

Microalbumin: Urinary Biomarker of Cardiovascular Risk Assessment

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Abstract

Microalbuminuria is an early sign of vascular damage. Now-a-days it is considered as a predictor of worse outcome for both renal and cardiac patients. In this review we investigate the magnitude of relationship between microalbuminuria and incident coronary heart disease and mortality. Microalbuminuria is an independent predictor of coronary heart disease and all cause mortality. It is demonstrated that cardiovascular and renal risk is elevated even in the high normal range of microalbuminuria. Early detection of microalbuminuria, or therapies that prevent or delay the development of microalbuminuria, and all measures that prevent it, may help to prevent or delay cardiovascular events.

Keywords: Cardiovascular events, Microalbuminuria, Urinary biomarker.

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Introduction

Cardiovascular disease is a leading cause of morbidity and mortality among non-communicable diseases (NCD) and it comprised 46% of all NCD deaths in 2012.¹ It is the leading cause of death in the United States.² Several primary and secondary interventions reduce the risk of cardiovascular morbidity and mortality in high risk groups. Increased attention has been given to the role of microalbuminuria (MAU) as a cardiovascular (CV) risk indicator, particularly in patients with diabetes mellitus (DM) and hypertension. The risk of CV morbidity and mortality is estimated to be 1.8 times higher in diabetic persons with MAU than for those with normoalbuminuria.^{3,4}

What is microalbuminuria?

MAU is defined as urinary albumin excretion of 20-200 µg/min or 30 -300 mg/24 hours.⁵ MAU can also be

defined in terms of the urinary albumin to creatinine ratio. A ratio greater than 30 mg/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.⁶

Prevalence and Risks

In different cross-sectional studies, the prevalence of MAU was 20-40% in patients with diabetes⁷ and 10-15% in middle aged individuals without diabetes.^{3,4,7-9}

MAU is reported to be associated with risk factors of vascular endothelial injury¹⁰⁻¹³ i.e it is associated with development and progression of coronary heart disease (CHD)¹⁴⁻¹⁷ and cardiovascular disease (CVD).¹⁸⁻²² Moreover, MAU is also recognised as predictor of CV and all-cause mortality in general population^{14,18,23,24} and type 2 diabetic patients.^{25,26} Although it is declared that MAU is a predictor of CV events and of progression to overt nephropathy, it is now recognized that the risk is elevated even in the high normal range of MAU, that is below 30 mg/day.²⁷

Objectives

We reviewed the literature on MAU and its relationship to CV events in high risk patient, for example patients with DM and/or hypertension. The specific objectives were to determine the association of CV events with MAU.

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Method

A structured literature search was conducted to identify published original evaluation of the association between MAU and cardiovascular events in patients with DM and/or hypertension. The search was limited to studies that appeared up to 2015 from 1974. We used the literature database MEDLINE and searched the internet by using the keywords 'cardiovascular events', 'microalbuminuria' and 'urinary biomarker'. Both medical subject headings (MeSH) and free text search terms were used. The search was limited to studies in humans and in the English language literatures. Editorials, letters etc. were excluded.

Nature of the link between microalbuminuria and cardiovascular disease

Can microalbuminuria cause cardiovascular disease i.e. atherothrombosis?

MAU does not directly cause CV events; it acts as a marker for identifying high risk people for such events. MAU is caused by glomerular capillary injury and so it may be a marker for diffuse endothelial dysfunction.²⁸ There is also leakage of macro-molecules other than albumin, such as low density lipoproteins into the vessel wall that may lead to inflammatory responses and in turn start the atherosclerotic process.²⁹

Can atherothrombosis cause microalbuminuria?

It has been suggested that MAU is simply a marker of generalized atherosclerosis and this explains its association with clinical CVD. To test this hypothesis, the association between MAU and CVD with that between peripheral arterial disease (an accepted marker of generalized atherosclerosis) and CVD in an age, gender and glucose tolerance stratified sample (n=631) of a population based cohort of individuals who were aged 50 to 75 year was compared and followed prospectively for five years. This study showed that both MAU and peripheral arterial disease were strongly associated with five year risk of CV death. However, only approximately 25% of individuals with MAU also had peripheral arterial disease and vice versa.³⁰

Microalbuminuria and Hypertension

MAU has been seen in approximately 40% patients with established essential hypertension³¹ and is a predictor of a higher risk for cardiovascular and probably renal dysfunction. MAU was proposed by the European

Society of Hypertension guidelines as one of the best cost effective tools to diagnose target organ damage in hypertensive patients.³²

Microalbuminuria as a cardiovascular risk marker in hypertensive diabetic patients

MAU is independently associated with inflammatory markers in early type 2 diabetic nephropathy.^{33,34} If it is linked to the development of diabetic renal disease, it can also influence the endothelial dysfunction and atheroma formation, since atherosclerosis is an inflammatory disease as proposed by Ross.³⁵ A systematic review by Dinnen and Gerstein reported that type 2 DM with MAU was associated with 2.4 fold increased risk for cardiovascular death as compared with normoalbuminuria.³⁶ The same finding were reported in type 1 diabetic patients.³⁷

Microalbuminuria as a cardiovascular risk marker in hypertensive non-diabetic patients

Parvings and colleagues observed that level MAU was directly correlated with blood pressure in uncontrolled hypertensive non-diabetic patients and it tended to be reduced whenever a better blood pressure level was obtained.³⁸ These results were later confirmed by various studies.^{22,27,39}

Microalbuminuria and coronary artery disease

MAU, a marker of endothelial cell dysfunction, is associated with atherosclerosis and is a predictor of coronary artery disease (CAD). It has been suggested that patients with CAD have exaggerated exercise-induced urinary microalbumin excretion but this is controversial. Patients with exercise-induced myocardial ischaemia have pre-exercise urine microalbumin excretion. Exaggerated urine microalbumin excretion in response to exercise is not associated with exercise-induced myocardial ischaemia.

Both renal dysfunction and left ventricular hypertrophy (LVH) are signs of end-organ damage, risk markers of CV disease and chronic heart failure. In a cross-sectional study, in a selected population, LVH was more prevalent in subjects with renal dysfunction and both creatinine clearance and MAU were independently associated with the presence of LVH.⁴⁰

Urinary excretion of albumin also increases during acute myocardial infarction⁴¹ but little is known on the prognostic significance.

Association of microalbuminuria with plaque formation

MAU is considered a noted atherosclerotic risk factor, both in diabetic and in general population. A prospective, population-based study done over 7 years showed that albumin creatinine ratio (ACR) is positively related to plaque-initiation and plaque growth. This relationship is substantially modified by fibrinogen in previously plaque-free subjects.⁴²

Association of albuminuria with systolic and diastolic left ventricular dysfunction in type 2 diabetes

A study to compare systolic and diastolic function in American Indians with DM based on albuminuria status revealed left ventricular systolic function was lower in the groups with albuminuria. Similar findings were noted in diastolic LV filling with lower mitral E/A ratios and longer deceleration times in groups with albuminuria. Albuminuria is independently associated with LV systolic and diastolic dysfunction in type 2DM; this may explain in part the relationship of albuminuria to increased CV events in diabetic population. Screening for albuminuria identifies individuals with high CV risk and possible cardiac dysfunction.⁴³

Microalbuminuria as a risk factor for peripheral vascular disease

MAU and peripheral artery disease represent 2 different forms of target organ damage due to raised blood pressure. A 12 year duration TAS-GR (Three Areas Study in Greece) study was done to investigate the association between blood pressure with MAU and the appearance of peripheral artery disease. It observed that MAU was statistically correlated to peripheral artery disease. Blood pressure levels seemed to predict the appearance of MAU and peripheral disease after 12 years. Microvasculature and macrovasculature abnormalities showed a significant relationship, suggesting a common pathogenetic mechanism.⁴⁴

Treatment of microalbuminuria

The presence of albuminuria serves as a powerful tool to identify those patients requiring an integrated intervention on CV risk factors. The PREVENT IT (Prevention of Renal and Vascular End Stage Disease Intervention Trial) study is the only one where therapeutic intervention aimed to evaluate if lowering urinary albumin excretion would reduce CV events in microalbuminuric subjects. Treatment with fosinopril had a significant effect on urinary albumin excretion and a

trend in reducing CV events with a 40% lower incidence.⁴⁵ LIFE study showed the urine albumin level in 568 patients with diabetes and hypertension, who were treated with losartan was significantly lower than that in 609 control patients treated with atenolol. In addition, the CV mortality and all-cause mortality in losartan treated patients were significantly lower than that in control group.⁴⁶

MAU is a treatable marker. Early intervention started before progressive glomerulosclerosis and scarring is initiated may be important to maximize reno- and cardio-protection. Every halving of albumin excretion is associated with an 18% reduction of CV events.⁴⁷ In general, agents that act on the renin angiotensin axis (Angiotensin receptor blocker and angiotensin converting enzyme inhibitor) slow the progression to overt nephropathy. The use of combination of ACEI and ARB in patients with MAU and high CV risk is not effective and should not be recommended.⁴⁸

Microalbuminuria: Beyond

The current gold standard for detection and prediction of diabetic kidney disease (DKD) is MAU. However, it has several limitations, such as lower sensitivity and larger variability. It is urgent to explore markers with higher sensitivity and specificity for earlier detection of kidney disease. In near future, it will surely propose more sensitive and specific urine biomarkers than MAU for CV risk evaluation.⁴⁹

Some new and important urinary biomarkers are in pipeline, such as: transferrin, immunoglobulin G, immunoglobulin M, Cystatin C, podocytes, type IV collagen, 8-oxo-7, 8-dihydro-2'-deoxyguanosine, ceruloplasmin, monocyte chemoattractant protein-1 and so on.⁵⁰ Urinary transferrin is considered to be a more sensitive marker of glomerular damage in diabetic patients based on theory analysis and experimental results.⁵⁰ Urinary IgG excretion is higher in diabetic patients compared to healthy controls, and its excretion in diabetic patients with normoalbuminuria predicts the development of microalbuminuria.⁵¹ Podocytes are key structural elements of the glomerular filtration barrier. It is accepted that podocytes' injuries play an essential role in the progression of DKD.⁵² Monitoring urine podocytes and podocyte-specific proteins can reveal potentially interesting urinary markers for the early diagnosis of DKD.⁵³ Urinary ceruloplasmin is also a

promising marker of DKD.⁵¹ Recently, a study from uni-nephrectomized diabetic rats indicated urinary osteopontin, heart-type fatty acid binding protein appeared before the classical biomarkers of diabetic nephropathy, another study suggested urinary mRNA levels of α -smooth muscle actin, fibronectin and matrix metalloproteinase-9 might be novel biomarkers of diabetic kidney disease.⁵⁴ McKittrick reported that urinary matrix metalloproteinase activity might be a sensitive, noninvasive, and clinically useful biomarker for predicting vascular remodeling in diabetic renal and vascular complications.⁵⁵ High level of Cystatin C (cys-C), a small protein molecule mainly used as a biomarker of kidney function, is associated with adverse outcomes and risk stratification of the spectrum of CVD and CAD. (peripheral arterial disease, stroke, abdominal aortic aneurysm, heart failure, coronary artery disease).⁵⁶

The above mentioned results are from small patient population and from animal experiments, which lead to limited use for clinical practice. We need larger perspective studies to confirm the utility of these biomarkers.

Conclusion

MAU, previously only has been investigated for detecting early diabetic nephropathy, with the aim to prevent further progression of diabetic nephropathy. Epidemiologic and clinical evidence has established a pathophysiologic link between MAU and cardiovascular and cerebrovascular disease in patients with diabetes and hypertension as well as in the general population. This correlation is observed even at levels of albuminuria below the conventional threshold for MAU. Screening for urinary albumin excretion can help clinicians anticipate a patient's risk and should prompt the early introduction of a multifactorial intervention strategy that aim to improve the overall CV risk factor profile as well as prevent further loss of renal function.

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