ABSTRACT

Microalbuminuria (MA) in individuals with diabetes mellitus (DM) is associated with markedly reduced survival, increased risk of cardiovascular disease and is predictive of later development of an overt Diabetic Kidney Disease (DKD) and progressive renal failure. Patients with type 1 DM from 5 years after diagnosis and type 2 DM from the time of diagnosis should be screened annually for MA by sensitive stick test in spot collection or Albumin Excretion Rate (AER) in the timed collection of urine. AER of 20-200 \( \mu \text{g/min} \) (30-300 \( \text{mg/24hr} \)) or Albumin : Creatinine ratio (ACR) >2.5 is labelled as MA. ACE Inhibitor / Angiotensin II Receptor Blocker (ARB) therapy along with improved glycaemic control is the key to prevent or slow the progression of DKD.

INTRODUCTION

Diabetic Kidney Disease is the leading cause of End Stage Renal Disease (ESRD) and diabetes related morbidity and mortality. The prevelance of M.A. in type 1 DM is quoted between 4%-20% and in type 2DM around 20%-36% and is a significant problem in diabetic clinics.1,2 MA in individuals with both type 1 and type 2 DM is associated with markedly reduced survival and increased risk of cardiovascular disease as well as predictive of the later development of overt diabetic kidney disease and progressive renal failure.

The description of a radioimmunoassay by Keen & Chlouverakis in 1963 allowed the measurement of previously undetectable levels of urinary albumin. This led to the landmark report in 1969 that a proportion of patients with type 2 DM in Bedford had elevated urinary albumin excretion, so called microalbuminuria (MA) and importance of which was fully appreciated in 1982 describing MA as important indicator of the later development of overt diabetic kidney disease.3

Key Words: Microalbuminuria, Diabetes Mellitus, Diabetic Kidney Disease.

MICROALBUMINURIA: DEFINITION AND ASSOCIATION WITH DIABETIC KIDNEY DISEASE

Traditionally, the onset of DKD is thought of as the presence of clinically detectable dipstick positive proteinuria, equivalent to a urinary albumin excretion of >300mg/day. There is strong evidence of an individual susceptibility to DKD in type 1 and increasingly in type 2 DM.4 The susceptibility seems to be genetic, but as yet there is no way of identifying those who are at risk of DKD, other than an early increase in urinary albumin excretion rate (AER).5 Preliminary studies on MA used different cut off points of urinary AER but persistent MA is now defined as an AER between 20-200 \( \mu \text{g/minute} \) (30-300 \( \text{mg/day} \)) in at least two of three consecutive urinary collection and 30-88 \( \mu \text{g Alb/ mg creatinine} \) in spot collection or Albumin Creatinine Ratio (ACR) >2.5.6 Microalbuminuria can occur within one year of type 1 DM, but persistent rise of AER is more common after 5 years.7 Once persistent MA has developed, the AER rises by between 7%-18.6% per year. Over 80% of patients with MA progress to DKD (table-I) and at
urinary AER $>100\mu g/\text{minute}$, it rises to 100%.\textsuperscript{3-6} MA is considered to be predictor of later disease, to the extent that it is commonly known as incipient nephropathy. However, renal biopsy studies have provided evidence that this phase does not merely predict DKD but is associated with significant glomerular disease. Walker et al found patient with MA having glomerular basement membrane thickening, expansion of the mesangial matrix volume fraction and matrix volume as compared to normoalbuminuric controls.\textsuperscript{3} Fioretto et al arrived at similar results in those with an AER $>31\mu g/\text{minute}$. Patients with MA also have evidence of renal arteriolar hyalinosis and interstitial expansion which is associated with more rapid decline in glomerular filtration rate and 50% of patients reach ESRD in 7-10 years. The early pathologic changes and albumin excretion abnormalities are reversible with normalization of plasma glucose. However, once nephropathy becomes overt, pathological changes are irreversible.

Microalbuminuria in type 2 DM may be associated with renal lesion different from type 1 DM in following respect:

- MA or overt nephropathy may be present when type 2 DM is diagnosed, reflecting its long asymptomatic period.
- Hypertension (HTN) accompanies MA or overt nephropathy in type 2 DM more commonly.

- MA may be less predictive of progression to overt DKD in type 2 DM. Patients with MA had greater glomerular volume, mesangial sclerosis and arteriolar hyalinosis in study of type 2 DM in Europe than non diabetic controls.\textsuperscript{9}

Thus it may well be appropriate to abandon the term “incipient nephropathy” and recognise that development of MA indicates significant renal disease in 43% patients.\textsuperscript{10} It represents a treatable phase of disease which should be targeted for intervention.

**MICROALBUMINURIA AND CARDIOVASCULAR DISEASE**

In addition to the risk for advanced renal disease in DM, it is an important marker of cardiovascular morbidity and mortality in type 2 DM.\textsuperscript{11} Indeed it is more predictive of cardiovascular death than of end stage renal disease. This increased risk in type 2 DM operates at levels of AER only minimally above the normal range and that an AER $>10\mu g/\text{min}$ should be targeted for intervention. Earle et al, in a cross sectional study, found that MA was an independent risk factor for silent myocardial ischaemia, suggesting presence of significant Coronary Artery Disease (CAD) during the phase of MA.\textsuperscript{12}

**MICROALBUMINURIA AND BLOOD PRESSURE (BP)**

Considerable debate centres on the association between BP and MA, with controversy over whether a rise in BP predate the rise in AER or occurs after the development of MA. In the UK microalbuminuria collaborative study (UKMCMS), a longitudinal study of 137 patients with type 1 DM mean arterial pressure (MAP) was higher from baseline in those who developed MA than those who remained normoalbuminuric.\textsuperscript{13} By contrast, in Cohorts reported from Danish studies, the rise in BP occurred after development of MA.\textsuperscript{14}

Therefore in type 1 DM, it remains uncertain whether rise in BP predate MA or vice-versa. In type 2 DM there seems to be less controversy, higher arterial pressure being a risk factor for future development of MA and increasingly lower BP are target for treatment. During the phase of MA in both type 1 and type 2 DM, both systolic and diastolic pressure rise with AER. The exact prevalence of hypertension in those with type 1 DM and MA depends upon the changing definition of hypertension. In a Danish study, the prevalence of HTN using WHO criteria Systolic blood pressure (SBP) $\geq 160$ mmHg and Diastolic blood pressure (DBP) $\geq 95$ mmHg was 15% in those with normal AER, 26% in those with MA and 61% in those with macroalbuminuria. When criteria for HTN from 5\textsuperscript{th} report of JNC, (SBP $\geq 130$ mm of Hg., DBP $\geq 80$ mm of Hg) were used the prevalence rose to 42%, 52% and 79% for normoalbuminuric, microalbuminuric and macroalbuminuric patients respectively.\textsuperscript{15} \textsuperscript{7\textsuperscript{th}} JNC has recommended SBP of 115 mm of Hg and DBP of 75 mm of Hg and the risk of cardiovascular disease doubles with each increment of 20/10 mm of Hg. Patients with SBP of 120 to 139 mm of Hg or a DBP of 80-89 mm of Hg should be considered as Prehypertensive and require health promoting measures to prevent Cardio Vascular Disease (CVD).\textsuperscript{16}