Microalbuminuria, Cardiovascular, and Renal Risk in Primary Hypertension

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Abstract. Microalbuminuria is defined as abnormal urinary excretion of albumin between 30 and 300 mg/d. It can be measured accurately by several widely available and sensitive methods. This abnormality can be found in 8 to 15% of nondiabetic patients with primary hypertension, although its prevalence varies greatly in the literature, likely due to differences in the methods used to detect it and to the criteria applied in the selection of patients. The pathogenetic mechanisms leading to the development of microalbuminuria are still not completely known. BP load and increased systemic vascular permeability, possibly due to early endothelial damage, seem to play a major role. Increased urinary albumin excretion has been associated with several unfavorable metabolic and nonmetabolic risk factors and subclinical hypertensive organ damage. In fact, a higher prevalence of concentric left ventricular hypertrophy and subclinical impairment of left ventricular performance, as well as the presence of carotid atherosclerosis, have been reported in patients with microalbuminuria. These associations might per se justify a greater incidence of cardiovascular events. Long-term longitudinal studies have recently confirmed the unfavorable prognostic significance of microalbuminuria in hypertensive patients. It has also been hypothesized that microalbuminuria might be a forerunner of overt renal damage in primary hypertension. Clinical studies, however, have shown conflicting results, and this hypothesis has to be considered tempting but speculative at present. In conclusion, microalbuminuria is a specific, integrated marker of cardiovascular risk and target organ damage in primary hypertension and one that is suitable for identifying patients at higher global risk. A wider use of this test in the diagnostic work-up of hypertensive patients is recommended.

BP level per se has long been acknowledged as an unreliable indicator of subsequent morbid events in patients with primary hypertension. More recently, the concept that global cardiovascular risk, rather than the severity of hypertension, should guide both the decision to begin treatment and the identification of individual target pressure levels has been endorsed by international agencies (1,2). In fact, results of large epidemiologic studies (3) have clearly demonstrated that regardless of the severity of hypertension, the cost effectiveness of BP reduction by means of drug therapy is greater in the presence of target organ abnormalities and/or co-morbidities. In this context, assessment of subclinical organ damage, namely left ventricular hypertrophy and peripheral atherosclerosis, has become a key element in evaluating hypertensive patients, because its presence entails a higher cardiac and cerebrovascular risk (4). The prevalence of left ventricular hypertrophy and peripheral atherosclerosis, however, very much depends on the diagnostic technique employed. Routine use of ultrasound technology, for example, leads to higher sensitivity in detecting cardiac and vascular structure abnormalities and allows for the identification of a larger number of high risk patients. On the other hand, the high prevalence of hypertension and its financial impact on healthcare systems in Western countries should be carefully taken into consideration before recommending routine application of an extensive diagnostic approach to the stratification of risk. Thus, the development of low cost, accurate, clinical tools to identify hypertensive patients at highest risk is of the utmost importance.

Definition of Microalbuminuria and Measurement Techniques

Microalbuminuria, i.e., abnormal urine excretion of albumin between 30 and 300 mg/d, is found in 8 to 15% of hypertensive patients and cannot be detected by conventional urine tests (5–8). However, several sensitive, reliable techniques (radioimmunoassay, enzyme-linked immunosorbent assay, nephelometry) have now become widely available in clinical practice (9). The relatively large variability in the prevalence of microalbuminuria reported in nondiabetic hypertensive patients is likely due to differences in the techniques used to detect it and in the criteria used for patient selection. Thus lower values have been reported in patients taking antihypertensive drugs, especially those that interfere with the renin-angiotensin system (RAS), or in those with a milder degree of hypertension. In addition, the modality of urine collection (spot versus 24-h)

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and the number of samples collected for each patient significantly contribute to the observed differences.

**Mechanisms of Nondiabetic Microalbuminuria**

The pathogenetic mechanism(s) underlying the development of microalbuminuria are currently poorly known. The severity of BP load and the increased systemic permeability to albumin, possibly due to early endothelial dysfunction, seem to play a major role, although several data suggest an interplay with a number of additional factors, such as lipids abnormalities, prothrombotic factors, increased activity of the RAS, and systemic inflammation. Finally, a functional hemodynamic abnormality and/or the presence of structural changes within the kidney cannot be ruled out as causes of microalbuminuria. Irrespective of its exact nature and pathogenesis, the unfavorable prognostic significance of microalbuminuria has recently been confirmed by long-term longitudinal studies (10,11). On the basis of these data, an increased urinary albumin excretion (UAE) can be regarded as a specific, cost-effective tool for the identification of patients at highest risk and searching for microalbuminuria can be recommended as part of the initial work-up of every hypertensive patient.

**Microalbuminuria Identifies Patients at High Cardiovascular Risk**

An increased UAE has been associated with a number of unfavorable metabolic and nonmetabolic risk factors, such as older age, longer duration of hypertension, cigarette smoking, increased BP load and variability (the so called non dipping phenomenon), higher uric acid levels, worse lipid profile, insulin resistance, endothelial dysfunction, increased activity of the RAS, and BP salt sensitivity (12). Furthermore, microalbuminuria is a concomitant of subclinical organ damage in nondiabetic hypertensive patients (6,13). In a group of 211 untreated patients with primary hypertension, we have observed a higher prevalence of unfavorable left ventricular geometric patterns, especially concentric hypertrophy in association with increased UAE (14). Moreover, the subgroup of patients with microalbuminuria showed subclinical impairment of left ventricular function, a finding that has recently been confirmed by a larger multicenter study (15). Further support to the role of microalbuminuria as a marker of cardiac risk derives from data by Tuttle et al. (16), who showed a correlation between increased UAE and the severity of coronary heart disease at angiography. In another study, Berton et al. (17) showed that the presence of microalbuminuria strongly predicts mortality in patients with acute myocardial infarction, even after adjusting for several other confounders, such as age, the presence of hypertension, heart failure, and serum lipids. Increased UAE has also been related to peripheral atherosclerosis and increased carotid intima-media thickness (IMT) in some but not all studies (13,18). In light of the well-known association between carotid atherosclerosis and cerebrovascular damage (both asymptomatic vascular lesions and acute events), it is not unexpected that microalbuminuria has been shown to be a predictor of ischemic stroke, even after correction for the presence of several confounding factors (19). In line with these findings, in a preliminary study, we found an increased prevalence of asymptomatic cerebral vascular lesions, as evidenced by nuclear magnetic resonance imaging, in hypertensive patients with microalbuminuria as compared with a group of well-matched hypertensives with normal albuminuria (20). In a series of 279 patients evaluated at our institution, UAE was positively associated to the presence of ultrasound-determined left ventricular hypertrophy (LVH) and carotid atherosclerosis. Microalbuminuric patients were 21 times more likely to have both LVH and increased IMT (CI, 4.6 to 100; \( P < 0.0001 \)) as compared with those with normal albumin excretion (Figure 1). These findings confirm previous studies showing an association between increased UAE and subclinical organ damage in primary hypertension and may, at least in part, account for the strong cardiovascular predictive power of microalbuminuria. This inexpensive, widely available test could represent an alternative approach to risk stratification that is suitable for use in the clinical setting. In fact, by the use of an innovative statistical approach, such as the artificial neural networks and a few low-cost and easily obtainable data (i.e., age/gender, smoking habits, history of cardiovascular disease, body mass index, BP severity, total cholesterol, and the presence/absence of electrocardiography-detected LVH) plus UAE, we were able to predict the presence of organ

![Figure 1. Urinary albumin excretion and target organ damage in 279 patients with essential hypertension. Urinary albumin excretion was analyzed on the basis of the presence/absence of left ventricular hypertrophy (LVH+/LVH−) and increased intima-media thickness (≥ 1.1 mm) (IMT+/IMT−). The prevalence of microalbuminuria (%) is reported in each group. The odds ratio for a microalbuminuric patient of having both LVH and increased IMT is 21 (CI, 5.4 to 190; \( P < 0.0001 \)).](image-url)
damage and allocate patients in different risk classes with an accuracy that is almost superimposable to what can be obtained by extensive diagnostic evaluation and target organ damage assessment (Figure 2).

Is Microalbuminuria a Forerunner of Renal Damage?

Hypertension has recently been reconsidered (reevaluated) as a cause of chronic renal failure. Evidence from large prospective studies suggest that even mild increases in BP entail, in the long term, a strong independent risk of developing end-stage renal disease (21). While benign nephrosclerosis occurs less frequently than other hypertensive complications (such as stroke and myocardial infarction), the large number of patients with high BP, together with the high social and financial costs of renal replacement therapy, make the prevention of this complication a relevant public health problem. In fact, hypertension together with diabetes mellitus is currently a leading cause of end-stage renal disease in the USA as well as in Europe. In the quest for new clinical tools that enable the identification of patients at highest renal risk, microalbuminuria has emerged as a strong candidate. It has been proposed that this subclinical condition may signal the presence of functional and/or structural renal abnormalities that precede and predict the onset of GFR deterioration. In a relatively small retrospective study, microalbuminuria predicted subsequent loss of renal function, despite similar baseline clinical characteristics and current BP levels through the study period (22). Other studies that specifically addressed this issue are, however, not consistent with this hypothesis (23). Interestingly, increased renal vascular resistance, a parameter that has previously been shown to correlate with the severity of renal impairment in patients with chronic renal failure, has been reported in patients with long-standing primary hypertension and microalbuminuria (24,25). More recently, provocative data from a large cross-sectional study indicate that high normal albuminuria (somewhere between 15 and 30 mg/d) is associated with hyperfiltration and similarly to diabetes mellitus, it could anticipate a decline in renal function (26). In conclusion, although large, well-conducted prospective studies addressing this issue are yet to be carried out, the predictive value of microalbuminuria for hypertension-induced renal damage is at present a tempting but speculative hypothesis.

Conclusions

A thorough assessment of cardiovascular risk is a prerequisite for successful and cost-effective antihypertensive treatment. However, it has recently been shown (27,28) that the more accurate (and expensive) the diagnostic work-up, the higher the percentage of patients at high risk correctly identified. Microalbuminuria is an integrated marker of cardiovascular risk and has been positively and linearly related to the presence and severity of target organ damage. The evaluation of UAE can be regarded as a specific and inexpensive way to identify hypertensive patients at highest global risk, although its renal prognostic value is at present uncertain. While the increasingly broad use of ultrasound techniques in the evaluation of overall risk profile awaits further confirmation from large properly devised studies, we propose searching for microalbuminuria as part of the initial work-up of every hypertensive patient.

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References


