

MICROALBUMINURIA IN ESSENTIAL HYPERTENSION

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Introduction

The detection of small amounts of urinary albumin excretion (UAE), a condition known as microalbuminuria, by using sensitive immunological methods was initially used in the evaluation and management of renal damage in diabetes. In the last few years, however, it has received increased attention as a prognostic marker for cardiovascular and/or renal risk in non-diabetic subjects [1–11]. Consequently, microalbuminuria assessment is now recommended in a risk stratification strategy for hypertension management [12], since its presence indicates early organ damage and, rarely, a clustering of cardiovascular risk factors. As the ESH/ESC guidelines indicate, microalbuminuria is a reliable prognostic marker, which is widely available and at low cost [12]. Moreover, some preliminary data indicates that microalbuminuria is potentially an intermediate endpoint during antihypertensive treatment [11, 13].

Definition and prevalence

Microalbuminuria has been defined as an UAE higher than the threshold value obtained from studies assessing the risk for developing nephropathy in diabetes (UAE \geq 30–300 mg/24 h or \geq 20–200 μ g/min). The albumin/creatinine ratio from spot urine, preferably that first voided in the morning (\geq 3–30 mg/g or \geq 30–300 μ g/mmol), is equivalent to the values during a 24-hour urine collection [14]. On the basis of this threshold the prevalence of microalbuminuria in hypertension depends on the characteristics of the patients included, the lowest in Primary Care settings (around 10–12%) and the highest in referral Hypertension Clinics (up to 30%).

At the time of assessing UAE two aspects need to be considered, reproducibility and circadian variability. Since a large intra-individual variability exists, at least two UAE assessments need to be collected. If discrepancies between the UAE values exist, a third sample should be requested. There is frequently a reduction of UAE at night to around 20% of that excreted during daytime activity. Consequently, the first voided urine analysed shows the UAE values at their lowest.

Recently the information collected from prognostic studies (see below) has challenged the concept of using microalbuminuria as a qualitative parameter and indicated that quantitative values should be considered [14].

Mechanisms of microalbuminuria

Microalbuminuria in essential hypertensive patients is the consequence of an increased transglomerular passage of albumin rather than the result of a decrease in the proximal tubule reabsorption of albumin. It may result from haemodynamic-mediated mechanisms and/or functional or structural impairment of the glomerular barrier [15]. As regards the haemodynamics, hyperfiltration, with the consequent increment in glomerular pressure, is of particular importance. It is probably mediated by abnormal transmission of systemic hypertension to the glomerulus through a disturbance in glomerular autoregulation and/or from progressive loss of functioning nephrons. Of the non-haemodynamics, functional abnormalities of the glomerular basal membrane have been claimed, although some evidence has been against this in hypertension. More widely accepted, however, is that microalbuminuria reflects the kidney expression of a more generalised state of endothelial dysfunction.

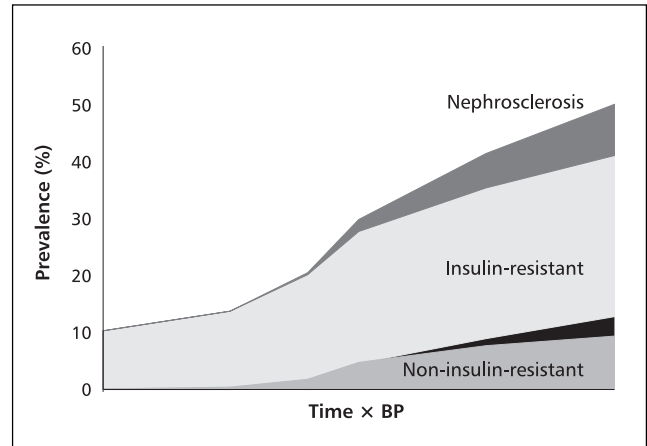


Figure 1. Diagram showing factors related to the prevalence of microalbuminuria in essential hypertension. Microalbuminuria may be the consequence of a double product, which is time of hypertension per blood pressure (BP) values. If the patient has insulin-resistance, microalbuminuria can be present even when the double product of time and pressure is small. By contrast, subjects without insulin-resistance need a length of time and/or high blood pressure values to develop microalbuminuria. Over and above these scenarios, the development of nephrosclerosis, less prevalent in non-insulin resistance, adds a new component to the risk of having microalbuminuria

Factors related to microalbuminuria

Factors related to the presence of microalbuminuria in essential hypertension have been analysed in cross-sectional as well as in a few prospective studies (reviewed in [16]). From these studies it seems that the significance of microalbuminuria in essential hypertension is much broader than expected, and several factors may influence the presence of microalbuminuria. Both cross-sectional and follow-up studies have indicated that both BP values and hyperinsulinaemia are the main factors associated with the risk (Figure 1).

In *cross-sectional* studies, microalbuminuria has been related to BP values and to hyperinsulinaemia as an expression of insulin resistance. The importance of BP values and alterations in the carbohydrate metabolism has been corroborated by a small number of follow-up studies. Blood pressure values achieved over time and changes in fasting glucose were the most important factors, not only for developing new onset microalbuminuria but also in reducing urinary albumin excretion during antihypertensive treatment.

The influence of glomerular filtration rate (GFR) on the microalbuminuria of hypertension merits a comment. The prevalence of microalbuminuria increases as the GFR decreases, although not always in parallel. Moreover, when GFR is $<$ 60 ml/min/1.73 m², the probability of UAE normalisation during antihypertensive treatment is clearly reduced [17].

Other potential factors associated with the presence of microalbuminuria are salt-sensitivity, overactivity of the renin-angiotensin system, inflammation, genetics, obesity, and smoking.

Prognostic value

The potential prognostic value of microalbuminuria to cardiovascular disease has been assessed among diabetics and non-diabet-

ics in the general population, postmenopausal women, and high cardiovascular risk patients. In all of these the highest UAE values observed at the beginning of each study were followed by an increase in morbidity and mortality cardiovascular risk. The UAE threshold value pointing to an increment of risk was largely below the UAE value of 30 mg/24 hours, regardless of the population studied, and the relationship between UAE and risk was continuous at below 30 mg/24 hours.

A key point in considering UAE as an intermediate objective arises from the demonstration that a reduction in urinary proteins is followed by a significant reduction in cardiovascular and/or renal events. Until now only two studies have been published [18]. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) has amply demonstrated that the rate of the primary composite cardiovascular endpoint of cardiovascular death, fatal or non-fatal stroke, and fatal or non-fatal myocardial infarction, increases 4-fold to 5-fold from the lowest to the highest decile of the albumin/creatinine ratio. Schrader et al. [13] observed that normalisation of UAE during treatment was associated with a trend towards fewer cardiovascular events as compared with persisting microalbuminuria. Conversely, newly developed proteinuria was associated with a trend towards increasing events. Together, these two studies bring forth information that in-treatment levels of albumin are closely related to the risk of a subsequent cardiovascular event. Future studies with appropriate design and analysis are required to give credence to microalbuminuria as an intermediate objective [19].

Recommendation for UAE assessment

Microalbuminuria assessment is now recommended at the initial evaluation of a patient with hypertension. Two first-morning voided urine samples should be tested for the albumin/creatinine ratio. No recommendation exists, however, concerning when UAE measurement should be repeated if it is considered as an intermediate objective. If so, the proposed algorithm is presented in Figure 2.

Treatment of hypertension with microalbuminuria

Blood pressure reduction is the most important determinant of diminishing UAE during antihypertensive treatment. Renin-angiotensin system blockers are superior to other antihypertensive agents in reducing UAE in subjects, mainly those in the high range

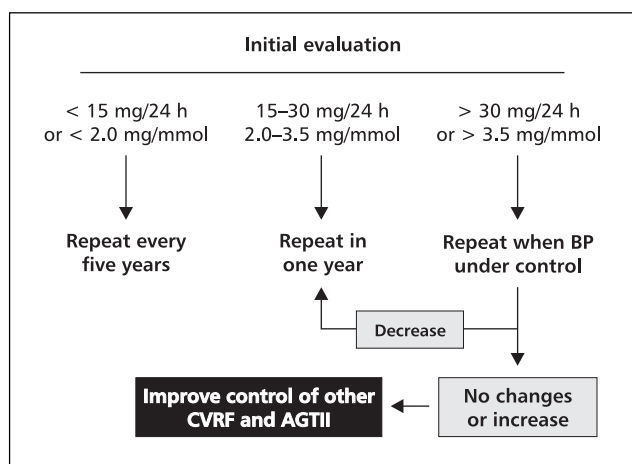


Figure 2. Algorithm for the assessment of urinary albumin excretion (expressed in mg/24 h or albumin/creatinine ratio) in hypertensives according to the initial values; BP — blood pressure; CVRF — cardiovascular risk factors; AGTII — angiotensin II

of BP. If such treatment reduces BP enough to achieve BP goals, differences in the UAE reduction among antihypertensive classes become smaller, or no differences are observed at all [20, 21].

The role of additional interventions for BP reduction needs to be considered. Statins (agents with ancillary properties beyond their lipid-lowering capabilities) have demonstrated that they ameliorate the course of renal function in type 2 diabetic patients. Furthermore, in hypercholesterolaemic subjects the lowering of LDL-cholesterol with atorvastatin may favourably affect microalbuminuria [22]. It remains to be seen whether this effect can be attributed to lipid lowering alone, improving endothelial function or lowering patterns of LDL oxidation. If in hypertension the UAE reduction with statins is still significant on top of antihypertensive therapy, this needs to be assessed in carefully designed studies. The role of insulin-sensitisers, glitazones, and anti-obesity drugs, including rimonabant, requires further studies. A multiple therapeutic approach to hypertensives with microalbuminuria may contribute to a better reduction on UAE due to the frequent clustering of cardiovascular risk factors.

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