

JOURNAL FÜR HYPERTONIE

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*Journal für Hypertonie - Austrian Journal of Hypertension 2002;
6 (Sonderheft 3), 36-38*

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R. Donnelly

SHOULD MICROALBUMINURIA BE A THERAPEUTIC GOAL IN HYPERTENSIVE PATIENTS WITH TYPE-2 DIABETES?

INTRODUCTION

Cardiovascular disease is the leading cause of death among patients with type-2 diabetes mellitus (T2DM), and hypertension is roughly twice as common in diabetic compared with non-diabetic subjects. The UK Prospective Diabetes Study (UKPDS) showed that BP reduction is even more effective than glycaemic control in reducing diabetes-related deaths, major cardiovascular events and the incidence of heart failure in this high-risk population. In addition, several long-term follow-up studies have shown that increased urinary albumin excretion is an important early hallmark of renal and vascular damage. This interview considers the clinical and prognostic significance of microalbuminuria as a therapeutic target in hypertensive patients with T2DM.

WHAT IS MICROALBUMINURIA AND HOW IS IT DETECTED?

Diabetic nephropathy – still the leading cause of endstage renal failure in many countries – is characterised by dipstick (Albustix) positive proteinuria (> 0.5 g per 24 hours), increased BP and declining renal function, but an even earlier stage of “incipient nephropathy” (or “microalbuminuria”) is defined as urinary albumin excretion rate (AER) of 20–200 $\mu\text{g}/\text{min}$ (aequivalent to an albumin-creatinine ratio [ACR] of 10–25 mg/mmol on a random sample). Such small amounts of urinary protein are not detectable by routine Albustix testing. Having excluded other causes of proteinuria (eg, infection), microalbuminuria is usually diagnosed on the basis of three positive tests (AER, ACR or a mixture of both) over a 3–6 month period; ACR is usually measured on

an early morning sample, and AER is best measured on an overnight (8 hr) urine collection. Annual screening for microalbuminuria should be included in the routine diabetes complications assessment.

HOW COMMON IS MICROALBUMINURIA?

Epidemiological studies of renal disease in T2DM report prevalence rates for microalbuminuria ranging from 8 % to 32 %; the majority of estimates are around 25 %. The prevalence of overt proteinuria is approximately 15 %. In the UKPDS, 12 % of patients had microalbuminuria and 2 % had proteinuria at the time of diagnosis of T2DM. People of Asian or African origin seem to be particularly susceptible to diabetic renal disease, and microalbuminuria is more among patients with hypertension and/or poor glycaemic control.

WHAT IS THE PROGNOSTIC SIGNIFICANCE OF MICROALBUMINURIA WITH RESPECT TO CARDIOVASCULAR AND RENAL OUTCOMES?

Less than 5 % of deaths among patients with T2DM are attributable to renal disease. The majority of deaths results from acute myocardial infarction, heart failure and stroke. A meta-analysis of 8 studies found that the death rate among patients with T2DM and microalbuminuria was more than double the rate in people with normal urinary albumin levels; relative risk ratios were 2.4 and 2.0 for overall and cardiovascular morta-

lity, respectively [1]. Overt proteinuria carries an even higher (5–8 fold) risk of premature death from macrovascular disease. Microalbuminuria is also highly predictive of the subsequent development of diabetic nephropathy; AER typically increases by 25 $\mu\text{g}/\text{min}/\text{year}$.

That microalbuminuria is a powerful cardiovascular risk factor, independent of other abnormalities in patients with T2DM, has been confirmed by several large studies. For example, in the WHO Multinational study of Vascular Disease in Diabetes, all-cause mortality ratios for “light” and “heavy” proteinuria among patients with T2DM (relative to diabetic subjects with no proteinuria) were 1.5 and 2.8 respectively [2]. Similarly, in the 12-yr follow-up of subjects in the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), the relative risks for cardiovascular mortality (after controlling for age, sex, glycaemic control, insulin use, alcohol intake, cardiovascular disease history, antihypertensive drug use and retinopathy severity) were 1.84 for those with microalbuminuria and 2.61 for those with gross proteinuria. The corresponding relative risks for deaths from CHD, stroke or all-causes were also highly significant: 1.96, 2.20 and 1.68, respectively, for microalbuminuria; and similarly 2.73, 2.33 and 2.47 for gross proteinuria [3]. Thus, increased urinary albumin excretion is associated with increased all-cause mortality, and in particular increased deaths from CHD and stroke.

IS MICROALBUMINURIA A CARDIOVASCULAR RISK FACTOR IN NON-DIABETICS?

Microalbuminuria is present in 10–15 % of middle-aged nondiabetic subjects in whom it is also predictive

of cardiovascular disease and associated with clinical markers of endothelial dysfunction and insulin resistance. A relationship between microalbuminuria and poor cardiovascular outcome has been observed in treated hypertensives [4], elderly subjects, those with pre-existing cardiovascular or peripheral arterial disease, and otherwise healthy individuals.

A recent European study followed a cohort of otherwise healthy postmenopausal women from 1976 to 1995 [5]. The cardiovascular mortality rate for women in the highest quintile of urinary albumin concentration was 13.2 per 1000 years compared with 2.6 per 1000 years in women without detectable albumin in the urine; the age-adjusted rate ratio between the two groups was 4.4. Thus, microalbuminuria is predictive of the risk of future cardiovascular mortality, independent of hypertension or diabetes, among postmenopausal women. In the HOPE study, 15 % of non-diabetics had microalbuminuria at baseline, and cardiovascular risk increased steadily with increasing albumin-creatinine ratio (even at levels below the arbitrary threshold for defining microalbuminuria).

IS MICROALBUMINURIA A TARGET FOR THERAPEUTIC INTERVENTION?

Yes, I believe it is. For example, end-points related to diabetic renal disease were included in the blood pressure substudy of the UKPDS. Mean BP in the two treatment groups was 144/82 vs 154/87 mmHg (i.e a difference of 10/5 mmHg maintained over 10 years), and the tight BP control group had fewer microvascular complications. The trend for reduced risk of fatal and nonfatal renal disease was

not statistically significant (RR 0.35 and 0.58, respectively), but 5 out of 6 surrogate outcomes (eg, microalbuminuria and proteinuria; each were measured at 3-yearly intervals) favoured a beneficial effect of tight BP control. The incidence of microalbuminuria at 6 years was significantly reduced in the tight BP control group: 20.3 % vs 28.5 % (RR 0.71).

In my view, the presence of microalbuminuria (especially but not exclusively in type-2 diabetes) indicates that an individual patient is at even higher cardiovascular risk and thus merits intensified treatment of all risk factors, in particular tight blood pressure control using a combination of drugs likely to reduce AER and confer both renal and cardiovascular protection.

WHAT IS THE EFFECT OF ANTI-HYPERTENSIVE THERAPY ON URINARY ALBUMIN EXCRETION RATE?

Blood pressure reduction is the most powerful intervention to lower AER, and it is generally accepted that a fall in urinary protein excretion reflects improved endothelial barrier function and a better renal and cardiovascular outcome. Several studies and meta-analyses have sought information on the relative effects of different anti-hypertensive drug classes on AER and renal function. For example, a meta-analysis of studies lasting more than one week showed that ACE inhibitors reduce urinary protein levels by an average of 40 %, compared with a 17 % reduction with other BP-lowering drugs [6]. However, in a meta-analysis restricted to randomised controlled trials of > 6 months duration, decreases in AER with ACE inhibitors were proportional to reductions in BP in both diabetic and

non-diabetic subjects [7]. More recently, however, renin-angiotensin system blockade has been shown to retard progression of incipient nephropathy in T2DM, and to have cardiovascular and anti-proteinuric effects that are at least in part independent of BP reduction [8]. Dihydropyridine calcium channel blockers have the weakest effect on AER [6]. Tight BP control as part of an intensified multiple risk-factor intervention approach is the main priority in treatment.

DO DIURETICS IMPROVE MICROALBUMINURIA?

Yes, there is evidence that indapamide reduces AER, and in a comparative monotherapy study with captopril the diuretic was equivalent to the ACE inhibitor in reducing microalbuminuria in hypertensive patients with T2DM [9]. In practice, of course, most patients with microalbuminuria require combination antihypertensive therapy to achieve maximal reductions in BP and AER. Thus, indapamide will usefully enhance the anti-proteinuric effect, as well as the BP-lowering effect, of ACE inhibitor therapy, and therefore this combination is ideal for hypertensive patients with T2DM and microalbuminuria. The recent NESTOR trial is particularly helpful in this context.

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