Microalbuminuria and Prevention of Renal Insufficiency and Cardiovascular Diseases

Michel Marre

Microalbuminuria, a slightly elevated urinary albumin excretion, predicts renal failure in insulin-dependent diabetic patients and premature cardiovascular mortality in non–insulin-dependent diabetic patients and in the general population. It can be related to all currently established cardiovascular risk factors. Regarding the relationship between urinary albumin and blood pressure, microalbuminuria seems to be an early indicator of renal disease, causing high blood pressure in some instances, whereas it looks like the consequences of renal damage produced by severe hypertension in other instances. To establish whether microalbuminuria is an integrated risk marker for renal and cardiovascular events, or truly a risk factor, and to validate the usefulness of some peculiar treatment strategies, clinical trials are required, taking microalbuminuria as a selection criteria, and renal and cardiovascular events as endpoints. Am J Hypertens 1998;11:884–886 © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: Microalbuminuria, diabetes mellitus, blood pressure.

The term microalbuminuria indicates an albumin excretion rate (AER) greater than the range of normal values, but less than those giving positive test strips for the screening of proteinuria in the clinical setting. By convention, microalbuminuria indicates an AER of 30 to 300 mg/24 h (or 20–200 μg/min, or 20 to 200 mg/L); the AER for normoalbuminuria is < 30 mg (or 20 μg/min, or 200 mg/L) and for macroalbuminuria > 300 mg/24 h (or 200 μg/min, or 200 mg/L). The intra- and intersubject variability of the AER is high (30 to 60%), but two to three positive results from three samples allows adequate classification.¹ The prognostic significance of microalbuminuria is valuable; its pathophysiologic significance is variable, but its usefulness for treatment decisions remains to be established.

PROGNOSTIC SIGNIFICANCE

In insulin-dependent diabetes mellitus (IDDM), microalbuminuria indicates early renal involvement and predicts diabetic nephropathy.² In non–insulin-dependent diabetes mellitus (NIDDM), microalbuminuria predicts premature mortality, mainly through cardiovascular events, and, to a minor extent, uremia.³ This predictive value is also applicable to nondiabetic, elderly subjects.⁴ Microalbuminuria is an independent predictor for coronary heart disease in men of the general population aged > 40 years.⁵ As microalbuminuria precedes proteinuria, the prognostic value of microalbuminuria seems identical (but perhaps more sensitive) to that of proteinuria for cardiovascular mortality in the general population.⁶ However, the prognostic significance of microalbuminuria for cardiovascular mortality remains still to be established in essential hypertension. In a 6.3-year follow-up study of hypertensive patients with or without diabetes mel-

From the Centre Hospitalier Universitaire, Angers, France.
This material was first presented at a workshop organized with the help of an educational grant from the Groupe de Recherche Servier–France in Paris on December 11, 1996.
Address correspondence and reprint requests to Michel Marre, Service de Médecine B, Centre Hospitalier Universitaire, 49033 Angers, France.

© 1998 by the American Journal of Hypertension, Ltd.
Published by Elsevier Science, Inc.
litus, Agewall et al found that microalbuminuria was of prognostic significance for cardiovascular mortality in hypertensives with diabetes mellitus, but only macroalbuminuria was of prognostic significance for hypertensives without diabetes mellitus.7

**PATHOPHYSIOLOGIC SIGNIFICANCE**

**Contributors to Microalbuminuria** A number of contributors were related to microalbuminuria through cross-sectional studies.8 Some determinants are constitutional (male gender, ethnicity), others are physical (age, blood pressure, obesity, hyperglycemia, hyperlipemia, hyperinsulinemia), and still others are behavioral variables (smoking habits, high-fat diet). Thus, virtually all previously recognized cardiovascular risk factors were related to microalbuminuria. However, multiple regression analysis indicates that they do not account for the whole AER variance, and that there may be some other, still unknown determinants for microalbuminuria.

Clinical and experimental studies support that all of the above-mentioned determinants can provoke microalbuminuria through elevation of intraglomerular pressure.8 However the clinical studies have established in diabetic and hypertensive subjects that microalbuminuria is a concomitant of generalized leakage of macromolecules through small and large vessels. Thus, microalbuminuria can signal malignant angiopathy, perhaps a consequence of endothelial dysfunction.9

**Microalbuminuria and Blood Pressure: Is Kidney the Victim, or the Culprit?** The relationship between AER and blood pressure is ambiguous. A statistically significant relationship is easily obtainable in one given population. However, the type of relationship may differ from one population to another. This is illustrated in Figure 1, in which the relationship is given for two groups: one of patients with IDDM and another of patients with essential hypertension. The relationship is clear between AER and systolic blood pressure in both groups, but the curve is shifted to the left for the IDDM group compared with the hypertensive group. In the IDDM patients, early renal lesions due to IDDM cause elevation of blood pressure, whereas microalbuminuria (just as with ventricular hypertrophy) signals renal involvement due to the severity of essential hypertension in the second group. Thus, considering microalbuminuria in normotensive individuals, we may speculate that determinants of elevated glomerular capillary pressure may cause early glomerular lesions (signaled by microalbuminuria) and secondary hypertension. The relationship between such potential determinants (eg, weights, lipids, smoking, or some genetic polymorphisms) and microalbuminuria constitution must be analyzed through longitudinal and intervention studies. In this circumstance, microalbuminuria can be considered an intermediate risk factor for kidney and cardiovascular functions. Conversely, microalbuminuria may be only a risk marker in patients with severe essential hypertension. In the first instance, new treatment strategies should aim at reducing new risk factors for constitutional microalbuminuria (eg, all determinants of angiotensin II production), whereas adequate blood pressure reduction (whatever the treatment used) should be the ultimate goal in the second instance.

**TREATMENT STRATEGIES AND MICROALBUMINURIA**

Microalbuminuria is a surrogate end-point in clinical trials. It is not clear whether early treatment strategies based on microalbuminuria identification lead to a clinical benefit in many populations. In IDDM patients, intensified insulin treatment can arrest nephropathy progression,8,9 but no data are currently available taking end-stage renal failure as the end-point in this respect. In the same patients, early ACE inhibition prevents diabetic nephropathy,10 but no study was undertaken taking glomerular filtration rate progression as the primary end-point. However, early ACE inhibitors are currently recommended for normotensive IDDM patients with microalbuminuria.11

Regarding NIDDM patients, there is no evidence for the superiority of ACE inhibitors or any other antihypertensive drugs to ameliorate renal and cardiovascular prognosis of NIDDM with microalbuminuria.11 In nondiabetic renal disease, no trial was performed...

**FIGURE 1.** Relationship between systolic blood pressure and urinary albumin excretion in 134 patients with insulin-dependent diabetes mellitus (IDDM; open circles), and in 64 nondiabetic patients with essential hypertension (black circles).
based on microalbuminuria identification, as in essential hypertension or in the general population.

CONCLUSION

Microalbuminuria is an intermediate risk marker for renal and cardiovascular prognosis, and a surrogate end-point in clinical trials. New studies are required to ascertain the potential roles of various potential risk factors for constitutional microalbuminuria, and to evaluate the clinical utility of treatment strategies based on microalbuminuria identification.

REFERENCES