

## INTRODUCTION

CVD is a leading cause of morbidity and mortality among non communicable diseases (NCD). Prevalence of coronary heart disease (CHD) is between 7-13% in urban and 2-7% in rural India. A conservative estimate indicates that there could be 30 million CHD patients in India of which 14 millions are in urban and 16 million in rural areas. If the current trend continues by the year 2020, the burden of CVD in India will surpass other regions of the world. The country wise statistics of the WHO on non communicable disease estimates that NCD accounts for 53% of the total deaths in India, out of which CVD have a major share of 24%. It is the first among top five causes of deaths in India.

CVD has many established risk factors, with the residual variance in CHD may be attributable in part to unknown factors. This indicates that non established CHD risk factors might be operational in CHD incidence and mortality. Microalbuminuria (MAU) may be one of these independent risk factors other than established one. According to steno-hypothesis (exist since 1989) albuminuria in insulin dependent diabetes mellitus is not only a indication of renal disease but a new independent risk marker of proliferative retinopathy and macroangiopathy.

## MICROALBUMINURIA: DEFINITION AND PREVALANCE

MAU is defined as urinary albumin excretion (UAE) of 20-200mcg/min or 30-300 mg/24 hours. MAU can also be defined in terms of the urinary albumin to creatinine ratio (UACR). A UACR > 30mg/gm in the first voided, clear and midstream morning urine sample is considered abnormal and persistent MAU is defined as the presence of MAU in two or three consecutively collected samples preferably within a period of six months.

In different cross-sectional studies, the prevalence of MAU is 20-40% in patients with diabetes, 40% in poorly controlled hypertension and 10-15% in middle age general population. The prevalence of MAU is associated with the duration and severity of hypertension.

## MICROALBUMINURIA AND CLINICAL OUTCOMES

Data from various clinical studies show that MAU is associated with an increased risk of all cause and cardiovascular mortality, cardiac abnormalities, cerebrovascular disease and peripheral arterial disease. Relationship between urinary albumin excretion and adverse clinical outcome is continuous one and starts below the threshold for definition of MAU.

## MAU AND MORTALITY

The association between MAU and mortality was apparent from studies, like Heart Outcome Prevention Evaluation (HOPE) that involved high risk patients (> 55 yr. of age with CVD or DM plus at least one CV risk factor). This study show that all cause mortality was 9.4% among patients without MAU and 18.2% among patients with MAU. There is a linear relationship between MAU level and CV events extending below the traditional MAU threshold. MAU among patients with T2DM was associated with a 2.4-fold increased risk of CV death as compared with normoalbuminuria, as reported in a systemic review by Dinneen and Gerstein.

The presence of MAU is associated with increased all cause mortality in general population. The Prevention of renal and vascular end stage disease (PREVEND) study showed a direct linear relationship between albuminuria and risk of CV death in the general population even at levels of albumin excretion extending below the traditional MAU threshold or "normal" range (15-29 mg/day) and was increased more than 6 fold when albumin excretion exceeded 300 mg/day.

## MAU AND CARDIAC DISEASE

Cardiac abnormalities like left ventricular dysfunction, left ventricular hypertrophy, ECG abnormalities and coronary heart disease are well associated with MAU. The Strong Heart Study demonstrated a significant association between microalbuminuria and echocardiographic parameters of LV systolic and diastolic function in a cohort study. The larger Losartan Intervention for Endpoint reduction in hypertension (LIFE) study demonstrated increased UACR resulted in increasing risk of CV morbidity and mortality among hypertensive patients with left ventricular hypertrophy. PREVEND study in nondiabetic patients demonstrated a positive relationship between MAU and ECG changes (major ischemia vs. minor ischemia). Urinary albumin excretion (UAE) is as good as ultrasound (US) evaluation of cardiac and carotid structure for predicting cardiovascular risk in hypertensive patients and UAE in combination with US is very much accurate in detecting target organ damage as compared to routine examination. The presence of MAU in hospitalized patients with acute myocardial infarction is a strong prognostic marker of in hospital mortality and long term mortality. MAU is a marker of target organ damage and cardiovascular changes in patients with primary hypertension. The HARVEST study (hypertension and ambulatory recording Venetia

588 study) demonstrated that a 24hr. systolic blood pressure profile was higher in patients with MAU than in those with normoalbuminuria.

### MAU AND CEREBROVASCULAR DISEASE

MAU is common finding among patient with cerebrovascular disease. EPIC-norfolk study demonstrated that MAU was independently associated with a 50% increased risk of stroke. MAU is an independent risk factor for recurrence of stroke in older population with previous ischemic stroke, as shown in Portland study.

### MAU AND PERIPHERAL ARTERIAL DISEASE (PAD)

Studies to correlate MAU with PAD are very limited and needs additional investigation to clarify the relationship.

### HOW MAU-CVD LINKED TO EACH OTHER?

There are 4 possibilities:

1. MAU causes CVD
2. CVD causes MAU
3. MAU and CVD caused by common risk factors
4. MAU and CVD have common pathophysiological process
  1. MAU causes CVD: As per this hypothesis, MAU is caused by glomerular capillary leakage, so it may be associated with diffuse endothelial injury, causes leakage of macromolecules other than albumin leading to cascade of inflammatory responses which in turn start the atherosclerotic process. BUT no evidence/data suggest that MAU directly causes CV events.
  2. CVD causes MAU: To test this hypothesis a study has been designed where association between MAU and CVD has been compared with Peripheral Arterial Disease (accepted marker of atherothrombosis) and CVD. 631 individuals (age/gender/glucose tolerance stratified sample) were followed up for 5 years. This study showed that both MAU and CVD were strongly associated with 5 yr. risk of CV events. However, only approximately 25% of individuals with MAU also had PAD and vice versa. So the clear evidence for this hypothesis is lacking.
  3. Common underlying risk factor for MAU and CVD: Many cross sectional studies indicate that MAU is associated with many CV risk factors (Age, Male gender, Hypertension, Diabetes, Smoking, Obesity, and Dyslipidemia). At first glance it appears that MAU- CVD link can be explained by common underlying risk factor, but many studies have investigated and found that common risk factor explain only small part of association between MAU and CVD.
  4. MAU and CVD linked by a common pathophysiological process: An early event for CVD (atherothrombosis) as currently understood is endothelial dysfunction (measured by NO) and

chronic, low grade inflammation (measured by CRP/IL-6/TNF alpha). Impaired endothelial NO synthesis plays an important role in the association of MAU with CVD risk, with or without diabetes mellitus.

### WHOM TO SCREEN FOR MAU

The national kidney foundation guidelines recommend front-end UAE screen in all patients who are at risk for renal disease, including those with diabetes, hypertension, and family history of chronic kidney disease, age > 60yr, and racial and ethnic minorities. The American Diabetes Association (ADA) recommends an annual UAE test in all patients with type 1 diabetes of > 5 yr duration and in all patients with type 2 diabetes starting at time of diagnosis as a prognostic indicator of CVD risk.

The European society of hypertension 2007 guidelines considers MAU as one of the cost effective tools to diagnose target organ damage in hypertensive patient.

There is no evidence to support screening of general population for UAE at present.

### TREATMENT OF MAU

Renal targeted therapy designed to reduce proteinuria not only slow the progression of CKD, but also reduce CV risk as well. (PREVEND IT) is the only randomized trial to study the effect of albuminuria lowering in microalbuminuric, otherwise healthy individuals. It reported a 40% reduction in CV events over 4 year, who are treated with ACEI. Controlling blood pressure is the most important strategy to reduce UAE. The Steno-2 trial demonstrated that intensified BP, cholesterol, and glycemic control in patients with type 2 diabetes was associated with decreased risk for cardiovascular mortality. Based on these trials, summary of recommendation for patients with MAU is following:

1. ACEI/ARBs for renoprotection in diabetic patients.
2. Target BP for general population < 140/90, for diabetic < 130/80.
3. HBAIC < 7%.
4. Target LDL < 70mg/dl in CVD patients, for renal disease and diabetic < 100mg/dl.  
Correction of triglyceride, HDL and non HDL cholesterol level
5. Smoking cessation
6. Weight reduction and exercise.
7. Anti platelet therapy
8. Dietary salt restriction

### CONCLUSION

MAU is a risk marker of both renal and cardiovascular disease. MAU and CVD linked by a common pathophysiological process (generalized endothelial dysfunction). MAU is most effective tool to measure target organ damage in hypertensive patients. Risk of

adverse clinical outcomes start below the traditional MAU threshold. It is a treatable marker, and blood pressure control is most effective means to reduce MAU.

## REFERENCES

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