Microalbuminuria and Pulse Pressure in Hypertensive and Atherosclerotic Men

Roberto Pedrinelli, Giulia Dell’Omo, Giuseppe Penno, Simona Bandinelli, Alessio Bertini, Vitantonio Di Bello, Mario Mariani

Abstract—To identify the biological covariates of microalbuminuria (albuminuria $\geq 15$ μg/min) in nondiabetic subjects, brachial blood pressure, echocardiographic left ventricular mass, and other cardiovascular and metabolic parameters were evaluated in 211 untreated males (38 normal controls, 109 uncomplicated stage 1 to 3 essential hypertensives, and 64 patients with clinically stable atherosclerotic peripheral vascular disease either with $n=44$ or without $n=20$ essential hypertension) with normal cardiac and renal function. Compared with normoalbuminuric subjects, microalbuminuric subjects ($n=67$) were characterized by higher systolic blood pressure, comparable diastolic blood pressure, and, therefore, wider pulse pressure. Greater prevalence of hypertension, peripheral vascular disease, left ventricular hypertrophy, and reduced HDL cholesterol values further distinguished microalbuminuric from normoalbuminuric subjects in univariate comparisons. The risk of microalbuminuria increased by ascending pulse pressure quintiles in age-corrected logistic regression models, in which pulse pressure was more predictive than systolic pressure and was independent of mean pressure. When microalbuminuric status was regressed against a series of dichotomous (vascular and active smoker status) and continuous (age, pulse and mean pressure, left ventricular mass index, and HDL and LDL cholesterol) variables, only pulse pressure, left ventricular mass index, and smoking status were independent predictors. The association of increased albuminuria with wider pulse pressure, a correlate of the pulsatile hemodynamic load and conduit vessel stiffness as well as an important cardiovascular risk factor, may explain why microalbuminuria predicts cardiovascular events in nondiabetic subjects. The independence from concomitant vascular disease also suggests that wider pulse pressure, rather than representing a simple marker for atherosclerotic disease, influences albuminuria directly. (*Hypertension*, 2000;35:48-54.)

Key Words: albuminuria • pressure • hypertension, essential • vascular diseases • mass, ventricular

Microalbuminuria (ie, an abnormal urinary albumin excretion [UAE] in a range not detectable by the usual dipstick methods for urine protein) is associated with an increased cardiovascular risk in hypertensive patients3–2 and nondiabetic populations.3–5 Yet, why a renal parameter of glomerular origin behaves as a marker of atherosclerotic cardiovascular disease remains obscure, and the biological factors influencing UAE still await some deeper clarification.

To specify to a better extent the biological covariates of microalbuminuria in nondiabetic subjects, we have evaluated cross-sectionally a series of cardiovascular and metabolic parameters in a large group of normal control subjects, subjects with essential hypertension (EH), and patients with atherosclerotic vascular disease.

Methods

Subjects

The study was carried out on 211 eligible sedentary subjects referred to our unit from 1996 to 1998 for screening and treatment of hypertension and related cardiovascular risk factors. Inclusion criteria required male gender, negative urine dipstick test, normal urinary sediment and renal ultrasound, plasma glucose <7.8 mmol/L (120 mg/dL), serum creatinine <110 μmol/L (1.4 mg/dL), total serum cholesterol <7.8 mmol/L (300 mg/dL), body mass index (BMI) <27 kg/m², and preserved systolic cardiac function (ejection fraction >50%) (see Table 1 for the overall demographic and clinical characteristics). One hundred nine patients had stage 1 to 3 uncomplicated EH, 20 had atherosclerotic peripheral vascular disease (PVD), and 44 were affected by both conditions (EH/PVD). Thirty-eight normal subjects were the controls.

Clinical screenings were based on history, physical examination, routine tests, and neck and lower limb color-echo Doppler sonography in most subjects. All parameters reported in the present study were collected in a 2-week period.

Diagnosis of hypertension was based on casual blood pressure (BP) values $>140/90$ mm Hg and/or antihypertensive treatment at the first contact, and secondary forms of hypertension were excluded by routine examinations, including renal color-echo Doppler sonography and, if needed, angiography. If patients had received treatment, antihypertensive drugs were withdrawn 4 weeks before the study; no patient had ever been on lipid-lowering drugs. PVD was diagnosed by intermittent claudication (pain-free walking distance $>200$ m on a treadmill) confirmed by ankle-brachial pressure measurements $<0.9$ at one or both sides. According to institutional guidelines,
subjects were aware of the investigational nature of the study and agreed to participate. The study was carried out in accordance with the Declaration of Helsinki, and the protocol was approved by the local Ethical Committee.

**Experimental Procedures**

UAES was measured by nephelometry (Behring; limit of detection 0.1 mg/dL, interassay variation coefficient 3.5%) on samples collected from 8:00 PM to 8:00 AM during 3 consecutive days. Sitting BP was measured in the early afternoon by an automated oscillometric device (SpaceLabs 90207) throughout a 2-hour period. Wall thickness and chamber diameters were determined at or just below the mitral valve tips, by the leading edge–to–leading edge method on monodimensional and bidimensional echocardiograms (Hewlett-Packard Sonos 1000, with 2.5- and 3.5-MHz transducers) according to recommendations of the American Society of Echocardiography. Clinically significant aortic insufficiency was excluded in all subjects by Doppler examinations. Anthropometric measurements (height and weight) were made after each participant had removed his shoes and upper garments. Blood samples were obtained between 8:00 and 9:00 AM after an overnight fasting and 15 minutes of supine rest. Total cholesterol, HDL cholesterol, and triglycerides were assessed by enzymatic colorimetric techniques (Boehringer-Mannheim). Serum and urine creatinine levels were assayed by standard colorimetric methods.

**Data Processing**

UAES (µg/min) was the median of 3 consecutive overnight collections (median variation coefficient 25%). Microalbuminuria was defined as any UAES value ≥15 µg/min in the presence of a negative dipstick test for urine protein. Systolic BP (SBP) and diastolic BP (DBP) values were the mean of at least 10 recordings taken over a 2-hour period. Pulse pressure (PP) was the arithmetic difference between averaged SBP and DBP values. Mean BP (MBP) was calculated by the leading edge–to–leading edge method on Doppler examinations. Anthropometric measurements (height and weight) were made after each participant had removed his shoes and upper garments. Blood samples were obtained between 8:00 and 9:00 AM after an overnight fasting and 15 minutes of supine rest. Total cholesterol, HDL cholesterol, and triglycerides were assessed by enzymatic colorimetric techniques (Boehringer-Mannheim). Serum and urine creatinine levels were assayed by standard colorimetric methods.

**Statistics**

The association of microalbuminuria (coded as follows: 0, normoalbuminuria; 1, microalbuminuria) with continuous and categorical (including quintiles of PP) covariates was analyzed by logistic regression (maximum likelihood method) using a backward stepwise procedure (probability to remove, P<0.05) to identify the independent regressors. Odds ratios (ORs, ie, the exponentiated regression coefficients) were used to estimate relative risks and 95% CIs. Intraindividual association of continuous variables was evaluated by nonparametric Spearman rank correlation coefficients. Differences among continuous variables were tested by ANOVA covariated for age, and a multiple range test was used to evaluate differences among means. Categorical parameters were tested by Cochran-Armitage exact tests.

Data were reported as mean±SD or median and range in the presence of skewed data. Statistical significance was set at P<0.05 unless otherwise indicated.

**Results**

**Clinical Characteristics by Microalbuminuric Status**

Older age, higher SBP, comparable DBP, wider PP with the same SV, greater prevalence of hypertension, atherosclerotic PVD, cardiac hypertrophy, higher LVMI and MBP, and lower HDL cholesterol values distinguished microalbumin-
TABLE 3. Cardiovascular, Renal, and Metabolic Parameters According to Vascular Status (EH, PVD, and EH/PVD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n=109)</th>
<th>EH (n=20)</th>
<th>PVD (n=44)</th>
<th>EH/PVD (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50±17</td>
<td>51±11</td>
<td>57±7*</td>
<td>64±8*</td>
</tr>
<tr>
<td>Microalbuminuria, %</td>
<td>6</td>
<td>26</td>
<td>5</td>
<td>66†</td>
</tr>
<tr>
<td>UAE, μg/min</td>
<td>7 (3–24)</td>
<td>9 (2–271)</td>
<td>7 (3–17)</td>
<td>21 (3–248)</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>34</td>
<td>29</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>LV hypertrophy, %</td>
<td>5</td>
<td>53</td>
<td>9</td>
<td>59</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>127±9</td>
<td>150±15</td>
<td>125±9</td>
<td>164±21†</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>78±6</td>
<td>96±10</td>
<td>76±4</td>
<td>89±10†</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>50±8</td>
<td>55±12</td>
<td>49±10</td>
<td>74±19†</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>94±7</td>
<td>114±11</td>
<td>92±4</td>
<td>114±12</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>117±18</td>
<td>147±30</td>
<td>124±23</td>
<td>156±36</td>
</tr>
<tr>
<td>Stroke volume, mL/beat</td>
<td>75±13</td>
<td>80±17</td>
<td>79±15</td>
<td>73±18</td>
</tr>
<tr>
<td>Clearance, mL/s</td>
<td>1.8±0.5</td>
<td>1.9±0.6</td>
<td>1.7±0.5</td>
<td>1.5±0.6</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.1±1</td>
<td>5.4±1.0</td>
<td>6.2±1.0*</td>
<td>5.6±1.2*</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.1±0.3</td>
<td>1.2±0.3</td>
<td>1.0±0.3‡</td>
<td>1.0±0.3‡</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.4±1.1</td>
<td>3.6±1.0</td>
<td>4.2±0.7*</td>
<td>4.2±1*</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.3 (0.5–3.5)</td>
<td>1.4 (0.5–4.7)</td>
<td>1.8 (0.9–4.1)*</td>
<td>1.6 (0.9–5.4)*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25±3</td>
<td>26±3</td>
<td>25±3</td>
<td>25±3</td>
</tr>
</tbody>
</table>

Values are mean±SD, percentage, or median (range). All comparisons took age into account. *P<0.001 and †P<0.01 vs corresponding value for uncomplicated group. ‡P<0.001 vs EH group.

Clinical Characteristics by Vascular Status
Irrespective of BP, subjects with arteriopathy were older and had a more atherogenic lipid profile. Clinical characteristics of the study subjects are shown in Table 3.

Compared with patients with EH, patients with EH/PVD showed a greater frequency of microalbuminuria, higher UAE and SBP, lower DBP, wider PP, and similar MBP. Cardiovascular parameters did not differ between normotensive PVD patients and controls.

Intraindividual Correlations
Age-related influences were most evident on creatinine clearance (inversely, r=-0.44, P<0.001), PP (r=0.40, P<0.001), and, in decreasing order, SBP (r=0.23, P<0.001), UAE (r=0.20, P<0.004), and LVMI (r=0.18, P<0.01). Lipids and DBP were independent of age.

UAE was correlated with PP (Figure 1), SBP (r=0.38 for both, P<0.001), MBP (r=0.28, P<0.001), and, to a lower extent, DBP (r=0.18, P<0.02). Other statistically significant covariates of albuminuria were LVMI (r=0.21, P<0.01), total cholesterol (r=0.14, P<0.05), LDL cholesterol (r=0.21, P<0.01), and HDL cholesterol (inversely, r=-0.22, P<0.01).

PP was closely correlated with SBP (r=0.75, P<0.001) and MBP (r=0.43, P<0.001) but not DBP (r=0.10). Systolic and diastolic values were also correlated (r=0.69, P<0.001). The rank correlation of PP and SBP with LVMI was 0.17 (P<0.01) and 0.33 (P<0.001), respectively.

Risk of Microalbuminuria by PP Quintiles
The proportion of subjects with microalbuminuria (Figure 2, left panel; P<0.001) and their UAE levels (Figure 2, right panel; P<0.007) increased by increasing PP quintiles (cutoff points 45, 50, 59, and 68 mm Hg; n=40, 39, 46, 43, and 43).

The age-corrected risk of microalbuminuria did not differ from 1 in the intermediate PP quintiles and increased by 3.4-fold (95% CI 1.24 to 9.3, P<0.03) and 5.3-fold (95% CI 1.9 to 15, P<0.003) in the fourth and fifth quintile, respectively (Figure 3). The trend did not change when PVD patients were excluded from the analysis (cutoff points 44, 50, 54, and 60 mm Hg; n=29, 28, 30, 30, and 30; OR of the

Figure 1. Plot of UAE (log scale) vs PP. The rank correlation coefficient was 0.38 (P<0.001, n=211).
upper quintile versus baseline 5.8; 95% CI 1.41 to 24; 
P<0.02, n=147).

Pulsatile and Steady BP Components and Risk
of Microalbuminuria

The relative importance of PP, SBP, DBP, and MBP in predicting microalbuminuria was addressed in logistic regression models, including BP parameters alone and in combination. Because age was an univariate predictor of microalbuminuria risk (OR 1.39/10 years, 95% CI 1.05 to 1.56, P<0.01), all analyses included age as a covariate.

PP, as such, was associated (P<0.001) with a 62% increase in risk for every 10 mm Hg rise (95% CI 1.35 to 1.9) compared with a 41% increase for every 10 mm Hg rise in SBP (95% CI 1.22 to 1.59, P<0.001). When PP and SBP were combined, PP remained a significant (P<0.03) predictor of microalbuminuria (OR/10 mm Hg increase 1.43, 95% CI 1.03 to 1.83), and SBP did not (OR/10 mm Hg increase 1.17, 95% CI 0.99 to 1.45, P<0.02). The risk associated with PP (OR/10 mm Hg increase 1.55, 95% CI 1.26 to 1.85, P<0.001) was independent of MBP (OR/10 mm Hg increase 1.17, 95% CI 0.99 to 1.5, P<0.02); when evaluating SBP and DBP in the same model, higher SBP (OR/10 mm Hg increase 1.61, 95% CI 1.34 to 1.89, P<0.001) and lower DBP (OR/10 mm Hg decrease 0.096, 95% CI 0.092 to 0.099, P<0.03) predicted microalbuminuria.

Multivariate Components of the Risk
of Microalbuminuria

Among the dichotomous (vascular and active smoker status) and continuous (age, PP, MBP, LVMI, and HDL and LDL cholesterol) variables that distinguished (P<0.1) microalbuminuric from normoalbuminuric subjects in one-to-one comparisons, only PP (OR/10 mm Hg rise 1.6, 95% CI 1.3 to 1.9, P<0.001), LVMI (OR/10 g/m² 1.14, 95% CI 1.03 to 1.25, P<0.02), and smoking (OR 1.97, 95% CI 1.001 to 3.98, P=0.05) predicted microalbuminuria independently (Figure 4). The overall percentage of deviance explained by the model was 18%.

Discussion

The original finding of this cross-sectional evaluation of the biological covariates of microalbuminuria in a large and carefully screened group of nondiabetic males was the independent predicting power of a wider PP, a readily obtainable measure of pulsatile flow,9,10 in contrast with the lack of statistical weight of MBP, a surrogate measure of steady flow, 9,10 examined simultaneously with PP. The risk profile associated with progressive PP widening did not differ from 1 in the intermediate range of values and increased sharply only at $60$ mm Hg. A nonlinear trend implies that a threshold exists above which the renal impact of that hemodynamic factor becomes more evident and, reciprocally, that its influence may be obscured by other biological mechanisms at lower PP levels. PP also provided information additional to SBP, in spite of the strict collinearity between the 2 parameters. Risk of microalbuminuria was predicted by both lower DBP and higher SBP entered in the same logistic regression model, indicating that PP compounded the exaggerated rises in the latter and the less than proportional increments or actual decrements in the former. Determinants of PP include SV, rate of systolic ejection, and stiffness of the arterial tree.9,10 Because SV measurements did not vary across the spectrum of UAE values, increased arterial stiffness was a more likely cause
of the wider PP in our microalbuminuric subjects, probably because of arteriosclerotic degeneration of the major capacitance arteries, although other mechanisms cannot be ruled out on the basis of our data.11

An obvious question regards confounders, primarily atherosclerosis, a disease in which segmental macrovascular lesions and diffuse microvascular abnormalities tend to co-exist,12 affecting about one third of the components of our sample. Atherosclerosis may also increase UAE by damaging diffusely vascular endothelium,13 but our finding of a normal UAE in the group of normotensive patients with a fully developed arterial lower limb disease, in itself a harbinger of widespread macroangiopathy,14 does not support that prediction. It was only in the presence of an exaggerated PP, a likely result of the stiffening of large arteries through collagen neoformation and excess calcium deposition at the affected sites,11,15 that the prevalence of microalbuminuria increased strikingly. Our data, therefore, suggest an only indirect relation between atherosclerotic macroangiopathy and renal microvascular changes, with elevated BP, particularly its pulsatile elements, acting as the chain in the link; however, our data do confirm that subclinical kidney damage is frequent in EH that is complicated by PVD.3,16 The increasing prevalence of microalbuminuria by ascending PP quintiles in uncomplicated subjects analyzed separately from atherosclerotic patients and the overall results of the multivariate logistic regression analyses further discount a direct link between advanced atherosclerosis and albuminuria, in agreement with data from our17 and other18 laboratories. Cardiovascular risk factors such as dyslipidemia, diabetes, and smoking may influence both UAE20 and conduit vessel distensibility,10 but total and LDL cholesterol values were evenly distributed, and HDL cholesterol, albeit reduced in the present and in a previous study20 of microalbuminuric subjects, did not emerge as a critical factor in the statistical analyses. Furthermore, diabetics were excluded from the trial, and the albuminuric action of smoking, already shown in past studies21,22 and confirmed in the present study, was additive to that of PP. Thus, the strength of statistical association, its persistence after adjusting for potential confounders, and inferential reasoning make plausible a direct connection between microalbuminuria and elevated PP. Similar results were obtained in the studies that examined the behavior of PP23,24 and, more frequently, SBP (a measure of vascular compliance25 and a variable strictly related to PP) as determinants of albuminuria in unselected populations26,27 and hypertensive patients.22,28 Regarding mechanisms, an excessive pulsatile load altered gluteal arteriolar structure,29 and the same may happen at the renal level, where wall hypertrophy characterized the nephrosclerotic biopsies harvested from mildly proteinuric EH patients.30 In light of the recent demonstration of the relation between microalbuminuria and future development of renal insufficiency in EH,3 it may be relevant, in this context, to consider the independent association between increasing serum creatinine and faster pulse-wave velocity, a measure of arterial stiffness, in EH patients.31 SBP also frequently overcame DBP as a predictor of overt kidney damage and end-stage renal disease,32 a clinical condition in which arterial stiffness could also be hypothesized because, as expected,19 PP and, to a lesser extent, even UAE showed age-related changes, but demographic differences between normoalbuminuric and microalbuminuric subjects were not huge, and, besides, statistics accounted for this factor. 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is almost universal. Cross-sectional associations are to be taken with caution, though, and we are aware that our present cross-sectional findings might be compatible with exactly opposite interpretations, eg, an effect of urine albumin on PP. Prospective follow-ups of populations (less selected than ours and mainly composed of subjects referred to a tertiary diagnostic center) will be needed to evaluate in further detail any role of the pulsatile BP components on the kidney. The discrepancy between overnight measurement of urine and early morning BP recordings or gender-related phenomena in our all-male group should also be considered. Technical limits may also exist in that peripheral and central PPs differ to a variable extent, which is not a critical point, though, in view of the fact that differences in hemodynamic regimens are attenuated in middle-aged sedentary subjects.

Because brachial PP determination predicts morbid events in prospective cohorts of essential hypertensive subjects, our data may help to understand better why microalbuminuria behaves as a marker of cardiovascular risk in nondiabetic hypertensive subjects. Moreover, the association with other primary risk factors, such as increased LVMi and left ventricular hypertrophy, decreased HDL cholesterol levels, and tobacco smoking, legitimately qualifies microalbuminuria as an integrated marker of cardiovascular risk. The list of damaging factors associated with the presence of microalbuminuria may, however, be incomplete; as a matter of fact, additional mechanisms are likely (eg, see References 21 and 36), in view of the fact that our logistic model left \( \approx 80\% \) of the total microalbuminuria deviance unexplained. Furthermore, our cardiac mass data confirm the correlation with UAE, an association usually interpreted as a reflection of the prevailing pressor load on the kidney and the heart. Quite unexpectedly, however, the statistical link between the 2 parameters was independent of pressure, a result also recently reported by Gatzka et al. The data might perhaps be explained by circulating factors that are produced in greater amount by a hypertrophic heart and by an increasing renal permeability to albumin. This interesting possibility requires further evaluation in future studies.

In conclusion, the association of increased albuminuria with wider PP, a correlate of the pulsatile hemodynamic load and conduit vessel stiffness, which is in itself an important cardiovascular risk factor, and left ventricular hypertrophy may help to explain why microalbuminuria predicts cardiovascular events in nondiabetic subjects. The independence from concomitant vascular disease also suggests that wider PP, rather than representing a simple marker for atherosclerotic disease, influences albuminuria directly.

References


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