μg/min) was 24.5%; if a cutoff value of 20 μg/min had been chosen, this figure would have been almost unchanged. In the largest studies conducted to date, 37% of 123 patients had UAE values higher than 20 μg/min; of interest, only half of the population had never received antihypertensive medication before the studies. In smaller numbers of patients, the prevalence of microalbuminuria ranged between 11% and 23%. In all these studies, a significant positive correlation between casual as well as average daytime pressure and UAE was observed.

The mechanism of microalbuminuria in essential hypertension is poorly understood. For the first time, an attempt was made to assess the relation between intrarenal hemodynamics and UAE. RPF and GFR were similar in microalbuminuric and normoalbuminuric groups, and filtration fraction was not altered. If the presence of an elevated GFR and filtration fraction truly indicates the existence of an increase in intraglomerular capillary pressure, by analogy to animal models of renal injury, the present studies yielded negative
and angiotensin-converting enzyme inhibition, or a defect in the production of an endothelium-derived relaxing factor indispensable to the vasodilator effect of kinins remains hypothetical. It was demonstrated in isolated vessels and cultured human and bovine endothelial cells that the effect of various types of angiotensin-converting enzyme inhibitors may be mediated through an increased production of endothelium-derived relaxing factors. The present observation may thus suggest that microalbuminuria could be a marker of intrarenal endothelial dysfunction. It would be of interest to compare the renal effect of angiotensin-converting enzyme inhibitors and calcium antagonists, since these agents are known to exert their vasodilator action through non-endothelium-dependent mechanisms in hypertensive patients with or without microalbuminuria. In patients with mild hypertension, Hollenberg et al. observed that the renal vasculature was exquisitely sensitive to the intrarenal infusion of the endothelium-dependent dilator acetylcholine; in contrast, the response to acetylcholine was abolished in subjects with severe hypertension and advanced nephrosclerosis. However, the study was conducted in a small number of patients, and no mention of albuminuria was available.

In recent years, microalbuminuria was proposed as a marker of cardiovascular risk in nondiabetic and diabetic patients. In the diabetic population, the HDL cholesterol level was lower in microalbuminuric than normoalbuminuric patients. In patients with treated essential hypertension, it was reported that proteinuria at entry was higher in those patients who developed cardiovascular complications within a 10-year follow-up period. Our observation that HDL cholesterol was lower in microalbuminuric subjects suggests that microalbuminuria may be an early marker of renal vascular dysfunction as well as cardiovascular risk. Long-term follow-up of renal function in our population may be of great interest with regard to an eventual development of renal impairment despite effective antihypertensive therapy, whether associated or not with a reduction in albuminuria.

References
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