Microalbuminuria as A Risk Factor for Cardiovascular Disease: Review article

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Abstract

The earlier observations on the association between renal failure and increased rates for cardiovascular (CV) complications and death date back several decades. Similarly, it has long been noted that subclinical elevations of urinary albumin excretion (UAE) are related to higher risk of subsequent development of clinical nephropathy in patients with diabetes mellitus, and that increased UAE was associated with higher risk for CV events and mortality in both diabetic and non-diabetic individuals. Since then, a substantial amount of data have accumulated, providing solid evidence that both the decline in renal function and the elevation in UAE are independently associated with increased risk for cardiovascular disease (CVD). This article reviews the roles of microalbuminuria (MA) and chronic kidney disease (CKD) as risk factors for CVD, discussing the progress of the epidemiological and clinical evidence on the field.

KeyWords: CVD, Microalbuminuria, T2D.

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Introduction:

A small but abnormal albumin excretion in urine is known as microalbuminuria (MAU). MAU is a widely known predictor of diabetic nephropathy, essential hypertension (HTN), and cardiovascular disease (CVD). It is important that MAU be measured in all subjects with type 2 diabetes (T2D) and HTN, so that renal and cardiovascular adverse events can be properly managed and prevented(**1)**.

Mogensen was the first to describe the importance of microalbuminuria (MAU) not only as a renal risk factor but also as a powerful predictor of cardiovascular (CV) mortality in patients with type 2 diabetes mellitus (T2DM). Since the description by Mogensen, MAU has received special attention as a prognostic marker for CV or renal risk or both, even in non-diabetic subjects (**2**), Mounting evidence indicates a continuous relationship between urinary albumin excretion (UAE) and cardiorenal risk, similar to the relationship between blood pressure (BP) and risk of CV events (**3**)

MAU in a "healthy population" is not a benign condition, and the evidence has shown an association between MAU and increased CV risk and all-cause mortality.(**4**)

The American Diabetes Association (ADA) recommends testing for MAU in individuals with T2D on initial diagnosis of the disease and every year afterwards. (**5**)

Diabetic nephropathy is one of the most common and feared complication of diabetes mellitus. As the burden of diabetes is increasing worldwide, more and more patients with diabetic nephropathy are surfacing. It has also been associated with increased morbidity and mortality and it is one of the most common cause of end stage renal disease(ESRD) and initiation of renal replacement therapy (**6**).

From the early 80s, it was established that microalbuminuria is a good marker of subsequent proteinuria and chronic renal failure

in both insulin and non-insulin dependent DM patients, but in Type-2 DM patient it has increased mortality rate mainly from cardiovascular diseases. It was also observed that these patients had concomitant hypertension as well when their microalbuminuria is diagnosed. Studies have shown that microalbuminuria is not only an independent risk factor for cardiovascular diseases in hypertensive and diabetic patients but also for general population and it is also an important tool for predicting the mortality and morbidity in patients with cardiovascular and peripheral vascular diseases.(**6**)

The natural history of diabetic nephropathy in patients with T1DM and T2DM is similar. However, the timing of diabetes diagnosis in T2DM is difficult to assess, and often target organ damage is present when the diagnosis of T2DM is confirmed. T1DM allows a timeline picture of kidney disease progression starting with MAU and proceeds through stages of overt proteinuria, kidney function decline, and end-stage kidney disease. Nevertheless, this "classic" progression from MAU to macroalbuminuria is not seen in all patients. In fact, in patients with low levels of MAU (ACR of less than 100 mg/g) maintained for 2 to 3 years, it is possible to revert to normal UAE. Regression of MAU is facilitated by improved glucose, BP, and lipid control On the other hand, epidemiological evidence unequivocally shows that albuminuria is a marker of subclinical renal damage and is associated with the progression of CKD as well as CVD in patients with diabetes(**7**)

Prevalence & incidence:

Over the past few decades, the prevalence of albuminuria in US adults with diabetes mellitus (DM) has declined significantly, likely due to better glycemic and hypertension control and wider use of drugs inhibiting the renin–angiotensin system (RAS). These preventive strategies have also modified the phenotype of diabetic renal disease, with an increasing incidence of non-albuminuric patients. (**8**)

Nevertheless, the incidence of end-stage renal disease (ESRD) due to DM has not substantially changed. Furthermore, studies in the general population have demonstrated increased mortality and cardiovascular (CV) risk in the case of coexistence of DM and chronic kidney disease (DM-CKD) compared with either DM or CKD alone.(**9**) United States Renal Data System 2015 Annual Data Report: Epidemiology of Kidney Disease in the United States Bethesda, MD National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

The classic definition of diabetic nephropathy is the presence of MAU that normally appears 5 to 10 years after the diagnosis of diabetes and that without adequate treatment progresses to end-stage renal disease (ESRD). (**10**)

In patients with T2DM, the incidence of MAU showed an increase of 2.0% per year with a prevalence of 25% 10 years after diagnosis in the UK Prospective Diabetes Study (UKPDS).(**10**)

Based on UAE values, diabetic nephropathy has been categorized into stages: MAU and macroalbuminuria. Cumulative evidence suggests that the risk for developing diabetic nephropathy and CVD starts when UAE values are still within the normoalbuminuric range. (**11**)

Definitions:

The current definition of microalbuminuria (MA) is an amount of urinary albumin greater than the normal value, but also lower than what is detected by a conventional dipstick. Thus, the rate of urine albumin excretion (UAE) in microalbuminuria is 30 to 300 mg/24 hours. In other units, it can also mean 30–300 mcg/mg

creatinine (with the use of ACR in a spot urine collection) or 20–200 mcg/min on two out of three urine collections (if measured in a timed urine collection). This value is derived from studies that evaluated adults **(table1)**. (**12**)

Any urinary albumin value below these limits is considered as normal urinary albumin excretion (normoalbuminuria), whereas any value above them reflects the presence of macroalbuminuria or clinical proteinuria(**13)**.

Classification:

Table (1): Classification of urinary albumin excretion**(14)**

Category	24 hour urine collection (mg/24 hour)	Timed urine collection (µg/min)	Spot urine collection Albumin Creatinine Ratio	
			mg/g	mg/mm
Normoalbuminuria	< 30	<20	< 30	<3.4
Microalbuminuria	30 – 300	20 – 200	30 – 300	3.4 – 33.
Macroalbuminuria	>300	>200	>300	>33.9

For many years, the gold standard for measurement of MA was protein quantification in a 24-hour urine collection. This may be inconvenient for general practice patients as it requires the collection of all urine passed over the specified time in a specialized collection bag. Timed urine specimens are also prone to recording errors. (**15**).

The analysis of a spot urine sample and calculation of the ACR for measurement of albuminuria is strongly recommended by most authorities. The other two alternatives (24-hour urine collection and a timed specimen) are rarely necessary. **(16)**.

Microalbuminuria as a risk factor for CVD:

Microalbuminuria is an important early indicator for diabetic nephropathy and a significant risk factor for progression to proteinuria, ESRD, and mortality. Additionally, MAU is a predictor of cardiovascular mortality, as research indicates that individuals with MAU are at four-fold increase of death from CVD, particularly among the hypertensive population. (**17**)

Moreover, the presence of MAU was associated with increased risk of incident HTN and also diabetes. There is strong evidence that the relationship between MAU and other CV risk factors, such as diabetes, HTN, left ventricular hypertrophy, hyperlipidemia, overweight, and metabolic syndrome, contributes to an increase in CV mortality. (**18**)

Etiology:

Microalbuminuria develops from a dysfunction of the glomerular basement membrane (GBM) permitting albumin to enter the urine. The enzyme N-deacetylase is necessary to form heparan sulfate, which is how the GBM derives its negative charge. Furthermore, inadequate control of blood sugars inhibits this enzyme, reducing the negative charge on GBM and allowing excessive amounts of albumin to leak out. Advanced glycosylation end-products can also neutralize the negative charge of albumin by binding with the proteins of both the GBM and mesangial matrix. Additionally, hyperglycemia initiates the glycation of GBM and podocyte receptors interfering with the charge on GBM(**12**).

The current hypothesis, known as the 'Steno hypothesis,' is that systemic vascular endothelial dysfunction initiates the development of microalbuminuria and cardiovascular disease, as there is a strong correlation between these three variables. (**19**)

Therefore, having comorbidities that cause endothelial damage is considered a risk factor. These include increased age, insulin resistance, dyslipidemia, obesity, hypertension, decreased physical activity, and smoking. Some studies predict a genetic component linking together microalbuminuria, atherosclerosis, and even nephropathy. An increased UAE rate was seen

among patients with a deletion-deletion polymorphism of the ACE gene. (**20**)

Pathophysiology:

Among individuals with both T2D and HTN, the presence of MAU is associated with increased prevalence of CVD. Yang et al. proposed one pathway aimed at explaining the relationships among MAU, HTN, diabetes, and CVD. In this pathway, hyperglycemia and HTN lead to MAU, which in turn results in hyperlipidemia, a significant risk factor for CVD. Patients with T2D are more prone to dyslipidemia. Diabetes-induced dyslipidemia may be manifested by reduced high-density lipoprotein cholesterol (HDL-c), increased low-density lipoprotein cholesterol (LDL-c), and increased triglyceride (TG) levels in the blood.(**21**)

Microalbuminuria arises when GBM, a complex sieve, leaks an increased amount of albumin. The proposed mechanism is a combination of glomerular size enlargement, GBM thickening, mesangial expansion, and podocyte foot process effacement. Microalbuminuria can also occur via inadequate tubular reabsorption. **(22)**Dysregulated enzymatic metabolism of the extracellular matrix is the pathogenesis behind developing endothelial damage. (**19**)

Thus, at vascular places, other than just the renal system, the albumin can either leak out of or enter the vessel wall. When this happens, albumin can stimulate inflammation, lipid accumulation, and atherosclerosis, which eventually could form fixed albuminuria and decreased kidney function. (**23**)

Endothelial dysfunction as a possible mechanism of MA:

Normal healthy endothelium reduces vascular tone, regulates vascular permeability, limits platelets adhesion and aggregation, prevents activation of the coagulation cascade, and restricts leukocyte adhesion**(24)**

Because there is no plausible mechanism directly linking the atherothrombotic disease to the urinary albumin loss, endothelial dysfunction has been suggested to be, at least partly, the pathophysiological process that causes both increased renal albumin loss and coronary artery disease (**25**)

In the same context, (**26)** revealed that the mechanism of accelerated atherosclerosis in MA is uncertain, but endothelial dysfunction, abnormal vasodilatation, inflammation, insulin resistance or abnormal coagulation may be involved**(27)**

Endothelial dysfunction might be implicated in the increased permeability for albumin through the vascular wall and subsequently, the occurrence of MA **(24)**.

In the same context, studies in both diabetic and non-diabetic individuals indicate that elevated urinary albumin excretion is associated with abnormalities in tests of endothelial function (**28**)

Endothelial dysfunction is now considered to play a principal role in the initiation and progression of atherosclerosis. Consequently, generalized endothelial dysfunction might explain the prognostic value of MA in systemic cardiovascular events and end-organ damage **(24)**.

Significantly, the ubiquity of endothelium dysfunction, but most of all its localization in the coronary network, is likely to play a major part in the increased cardiovascular risk related to MA**(25)**.

MA diagnosis:

The presence of MAU implies dysfunction of the glomerular filtration barrier, which may result from hemodynamic-mediated mechanisms, functional or structural impairment of the glomerular barrier, or a combination of these. In normal conditions, UAE can change in day-to-day measurements. Moreover, age, sex, body mass index, a high-protein meal, and vigorous exercise can promote a transient

increase in albumin excretion. On the other hand, pathological conditions such as fever, congestive heart failure, urinary tract infection, and some drugs can also increase albumin excretion, so we have to consider all of these confounding factors when analyzing the urinary excretion of albumin.(**29**)

Although 24-hour urine collection is the gold standard for the detection of MAU, it has been suggested that screening can be carried out more simply. MAU can be tested from a first morning urine sample or at any time. In recent years, the albumin-to-creatinine ratio (ACR) from spot urine, preferably that first voided in the morning, may be considered equivalent to the values during a 24-hour urine collection (**30)**

There are different types of analysis to assess the presence of MAU. The urine dipstick, an insensitive marker for albuminuria, does not become positive until albumin excretion exceeds 300 to 500 mg/day. In normal conditions, UAE is less than 30 mg/day. When this value oscillates between 30 and 300 mg/day in a 24-hour urine collection or 30 to 300 mg/g of creatinine (urine albumin-to-creatinine ratio, or UACR) in a first morning sample, we used the term MAU, also known as “moderately increased albuminuria”. When albuminuria is more than 300 mg/day, it is considered macroalbuminuria. Although 24-hour urine collection is the gold standard for the detection of MAU, it has been suggested that screening can be carried out more simply. MAU can be tested from a first morning urine sample or at any time. In recent years, the albumin-to-creatinine ratio (ACR) from spot urine, preferably that first voided in the morning, may be considered equivalent to the values during a 24-hour urine collection.(**30)**

The gold standard for diagnosis is albumin measured in 24-hour urine collection (normal values of less than 30 mg/day, MAU of 30 to 300 mg/day, macroalbuminuria of more than 300 mg/day) or, more practically, the determination of urinary albumin-to-creatinine ratio in a urine morning sample (30 to 300 mg/g). MAU screening is mandatory in individuals at risk of developing or presenting elevated global CV risk. Evidence has shown that intensive treatment could turn MAU into normoalbuminuria. Intensive treatment with the administration of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, in combination with other anti-hypertensive drugs and drugs covering other aspects of CV risk, such as mineralocorticoid receptor antagonists, new anti-diabetic drugs, and statins, can diminish the risk accompanying albuminuria in hypertensive patients with or without CKD and diabetes(**31**).

Management of MA:

MAU is frequently present in asymptomatic patients. Recently, two meta-analyses assessed albuminuria as a surrogate endpoint for CKD progression in randomized controlled trials.(**32**).

Both articles found that the range in albuminuria was consistently associated with risk of end-stage kidney disease, lending support to the use of change in albuminuria as a surrogate endpoint for end-stage kidney disease. Given that MAU as a marker of target organ damage is associated with CV mortality and CKD progression, it is important to treat these patients intensively.(**33**)

***Renin–angiotensin–aldosterone system blockade intervention trials:**

Reduction of albuminuria under anti-hypertensive treatment is associated with reduced risk of clinical CV events and at the same time renal protection. There is cumulative evidence of the efficacy of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) for the treatment of HTN in this population.(**34**)

A few trials that focus the intervention on MAU have been designed. In the Action in

Diabetes and Vascular Disease (ADVANCE) trial, perindopril/indapamide was effective in preventing the onset of MAU, progression of MAU to macroalbuminuria, and even regression of albuminuria compared with placebo in patients with T2DM. (**35**)

Similarly, in the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial, olmesartan diminished the onset of MAU by 23% in T2DM. Dual renin–angiotensin–aldosterone system (RAAS) blockade between an ACEiplus an ARB should be avoided. This combination showed more cases of acute kidney injury and hyperkalemia without benefits.(**36**)

The combination of the standard therapy with an ACEi or an ARB with a mineralocorticoid receptor antagonist (MRA) is an interesting option for managing patients with albuminuria but has the inconvenience of frequent hyperkalemia in patients with CKD.(**1**).

In order to avoid the limitations of hyperkalemia of the traditional RAAS blockers in patients with CKD, new drugs have been developed. The new non-steroidal MRA finerenone (BAY948862) has better MRA selectivity than spironolactone and also reduced albuminuria and end organ damage more effectively than eplerenone. In the MinerAlocorticoid Receptor Antagonist Tolerability Study (ARTS), finerenone reduced albuminuria from baseline levels and had a lower incidence of hyperkalemia when compared with spironolactone in patients with chronic heart failure.(**37**).

Moreover, in the MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy (ARTS-DN) study, different oral doses of finerenone in patients with T2DM reduced albuminuria. The addition of the new potassium binder patiromer and the selective cation exchanger sodium zirconium cyclosilicate facilitated the use of traditional MRA in patients with CKD, reducing potassium levels.(**38**)

***Glucose-lowering agents:**

In recent years, new anti-diabetic agents appeared not only showing benefits in glycemic control but also reducing CV mortality and improving kidney function. The SGLT2 inhibitor acts as a glycosuric agent. In the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME), empagliflozin or placebo was added to standard care in patients with T2DM and CVD.(**39**)

Empagliflozin reduced new or worsening nephropathy, doubling of serum creatinine (1.5% of the empagliflozin versus 2.6% placebo; *P* <0.001%), and progression to macroalbuminuria (11.2% empagliflozin versus 16.2% placebo; *P* <0.001%). (**39, 40**)

Similarly, in the Canagliflozin cardiovascular Assessment Study (CANVAS), canagliflozin or placebo was added to standard care in patients with T2DM with CVD or at high risk of CVD. Active treatment with canagliflozin slowed the rate of eGFR decline and reduced UACR. Doubling of serum creatinine and new-onset macroalbuminuria were significantly reduced(**41**).

Moreover, in the recently published Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy study (CREDENCE), patients with T2DM and CKD were randomly assigned to receive canagliflozin or placebo. The relative risk of end-stage kidney disease was lower by 32% the relative risks of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes were lower by 34% The canagliflozin group had lower risks of hospitalization for heart failure and CV death, myocardial infarction, or stroke.(**42**)

***Endothelin receptor antagonists:**

Endothelin receptor antagonists reduce albuminuria and BP but can also cause sodium retention. A previous trial with the non-selective endothelin receptor antagonist avosentan in patients with diabetes and CKD was stopped prematurely because of an increased incidence of heart failure. By contrast, short-term treatment with low doses of the more selective endothelinA receptor antagonist atrasentan reduced albuminuria without causing significant fluid retention. Recently, the Study of Diabetic Nephropathy with Atrasentan (SONAR) was published and showed a reduction in the risk of renal events with no significant differences for hospitalization for heart failure and also mortality compared with placebo(**43**).

***Statins and fibrates:**

Drugs other than anti-hypertensives can influence MAU and renal function. Different meta-analyses showed reductions of MAU, proteinuria, and clinical deaths with statins. Fibrates showed also a reduction in albuminuria**(44).**

In patients with diabetic dyslipidemia, statin therapy has beneficial effects to cardiovascular CVD health. However, other than decreasing the LDL-c levels, the management of dyslipidemia in patients with T2D continues to be challenging. Diabetes, cigarette smoking, and dyslipidemia are well-known risk factors for CVD in the general population(**45**).

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