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General Medicine

ESTIMATING CARDIOVASCULAR RISK IN PATIENTS WITH MICROALBUMINURIA

KEY WORDS:

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ABSTRACT

Microalbuminuria is a marker for generalized vascular dysfunction. Its prevalence in United States and European general population surveys ranges from 6% to 10%. Increased risk for cardiovascular morbidity and mortality begins with albumin excretion rates that are well within normal limits. Although microalbuminuria interacts with the traditional cardiovascular risk factors, it has an independent relationship to renal and cardiovascular outcomes. For example, microalbuminuria doubles the risk for a cardiovascular event in patients with type 2 diabetes mellitus even after adjusting for the usual risk factors. Elevated rates of urinary albumin excretion predict target organ damage, notably renal disease, but are also related to left ventricular dysfunction, stroke, and myocardial infarction. Screening for microalbuminuria, which is recommended by several expert committees and associations, has become a readily accessible procedure. Screening can give clinicians prognostic information concerning cardiovascular risk and assist in guiding therapy. The goal of treatment is to prevent progression of, and even to reverse, microalbuminuria. Abundant evidence demonstrates that antihypertensive therapy is an important key to the control of urinary albumin excretion, and blockade of the renin-angiotensin system (with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) is the treatment of choice. These drugs have successfully halted or delayed the progression to nephropathy and have reversed elevated rates of albumin excretion to normal values, even when blood pressure reduction has been minimal.

Introduction

Microalbuminuria, which refers to the presence of small but abnormal amounts of albumin in urine, is the earliest indication of nephropathy, a type of kidney disease. In individuals with hypertension or diabetes mellitus, it is also an indicator of significantly increased risk of cardiovascular disease. Recent research has shown that albuminuria is linked to cardiovascular risk, even in those without diabetes. Microalbuminuria is consistently and independently associated with high blood pressure, and an increase in urinary albumin excretion rate has been linked to abnormalities in lipids, reduced insulin sensitivity, impaired endothelial function, peripheral vascular disease, and a prothrombotic state. Therefore, microalbuminuria serves as an indication of generalized vascular dysfunction. While specific cut-off points exist for defining the progression from normal albumin excretion rate to micro- and macroalbuminuria, these terms represent a continuum of renal and cardiovascular risk. Furthermore, this increased risk is evident even within the normal range of albumin excretion rate.

Microalbuminuria Prevalence

According to the Third National Health and Nutrition Examination Survey, 6.1% of men and 9.7% of women in the general population in the United States were found to have microalbuminuria, as defined by a urinary albumin-creatinine ratio (UACR) between 30 and 299 g/mg. It is noteworthy that this prevalence was reported in individuals without diabetes, hypertension, cardiovascular disease, or elevated creatinine. Studies in Europe have reported a prevalence of 5% to 7% of microalbuminuria in the general population.

Screening Criteria

Several expert committees and associations have highlighted the significance of microalbuminuria as a predictor of cardiovascular risk, leading to recommendations for screening. The American Diabetes Association (ADA) requires screening for microalbuminuria in individuals with type 2 diabetes at the time of diagnosis, and 5 years following the diagnosis of type 1 diabetes. Thereafter, annual screening is recommended. The National Institute for Clinical Excellence in the United Kingdom also recommends annual screening for microalbuminuria in patients with type 2 diabetes. The European Society of Hypertension-European Society of Cardiology guidelines suggest screening for microalbuminuria as part of the assessment of all patients with hypertension. The recently released guidelines of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) suggest that serum creatinine should be included in the initial evaluation of individuals with hypertension, and measurement of urinary albumin excretion or UACR may be performed as optional procedures.

Table 1. Definitions of urinary albumin excretion categories

Category	Spot Collection (UACR*) mg/mmol Creatinine	Spot Collection (UACR*) µg/mg Creatinine	Timed Collection (UAER) mg/24 h	Timed Collection (UAER) µg/min
Normal	Male <2.5 Female <3.5	<25 <35	<30	<20
Microalbuminuria	Male 2.5–30 Female 3.5–30	<25–299 <35–299	30–299	20–199
Clinical albuminuria (overt nephropathy)	≥30	≥300	≥300	≥200

UACR – urinary albumin–creatinine ratio; UAER – urinary albumin excretion rate.
* To be diagnostic for microalbuminuria, UACR values should be confirmed in two of three consecutive collections.

Microalbuminuria measurement

The typical urinary albumin excretion rate (UAER) in healthy

individuals ranges from 1.5 to 20 g/min, with a geometric mean of 6.5 g/min. However, in individuals who progress from microalbuminuria to clinical albuminuria, the UAER typically increases by an average of 25 g/min per year. While the quantitative laboratory measurement of UAER is precise, it necessitates specialized equipment that may not be available at the local primary care level.

A recently developed point-of-care method has been validated and demonstrated to have excellent sensitivity and specificity in calculating the urinary albumin-creatinine ratio (UACR). This new method is advantageous because urinary creatinine excretion is relatively constant, allowing for the correction of changes in urinary volume that can influence the urinary albumin concentration. Furthermore, the UACR provides immediate results, enabling the swift monitoring of treatment effects. The UAER and UACR measurements are closely related and can be correlated (Table 1). An algorithm for conducting initial and follow-up assessments for albuminuria is presented in Figure 1.

Expert committees generally advise measuring the UACR in an early morning urine sample. If a presumptive indication of microalbuminuria is observed, confirmation through the quantitative measurement of UAER in three timed urine samples is recommended. However, even a single determination of an elevated albumin concentration can predict renal and cardiovascular complications, although with less accuracy.

Interpreting UAER and UACR results requires considering various physiological and pathological factors. For instance, albumin excretion is typically 25% higher during the day and can vary up to 40-50% in day-to-day measurements. Several factors, such as age, sex, body mass index, exercise, and high-protein meals, can also impact UAER. The accuracy of measurement can be compromised by factors such as fever, congestive heart failure, and urinary tract infections. Similarly, UACR is influenced by ethnicity and certain pathological conditions that affect UAER. Additionally, men tend to have a lower UACR than women, given their greater muscle mass. Finally, the use of some prescription drugs can affect both UAER and UACR.

Microalbuminuria and cardiovascular risk

Other nontraditional risk factors that have been associated with microalbuminuria include obesity, dyslipidemia, smoking, sleep apnea, and psychosocial stress. Studies have also suggested that microalbuminuria may be a marker of early atherosclerotic changes and is associated with increased carotid intima-media thickness and coronary artery calcification, which are measures of subclinical cardiovascular disease. Additionally, microalbuminuria has been associated with an increased risk of future cardiovascular events, such as myocardial infarction and stroke, in both the general population and in patients with hypertension or diabetes.

These large-scale, prospective studies demonstrate the significant association between microalbuminuria and increased risk for all-cause mortality, as well as cardiovascular mortality. These associations have been observed in general populations and extend well into the normal range of urinary albumin concentration. For example, the Norwegian population study found that a UACR of 6.7 g/mg (0.76 mg/mmol) in three urine samples increased the risk for all-cause mortality 2.4-fold. Similarly, in a large Netherlands cohort, a twofold increase in urinary albumin concentration was associated with a relative risk of 1.29 for cardiovascular death. In a Danish study, a UACR of 0.65 mg/mmol was associated with a relative risk for ischemic heart disease of 2.3. In the Dutch cohort study of postmenopausal women, women in the highest quintile of urinary albumin excretion had a cardiovascular mortality rate four times that of women with normal urinary albumin excretion after adjusting for age, body mass index, smoking status, diabetes, and hypertension. These studies suggest that microalbuminuria is not only a marker for renal damage, but also a predictor of cardiovascular disease and mortality.

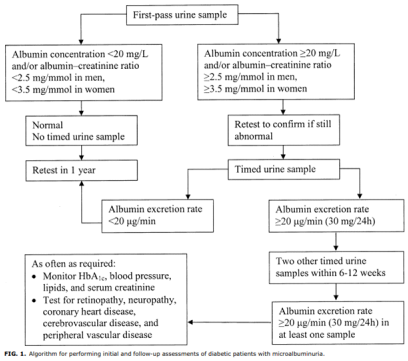

FIG. 1. Algorithm for performing initial and follow-up assessments of diabetic patients with microalbuminuria.

Microalbuminuria in high risk population

Hypertension

Microalbuminuria is commonly observed in individuals with essential hypertension, with prevalence rates ranging from 11% to 40% and increasing with age and duration of hypertension. In a cross-sectional study of over 10,000 patients with hypertension but without diabetes, those with microalbuminuria had higher rates of coronary artery disease, left ventricular hypertrophy, hyperlipidemia, peripheral vascular disease, myocardial infarction, and stroke compared to those without microalbuminuria. These differences were statistically significant ($P < 0.01$ for all). This suggests that microalbuminuria may be a marker of underlying cardiovascular disease in individuals with hypertension.

It is important to note that the presence of microalbuminuria in patients with hypertension may suggest the presence of underlying kidney damage, and is often considered a marker of early-stage kidney disease. As such, detection of microalbuminuria in patients with hypertension should prompt further evaluation of kidney function and potential kidney disease. Additionally, management of hypertension in patients with microalbuminuria should include not only blood pressure control, but also interventions to slow the progression of kidney disease and reduce cardiovascular risk.

Table 3. Association of microalbuminuria with all-cause mortality and cardiovascular morbidity and mortality in the HOPE study

Outcome	Microalbuminuria		
	Present (%)	Not Present (%)	Adjusted Risk* (95% CI)
All patients			
MI, stroke, CV death	23.1	13.8	1.83 (1.64–2.05)
HF hospitalization	6.9	2.2	3.23 (2.54–4.10)
All-cause mortality	18.2	9.4	2.09 (1.84–2.38)
Patients with diabetes			
MI, stroke, CV death	25	13.9	1.97 (1.68–2.31)
HF hospitalization	8.5	2.5	3.70 (2.64–5.17)
All-cause mortality	18.6	9.3	2.15 (1.78–2.6)
Patients without diabetes			
MI, stroke, CV death	20.4	13.8	1.61 (1.36–1.09)
HF hospitalization	4.6	2.1	2.20 (1.40–3.26)
All-cause mortality	17.4	9.4	2.00 (1.40–3.26)

CV = cardiovascular; HF = heart failure; HOPE = Heart Outcomes Prevention Evaluation; MI = myocardial infarction. Adapted from Gerstein HC et al: JAMA 2001;25:421.
* All, $P < .001$.

The development of microalbuminuria in persons with hypertension is believed to be related to vascular damage and leakage in the glomeruli, the small blood vessels in the kidneys that filter waste from the blood. In normal glomeruli, protein is not allowed to leak from the capillary lumen into the urine. However, an increase in intracapillary pressure or structural damage to the glomerular membrane can lead to the leakage of protein from the plasma into the initial urinary fluid, known as Bowman's space. The process leading to the development of microalbuminuria may vary with the severity of hypertension, with a hemodynamic cause related to significant increases in intraglomerular capillary pressure being more likely in mild hypertension, while glomerular injury may be more significant in moderate-to-severe hypertension.

Diabetes Mellitus

It's worth noting that microalbuminuria is considered an early sign of diabetic kidney disease (DKD), which is a common complication of diabetes. DKD is the leading cause of end-stage renal disease and a major cause of cardiovascular disease and mortality in people with diabetes. Early detection and management of microalbuminuria can help to prevent or delay the progression of DKD. Treatment strategies may include lifestyle modifications such as improving glycemic control and blood pressure, as well as medications such as ACE inhibitors or ARBs.

The presence of microalbuminuria in patients with diabetes is significantly associated with an increased risk of early mortality. Studies have found that patients with type 2 diabetes and microalbuminuria are at a four-fold higher risk of premature death from a cardiovascular event compared to those with normal levels of albumin excretion. Interestingly, this increased risk appears to start at levels of urinary albumin excretion rates (UAERs) between 8 and 10 μg/min, which is well below what is currently considered a normal range.

In a meta-analysis exploring the association between microalbuminuria and mortality in type 2 diabetes, it was found that microalbuminuria was linked to a twofold increase in cardiovascular morbidity and mortality (with an odds ratio [OR] of 2 and 95% confidence interval [CI] of 1.4 to 2.7), as well as more than doubling the rate of all-cause mortality (with an OR of 2.4 and 95% CI of 1.8 to 3.1). Even after adjusting for traditional risk factors, microalbuminuria was still linked to a twofold increase in the risk of a cardiovascular event.

In the HOPE study, which included over 9000 high-risk participants, microalbuminuria was present in 33% of patients with diabetes compared to 15% of those without diabetes. This condition was found to be a powerful predictor of all-cause mortality and various cardiovascular outcomes such as myocardial infarction, stroke, cardiovascular death, and hospitalization for heart failure. The study also showed that the risk of cardiovascular disease extends into the normal range of urinary albumin excretion rate.

Microalbuminuria and target organ damage

Left Ventricular dysfunction

The LIFE study examined patients with hypertension and left ventricular (LV) hypertrophy, 23% of whom had microalbuminuria. The study found that the presence and severity of microalbuminuria increased in patients with greater LV mass and dysfunction, regardless of systolic blood pressure, age, race, or coexisting diabetes. It is unclear whether there is a linear relationship between the degree of microalbuminuria and the severity of LV hypertrophy. In patients with type 2 diabetes, microalbuminuria is closely associated with systolic and diastolic LV dysfunction, even when considering other risk factors, and it increases the risk of hospitalization for heart failure by threefold.

Myocardial Ischemia and Infarct

Microalbuminuria can indicate the presence of silent myocardial ischemia, a condition where there is reduced blood flow to the heart muscle without any symptoms. ST-T changes on an electrocardiogram are a possible way to detect silent ischemia. Patients with microalbuminuria and ST-T changes have a significantly higher risk of cardiovascular and all-cause mortality than patients with the same electrocardiographic changes but no microalbuminuria. Therefore, measuring urinary albumin excretion in patients with ST-T changes can help to better assess their cardiovascular risk.

Microalbuminuria can be identified within a few hours after a heart attack. This condition is related to the size of the infarction and is also proportional to the rate of in-hospital death in patients, regardless of whether they have hypertension. Furthermore, microalbuminuria one week after the heart attack is a robust independent predictor of mortality within a year.

Cerebrovascular disease

Patients with cerebrovascular disease commonly exhibit microalbuminuria, and this finding is associated with an increased risk of stroke, independent of other risk factors for cerebrovascular disease. This association has been observed in both men and women.

In patients with type 2 diabetes and hypertension, a strong correlation between microalbuminuria and carotid artery intima-media thickness has been found, indicating that microalbuminuria might be a marker for early development of carotid artery atherosclerosis. This link between microalbuminuria and atherothrombotic stroke is suggested by these associations. In one study, microalbuminuria was found to be three times more common in patients who had an ischemic stroke than in those with risk factors for ischemic stroke other than microalbuminuria.

Managing microalbuminuria related risk

The main objectives of treatment are to reverse microalbuminuria and prevent its progression to persistent clinical albuminuria. Over the years, there have been significant changes in the evolution of microalbuminuria. The progression rates to nephropathy have decreased from those reported in the 1960s and 1970s, while the regression rates to normoalbuminuria have increased. These improvements can be attributed to more intensive hypertension treatment and the use of renin-angiotensin system inhibitors.

Based on observational data from diabetes trials, a threshold of mean arterial pressure (approximately 92 mm Hg) has been calculated at which no progression of microalbuminuria would be expected to occur. Patients with type 1 or type 2 diabetes who have remained normoalbuminuric have consistent mean arterial pressures of approximately 90 mm Hg. Theoretically, therefore, an argument could be made for a BP target of 125/75 mm Hg in the management of microalbuminuria.

Tight versus less tight control of BP

Newly diagnosed patients with type 2 diabetes and hypertension were divided into two groups - tight and less-tight BP control - in the United Kingdom Prospective Diabetes Study (UKPDS). The group with tight control (mean 144/82 mm Hg) saw a one-third reduction in the risk of developing micro- or macroalbuminuria compared to the less-tight control group (mean 154/87 mm Hg). This was observed in the study.
The Appropriate Blood Pressure Control in Diabetes (ABCD) trial demonstrated a similar finding, where aggressive blood pressure control over 5 years achieved a mean BP of 132/78 mm Hg in patients with type 2 diabetes, resulting in a slowed progression to micro- and macroalbuminuria. In comparison, the comparator group had a mean BP of 137/81 mm Hg. The results were consistent regardless of whether blood pressure reductions were achieved with enalapril or nisoldipine.

Treatment with ACE inhibitors

The 2-year EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes Mellitus (EUCLID) study enrolled patients with type 1 diabetes, normoalbuminuria, and BP of 155/90 mm Hg. The study found that treatment with lisinopril 20 mg/day, compared to placebo, significantly delayed an increase in the UAER during treatment. The group treated with lisinopril had a diastolic BP average of 74 mm Hg, which was significantly lower than the average of 77 mm Hg observed in the placebo group ($P < .0001$).55

A meta-analysis examining the effect of angiotensin

converting enzyme (ACE) inhibitor treatment on patients with type 1 diabetes and microalbuminuria found that the use of ACE inhibitors reduced the risk of progression from micro- to macroalbuminuria by 62% and increased the probability of regression to normoalbuminuria three-fold compared to placebo. The treatment effect of ACE inhibitors was found to vary with baseline urine albumin excretion rate (UAER), with patients having a baseline UAER of 200 g/min estimated to have a 74.1% reduction in UAER compared to those with a baseline UAER of 20 g/min who had a 17.8% reduction. These effects were independent of other baseline risk factors.

The HOPE study showed that the use of ramipril 10 mg/day resulted in a significant 30% reduction in the risk of primary cardiovascular end points in patients with type 2 diabetes and microalbuminuria, compared to a 15% reduction in patients with type 2 diabetes but without microalbuminuria. This suggests that the use of ACE inhibitors in patients with type 2 diabetes and microalbuminuria may have a greater cardiovascular protective effect.

Treatment with ARB

Several recent studies have examined the effects of angiotensin receptor blockers (ARB) in reducing the risk of progression to nephropathy and macroalbuminuria. In the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA-2) study, treatment with irbesartan 300 mg led to a 70% reduction in the progression to overt nephropathy (clinical albuminuria) compared to a control group receiving antihypertensive agents that excluded ACE inhibitors and ARBs. Both groups had similar diastolic BP (83 mm Hg), but the control group had 3 mm Hg higher systolic BP (144 vs 141 mm Hg). However, after adjusting for this difference, irbesartan 300 mg still showed superior efficacy.

The renoprotective effect of an ARB was demonstrated in the Microalbuminuria Reduction with Valsartan (MARVAL) study. Patients with type 2 diabetes and microalbuminuria, with and without hypertension, were assigned to receive either valsartan or the calcium channel blocker amlodipine. Despite similar reductions in blood pressure between the two groups after 6 months, valsartan reduced UAER by 44%, while amlodipine decreased it by only 8% ($P < .001$). Valsartan also showed a higher frequency of reversal to normoalbuminuria (29.9%) compared to amlodipine (14.5%) ($P < .001$). These results suggest that the efficacy of valsartan in reducing UAER is largely independent of blood pressure reduction. Additionally, in a normotensive subgroup with minimal but equivalent reductions in blood pressure, valsartan significantly reduced UAER but amlodipine did not.

Other Treatments

Some studies have evaluated other treatment options. For example, combination therapy with an ARB plus an ACE inhibitor may further reduce albuminuria, although the reduction may be related to greater lowering of BP.60,61

The PREMIER study investigated the effectiveness of diuretic plus ACE inhibitor therapy compared to enalapril alone in patients with type 2 diabetes and elevated urinary albumin excretion rate (UAER). The study found that low-dose perindopril plus indapamide treatment for one year effectively lowered BP and UAER compared to enalapril alone. Even after adjustment for the small difference in BP between the two treatments, the antialbuminuric effect of the diuretic plus ACE inhibitor therapy was significantly better (42% vs 27%, $P < .002$). Similarly, the NESTOR investigation found that indapamide is equally effective as enalapril in reducing BP and UAER in patients with type 2 diabetes, hypertension, and microalbuminuria.

Although ACE inhibitors and ARBs are primarily used for their ability to lower arterial hypertension, they have also been shown to achieve greater reductions in urinary protein compared to other antihypertensive drugs at equivalent blood pressure levels. Furthermore, some treatments, such as lipid-lowering therapy and insulin sensitization, have demonstrated that they can reduce albuminuria and protect target organs through mechanisms other than blood pressure reduction. In the Steno 2 study, patients with type 2 diabetes who received targeted, intensified, multifactorial interventions, including the use of an ARB or ACE inhibitor, had significantly fewer cardiovascular events, less retinopathy and neuropathy, and less progression of nephropathy after 7.8 years of treatment compared to those who received conventional treatment according to Danish Diabetes Association guidelines. These results suggest that the renoprotective effects of these agents may be due to more than just blood pressure reduction.

Conclusion

Microalbuminuria is a marker that can be easily measured and is an independent predictor of increased risk of cardiovascular morbidity and mortality in both the general population and in patients with diabetes and hypertension. Even apparently healthy populations in Europe and the United States have shown a significant prevalence of microalbuminuria. A linear relationship has been observed between the degree of urinary albumin excretion and cardiovascular risk. However, the underlying cause of the relationship between microalbuminuria and increased cardiovascular morbidity and mortality is currently unclear, and further studies are needed to explain this association.

There is strong evidence suggesting that using ARB or ACE inhibitors to block the renin angiotensin system is the most effective current approach to regress microalbuminuria and prevent its progression to nephropathy. Combining these drugs with a diuretic can also lead to antialbuminuric effects. By employing multifactorial pharmacologic interventions to normalize elevated urinary albumin, significant protection of cardiovascular and end organs is likely to be achieved.

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