Microalbuminuria Is a Marker of Left Ventricular Hypertrophy but Not Hyperinsulinemia in Nondiabetic Atherosclerotic Patients

Roberto Pedrinelli, Vitantonio Di Bello, Giosuè Catapano, Luigi Talarico, Franco Materazzi, Gino Santoro, Costantino Giusti, Franco Mosca, Elio Melillo, and Mauro Ferrari

Microalbuminuria predicts cardiovascular events in diabetic and nondiabetic patients. For a better understanding of the physiopathological importance of microalbuminuria in atherosclerotic disease, we evaluated the relation between urinary albumin excretion and arterial blood pressure, left ventricular mass, insulin, and lipid levels. The studies were conducted in patients with atherosclerotic peripheral vascular disease. Urinary albumin excretion (studied by nephelometry; an average of triplicate collections from 8 PM to 8 AM), casual blood pressure, echocardiographic left ventricular mass index and wall thickness, plasma immunoreactive insulin and C-peptide (both basally and after a 75-g oral glucose load), blood lipids, and fibrinogen were studied in eight normal subjects and 20 nonobese, nondiabetic male patients with angiographically documented atherosclerotic peripheral vascular disease and preserved renal function, 12 of whom were either hypertensive or on antihypertensive treatment. Eight patients were microalbuminuric (urinary albumin >20 μg/min) and 12 were not. Ankle-arm index and calf and foot transcutaneous oxygen tension were reduced in comparison with normal control subjects but superimposable between the two patient groups to indicate a comparable clinical progression of the vascular disease. In the microalbuminuric subjects, left ventricular mass index was greater, interventricular septum was thicker, and cardiac hypertrophy was more frequent than in nonmicroalbuminuric patients. The prevalence of hypertension tended to be greater and systolic blood pressure values were higher in the presence of microalbuminuria. Overall, a highly significant relation existed between urinary albumin excretion and left ventricular mass. Systolic blood pressure was greater and a history of arterial hypertension was more frequent among microalbuminurics, whereas diastolic blood pressure values showed a statistically significant correlation with both variables. No difference in postload blood glucose and basal and stimulated insulin and C-peptide existed between the two groups of patients. Plasma lipids and fibrinogen did not differ significantly. Urinary albumin excretion was mainly a covariate of left ventricular mass values in these nondiabetic patients with macrovascular disease, but the data do not support previous suggestions of microalbuminuria as a marker of either widespread atherosclerosis as such or insulin resistance. The association between microalbuminuria and cardiac hypertrophy can be explained by coexistent arterial hypertension, an abnormality widely prevalent in atherosclerotic patients, although the limits of conventional blood pressure measurements as an index of daily pressor load tend to mask it. The underlying presence of a major risk factor such as cardiac hypertrophy might explain the previously reported predictive power of microalbuminuria for cardiac events. (Arteriosclerosis and Thrombosis 1993;13:900–906)

Key Words • microalbuminuria • atherosclerosis • cardiac hypertrophy • hypertension • cardiovascular risk factors • insulin • insulin resistance • blood lipids

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documented association with other major and interconnected cardiovascular risk factors, such as insulin resistance, an elevated cardiac mass, abnormal circulating lipid levels, and overweight. However, although increased intraglomerular pressure and/or changes in perm-selectivity are the final causes of an increased UAE, the precise reason why microalbuminuria predicts cardiovascular disease is still unclear. A clarification of this problem is interesting from a physiopathological point of view and might lead to the clinical use of this parameter as a marker to identify cardiovascular disease and possibly to implement preventive strategies in subjects at high risk. However, the available studies on microalbuminuria and cardiovascular risk factors were performed for the most part in subjects without overt macrovascular disease at the time of first screening. Since risk factors tend to overlap widely between subjects who will and those who will not develop macrovascular disease, more straightforward information regarding a cause–effect relation might be obtained from patients with advanced atherosclerosis, in whom a link between microalbuminuria and widespread vascular damage as such has been hypothesized. This reason, we studied the relation between UAE and blood pressure levels, cardiac mass, plasma lipids, fibrinogen, and basal and glucose-stimulated insulin concentration in nondiabetic patients with angiographically documented peripheral vascular disease (PVD), in whom an excess risk of death, due mainly to coronary artery disease, has been documented.

**Methods**

**Subjects**

The criteria for the selection of patients were the presence of atherosclerotic PVD in subjects younger than 70 years of age with fasting blood glucose <120 mg/dL, serum creatinine <1.2 mg/dL, normal urinary sediment, absence of urinary tract infection, a body mass index (BMI) <30 kg/m², and without congestive heart failure, advanced chronic obstructive pulmonary disease, previous amputation, pain at rest, ischemic trophic ulcers, gangrene, renal artery stenoses or other secondary causes of hypertension, and accelerated or malignant hypertension. The 20 patients eventually included in the study had angiographically documented aortic-iliac-femoral atherosclerosis combined with abdominal or pelvic atherosclerosis. The 20 patients eventually included in the study had angiographically documented aortic-iliac-femoral atherosclerosis combined with abdominal or pelvic atherosclerosis.

**Blood pressure determination.** Systolic and diastolic blood pressures were measured in the morning on each participant by using an oscillometric cuff. 

**Metabolic indexes.** Anthropometric measurements (i.e., height and weight) were made after each participant had removed his shoes and upper garments.

**Echocardiographic studies.** Monodimensional and bidimensional echocardiograms were performed in the afternoon in the postabsorptive state with an Aloka SSD 870 apparatus (Mitaka-shi, Tokyo) with 2.5- and 3.5-MHz transducers. During the recording of the echocardiograms, the subjects were in a semisupine position, slightly rotated to the left. Two-dimensional images were obtained in the parasternal long-axis and short-axis views and apical four- and two-chamber views by using a standard transducer position. End-diastolic and end-systolic diameter, end-diastolic and end-systolic volume, and ejection fraction were calculated. No patient showed areas of akinesia, dyskinesia, or wall thinning that would invalidate the theoretical assumptions of the echocardiographic technique. To minimize the confounding influence of daily physical activity and to facilitate the collection procedure, we asked our patients to collect urine three times between 8 PM and 8 AM to be averaged for urinary albumin and creatinine measurement. The intraindividual variability of UAE was 40.6±6% (mean coefficient of variation±SD), a high variability that was consistent with previous studies. Microalbuminuria was defined as ≥20 μg/min according to conventional standards.

**Experimental Procedures**

**Urine collections.** To minimize the confounding influence of daily physical activity and to facilitate the collection procedure, we asked our patients to collect urine three times between 8 PM and 8 AM to be averaged for urinary albumin and creatinine measurement. The intraindividual variability of UAE was 40.6±6% (mean coefficient of variation±SD), a high variability that was consistent with previous studies. Microalbuminuria was defined as ≥20 μg/min according to conventional standards.
and 0.5, 1, 1.5, 2, and 3 hours after administration of the glucose load. In the same sessions serum samples were drawn for creatinine and for fasting total and high density lipoprotein cholesterol (HDL-C), triglycerides, and fibrinogen.

Transcutaneous oxygen pressure and ankle-brachial index. As a measure of the clinical evolution of the disease both at the microcirculatory level and in medium–large arteries, we measured transcutaneous (TC) $P_{O_2}$ and ankle–brachial index. TC $P_{O_2}$ was assessed through a Kontron Microgaps 7640 apparatus (Watford, Herts, England) and commercially available electrodes according to a standard procedure. Room temperature was kept constant at 22–23°C. The electrodes were calibrated with 20.9% oxygen with the subjects lying in a supine position. The examination was started after a steady-state TC $P_{O_2}$ value was maintained for about 20 minutes. It was measured on both the first metatarsal space of the feet and the calf about 20 cm below the knee, positioning a reference electrode in the right subcavicular position.

Ankle–brachial index was quantified by measuring systolic blood pressure at the brachial and bilateral posterior tibial arteries by Doppler (Stereodop, Promelec, Bourgeois, Guer, France).

Laboratory methods. Urinary albumin was measured by the immunoturbidimetric method with Behring antisem reagents (Istituto Behring SpA, Scoppito, Italy) with a limit of detection of 0.6 mg/dL and an interassay variation of 3.5%. IRI (sensitivity, 2.5±0.27 μIU/mL; within- and between-assay variation, 5.5–6.6% and 6.2–9.7%, respectively, in a range from 24.1 to 130.8 μIU/mL) and C-peptide (sensitivity, 0.125 ng/mL; within- and between-assay variation, 2.6–6.7% and 8.4–8.3%, respectively, in a range from 1.5 to 10.3 ng/mL) concentrations were measured by radioimmunoassay (Sorin, Saluggia, and Radin, Pomezia, Italy). Blood glucose was assessed by glucooxidase and plasma and urinary creatinine by standard colorimetry. Serum concentrations of total cholesterol and HDL-C (after precipitation of the low density lipoprotein [LDL] and very low density lipoprotein fractions by using phosphotungstic acid and MgCl$_2$) and triglycerides (average coefficient of variation of control pool, 2%, 5%, and 2%, respectively) were measured by enzymatic colorimetric techniques (cholesterol oxidase/peroxidase aminoantipyrine and glycerol phosphate oxidase/peroxidase aminoantipyrine, Menarini, Divisione Diagnostici, Firenze, Italy). Fibrinogen was assessed as thrombin-coagulable fibrinogen (average coefficient of variation of control pool, 7.2%). LDL-C was calculated as total cholesterol minus (HDL-C minus triglycerides/5).

Data Analysis

The statistical difference among mean values was evaluated by one-way analysis of variance (ANOVA) by using Duncan's test for multiple comparison testing. Frequency distribution was analyzed with the χ² method by applying the Yates' correction. Linear multiple regression analysis and correlation coefficients were calculated according to standard methods. A value of $p<0.05$ was chosen as statistically significant. The area under the curve (AUC) for glucose, insulin, and C-peptide response curves was calculated according to the trapezoidal rule. Data are expressed as mean±SEM.

Results

Eight patients had UAE values in the microalbuminuric range as opposed to 12 normoalbuminuric patients and eight control subjects. Age did not differ among the three groups (Table 1). Ankle–brachial index was >1 in control subjects and was reduced to a comparable extent in both microalbuminuric and nonmicroalbuminuric patients (Table 1). Calf and foot TC $P_{O_2}$ did not differ between patient groups, but it was higher in control subjects (Table 1). No significant differences in creatinine clearance existed among the three groups (Table 1), nor was any correlation found between individual creatinine clearance and UAE values ($r=0.13$, $p<0.06$, $n=28$).

Blood Pressure

Systolic blood pressure was higher in microalbuminuric than control patients (Table 1); otherwise, no significant differences existed regarding this parameter among the three groups.

Seven of eight (88%) patients in the microalbuminuric group either were on antihypertensive treatment or reported a history of hypertension at the time of the initial screening. Only five of 12 (42%) patients showed this characteristic in the nonmicroalbuminuric group, although the difference did not reach statistical significance ($\chi^2=2.5$, $p<0.1$).

Echocardiography

No differences in end-diastolic and end-systolic diameters existed among the three groups (Table 1). Interventricular septum was thicker (Table 1) and left ventricular mass index (LVMI) was greater (Figure 1) in microalbuminuric than in either nonmicroalbuminuric or control subjects. Seven of eight (87.5%) subjects in the microalbuminuric group had an LVMI ≥135 g/m², whereas only three of 12 (25%) showed values above that limit in the nonmicroalbuminuric group ($\chi^2=5.2$, $p<0.02$). Ejection fraction and cardiac index were superimposable (Table 1).

Both UAE ($r=0.77$, $p<0.0001$; Figure 2) and diastolic blood pressure values ($r=0.49$, $p<0.03$) correlated with LVMI, but the two parameters did not show an independent association with LVMI itself when used as independent variables in a multiple linear regression analysis. A statistically significant but weak correlation was found only between diastolic blood pressure and UAE ($r=0.46$, $p<0.04$).

Metabolic Indexes

Two-hour blood glucose was >140 mg/dL in five patients (three microalbuminuric and two nonmicroalbuminuric patients) ($\chi^2=1.5$; not significant). BMI and the blood glucose (Figure 2), IRI, and C-peptide levels (Figure 3) during the 3-hour period after the oral glucose load and the AUCs for blood glucose, IRI, and C-peptide did not differ to a significant extent in control, nonmicroalbuminuric, and microalbuminuric subjects, respectively (Table 1). No significant correlations existed between UAE, age, and blood pressure on one hand and the AUC values for blood glucose, IRI, and C-peptide on the other.
Total cholesterol, LDL-C, HDL-C, triglycerides, and fibrinogen did not differ significantly in the experimental groups (Table 1).

**Discussion**

We found a 40% prevalence of microalbuminuria in our patients, who were selected on the criteria of the presence of atherosclerotic PVD and the absence of diabetes, a finding that documents that, while microalbuminuria is indeed common in PVD, the atherosclerotic process per se is not its determinant. In fact, 12 of 20 of our patients had a normal UAE despite clearly

**Table 1. Experimental Parameters in Microalbuminuric and Nonalbuminuric Patients and Control Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Micro (n=8)</th>
<th>Nonmicro (n=12)</th>
<th>Control (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.1±3</td>
<td>63.6±2</td>
<td>57.6±4</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>157±7*</td>
<td>149±9</td>
<td>129±3</td>
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<tr>
<td>Diastolic BP (mm Hg)</td>
<td>86±5</td>
<td>83±2</td>
<td>83±2</td>
</tr>
<tr>
<td>Urinary albumin excretion (µg/min)</td>
<td>46±9.4‡</td>
<td>11.5±1.4</td>
<td>11±1.2</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min per 1.73 m²)</td>
<td>90±8.5</td>
<td>89±7</td>
<td>94±6</td>
</tr>
<tr>
<td>Calf TC PO₂ (mm Hg)</td>
<td>48.5±2.6†</td>
<td>49.3±3.6†</td>
<td>61.3±2</td>
</tr>
<tr>
<td>Foot TC PO₂ (mm Hg)</td>
<td>45.9±4‡</td>
<td>41.3±4.4†</td>
<td>59.9±4</td>
</tr>
<tr>
<td>Ankle-brachial index</td>
<td>0.74±0.09‡</td>
<td>0.63±0.08‡</td>
<td>1.07±0.01</td>
</tr>
<tr>
<td>Interventricular septum thickness (mm)</td>
<td>12.1±0.4§</td>
<td>10.0±0.3</td>
<td>10.5±0.6</td>
</tr>
<tr>
<td>Posterior wall thickness (mm)</td>
<td>12.4±0.6</td>
<td>11.5±0.7</td>
<td>11±0.7</td>
</tr>
<tr>
<td>End-diastolic diameter (mL)</td>
<td>50.8±1.3</td>
<td>47.8±1.2</td>
<td>49±0.6</td>
</tr>
<tr>
<td>End-systolic diameter (mL)</td>
<td>31.3±1.4</td>
<td>28.3±1</td>
<td>29.3±0.6</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>70±3</td>
<td>68±3</td>
<td>71±4</td>
</tr>
<tr>
<td>Cardiac index (L/min per m²)</td>
<td>3±0.3</td>
<td>3.2±0.2</td>
<td>3.3±0.1</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>247±16</td>
<td>224±10</td>
<td>226±11</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>180±14</td>
<td>155±9</td>
<td>171±9</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>30±79</td>
<td>36±4</td>
<td>30±6</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>191±25</td>
<td>164±23</td>
<td>128±171</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>252±66</td>
<td>262±42</td>
<td>207±50</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25±0.7</td>
<td>25.2±1.3</td>
<td>25.2±1.9</td>
</tr>
<tr>
<td>AUCₚₑₚ (10⁻³ mg/min per dL)</td>
<td>2.8±0.3</td>
<td>3.0±0.3</td>
<td>3.1±0.3</td>
</tr>
<tr>
<td>AUCᵣᵣ (10⁻³ µU/min per mL)</td>
<td>2.0±0.4</td>
<td>1.8±0.3</td>
<td>2.2±0.6</td>
</tr>
<tr>
<td>AUCᵣᵣᵣ (10⁻² ng/min per mL)</td>
<td>1.4±0.4</td>
<td>2.1±0.3</td>
<td>2.2±0.2</td>
</tr>
</tbody>
</table>

Micro, microalbuminuric patients; nonmicro, nonmicroalbuminuric patients; control, control subjects; BP, blood pressure; TC, transcutaneous; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; BMI, body mass index; AUC, area under the curve; gluc, blood glucose; IRI, immunoreactive insulin; C-pep, C-peptide.

Ankle-brachial index data refer to the most affected side. LDL-C is total cholesterol minus (HDL-C minus triglycerides/5).

Data are expressed as mean±SEM. *p<0.05, †p<0.01, ‡p<0.001, §p<0.004 vs. control subjects' values.

Figure 1. Bar graph showing left ventricular mass index (LVMi) in the three experimental groups. Data are expressed as mean±SEM. Controls, control subjects; microalb, microalbuminuric patients.

Figure 2. Scatterplot showing relation between left ventricular mass index (LVMi) and urinary albumin excretion rate (UAlb) in patients with atherosclerotic peripheral vascular disease (n=20) and control subjects (n=8). Controls; ○, nonmicroalbuminurics; ●, microalbuminurics.
documented macrovascular lesions and a comparable clinical evolution of vascular disease, at least to the extent assessed by limb pressure and TC PO₂ determinations. Thus, at variance with previous speculation, the mere presence of macrovascular disease cannot explain the appearance of microalbuminuria, at least in nondiabetic patients. Rather, the amount of UAE was related to cardiac mass over a range of normal to clearly elevated values, which suggests that microalbuminuria may signal a marked degree of cardiac hypertrophy, although the wide biological and methodological variability of this parameter probably makes this conclusion less certain in the range of borderline to slightly elevated cardiac mass values. Other authors reported similar findings in patients with uncomplicated hypertension, and altered systemic hemodynamics was probably the link in the chain between UAE and cardiac mass even in our sample, although both variables were weakly correlated with diastolic blood pressure values. In fact, a history of antihypertensive treatment or actual high blood pressure was present in 12 of 20 subjects, which reflects the large prevalence of this risk factor in PVD, and microalbuminuric patients had higher systemic blood pressure than control subjects, and, conversely, hypertensive patients were more represented in the microalbuminuric group. Furthermore, a multiple regression analysis performed using both urinary albumin and diastolic blood pressure as independent variables did not show an independent effect of the former on LVMJ, which strengthens the importance of coexisting hypertension as an explanation for our data. Furthermore, we are now aware that casual blood pressure poorly reflects the 24-hour pressure profile, a parameter that predicts, to a better extent, hypertensive cardiac hypertrophy. Thus, the low correlation between casual blood pressure values and cardiac mass was an almost predictable finding. Moreover, the low degree of association between UAE and casual blood pressure was not unexpected when considering that blood pressure recordings were performed in the daytime, whereas urine was collected mostly in the nighttime, when arterial pressure normally reaches its nadir. In this context, it would be of great interest to assess how many of our microalbuminuric patients belonged to the so-called “nondipper” group, in whom the lack of nocturnal blood pressure drop has been associated with a greater prevalence of cardiac hypertrophy. When considering that left ventricular hypertrophy predisposes the individual to ischemic heart disease, complex ventricular arrhythmias, and sudden death, the association with an increased cardiac mass may be the reason why microalbuminuria was previously found to be associated with coronary death. The absence of an evident correlation between casual blood pressure and both LVMJ and UAE in our patients may also help to explain why in that study the risk for coronary heart disease was not decreased by taking into account the presence of hypertension. Overall, UAE might be used clinically as an index of the 24-hour pressor load and its related target organ damage, but more studies are needed to evaluate this important option. However, factors other than high blood pressure may connect UAE and cardiac mass in atherosclerotic patients. In fact, at least as far as insulin-dependent diabetics are concerned, the presence of microalbuminuria seems associated with sodium–lithium countertransport overactivity, a mode of operation of the Na⁻–H⁺ antiport, a ubiquitous cell membrane transport system that regulates cell volume and growth. This system has been associated with increased cardiac mass and family history of cardiovascular morbidity and mortality, which suggest that atherosclerotic complications, microalbuminuria, and cardiac hypertrophy might have in common an abnormal Na⁺–H⁺ exchange, an only speculative hypothesis at this stage.

Neither basal nor stimulated blood glucose, insulin, or C-peptide (an index of insulin secretion) nor other biological covariates of insulin metabolism, such as triglyceride levels, differed consistently between microalbuminuric and nonmicroalbuminuric patients. Thus, the data do not confirm the suggested link between microalbuminuria and insulin resistance, at least in nondiabetic atherosclerotic patients. We cannot exclude the possibility that a real difference might have been obscured by the relatively small size of our sample which, however, had the statistical power to identify a clear difference in cardiac mass. A second important point is that the difference in postload insulin levels

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**Figure 3. Bar graph showing blood glucose after a standard oral glucose load (75 g) in control subjects (controls; n=8) and atherosclerotic patients without (No mic; n=12) and with (Mic; n=8) microalbuminuria. Only mean values are represented.**

**Figure 4. Bar graphs showing time course of immunoreactive insulin (IR; upper panel) and C-peptide (C-Pep; lower panel) after a standard oral glucose load (75 g) in control subjects (solid bars; n=8) and atherosclerotic patients without (hatched bars; n=12) and with (striped bars; n=8) microalbuminuria. Only mean values are represented.**
between patients as a whole and control subjects was not statistically significant. The lack of significant hyperinsulinemia in PVD was reported several years ago by other investigators, and it occurred despite other favoring factors, such as a likely physical deconditioning due to disease status, concomitant hypertension, or smoking habits. Thus, insulin resistance was apparently not a consistent feature in our atherosclerotic group, although this statement awaits a more accurate determination. Both insulin and insulin resistance have been implicated in the atherogenic process, but a logical deduction that could be drawn from our data is that factors other than an altered insulin metabolism must have driven the development of macrovascular disease, at least in a portion of our patients, a possibility that may be addressed in future studies.

Lastly, we did not find significant differences in cholesterol, triglyceride, and fibrinogen levels in our microalbuminuric patients, in contrast with the results obtained in insulin-dependent diabetic subjects characterized by an elevated UAE. We do not know the reasons for this discrepancy, which may be related to the specific disease status of diabetics, but, whatever the case, the data further suggest that microalbuminuria may be a correlate of cardiac mass in nondiabetic patients that can be explained by coexistent hypertension. Direct and inferential evidence suggests that UAE might be used as an index of the pressure load in this population, and the association with left ventricular hypertrophy may be used as an index of the pressure load in this population, and the association with left ventricular hypertrophy may explain why microalbuminuria predicted cardiac death in previous studies, although this conclusion must await the results of appropriate follow-up studies. Should this be the case, it would be of interest to compare the prognostic value of microalbuminuria with that of the cardiac hypertrophy so far considered to predict fatal and nonfatal cardiac events more powerfully than any other conventional risk factor.

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