REVIEW

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Microalbuminuria: Is it a valid predictor of cardiovascular risk?

ABSTRACT

Microalbuminuria strongly predicts cardiovascular morbidity and mortality, clinical nephropathy, and progression of renal disease in high-risk populations. We recommend screening patients with type 2 diabetes, older patients with type 1 diabetes, and older patients with stage 2 hypertension or higher (ie, ≥ 160/100 mm Hg).

KEY POINTS

Microalbuminuria is defined as albumin excretion of 20 to 200 µg/minute (30–300 mg/24 hours) in a 24-hour sample, or an albumin-to-creatinine ratio greater than 30 mg/g in a first morning midstream sample.

In type 2 diabetes, microalbuminuria is strongly associated with traditional cardiovascular risk factors and is a harbinger of later cardiovascular complications.

In type 1 diabetes, microalbuminuria might be an independent predictor of cardiovascular complications, particularly in patients older than 45 years.

In people older than 45 years with stage 2 or higher hypertension, microalbuminuria seems to be strongly associated with several traditional and nontraditional cardiovascular risk factors and with target-organ damage.

Whether microalbuminuria is a good predictor of cardiovascular disease in people with well-controlled essential hypertension remains to be determined.

PROTEIN IN THE URINE is bad, even in small amounts. We are finding that people with microalbuminuria—protein in the urine at levels too low to detect with standard dipstick tests—are at increased risk not only for overt kidney disease but also for cardiovascular disease and death.

In this article we review:

- The magnitude of the risk in people with diabetes, hypertension, and the metabolic syndrome
- Possible mechanisms of risk
- Our recommendations for measuring microalbuminuria in clinical practice.

DEFINITION OF MICROALBUMINURIA

The median daytime excretion of albumin, the major plasma protein, is 4 to 6 µg/minute in population-based studies, and the 90th percentile is about 20 µg/minute or 30 mg/24 hours.

The standard urinalysis dipstick, however, can detect albumin only at levels greater than 30 mg/dL—300 mg/24 hours if the output is 1 L. Anything above this level of excretion is called *macroalbuminuria*.

Microalbuminuria is defined as the range in between: urinary excretion of albumin of 20 to 200 µg/minute or 30 to 300 mg/24 hours.[1]

The albumin-to-creatinine ratio

Microalbuminuria can also be defined in terms of the urinary albumin-to-creatinine ratio (TABLE 1). A ratio greater than 30 mg/g in the first voided sample in the morning (clean, midstream) is considered abnormal.[1]

TABLE 1

Definitions of abnormal albumin excretion

MEASURE	NORMOALBUMINURIA	MICROALBUMINURIA
Albumin excretion rate*	< 30 mg/24 hours < 20 µg/minute	30–300 mg/24 hours 20–200 µg/minute
Albumin-to-creatinine ratio†	< 30 mg/g creatinine	30–300 mg/g creatinine

*24-hour collection
†First morning collection

The concentrations of albumin and creatinine in the first urine in the morning correlate very well with those in 24-hour samples, and an overnight albumin-to-creatinine ratio greater than 2 mg/mmol predicts urinary albumin excretion in the range of microalbuminuria with high sensitivity and specificity.[2]

Thus, it is not always necessary to obtain a 24-hour urine sample to have a reliable evaluation. Furthermore, the concentration of albumin in these early urine samples is highly predictive of morbidity and mortality in high-risk populations (ie, patients with established atherosclerotic vascular disease, diabetes, or more than one risk factor for atherosclerosis).

Urinary albumin levels vary widely from sample to sample

ISSUES IN MEASURING ALBUMIN EXCRETION

Urinary albumin levels can vary widely from sample to sample in the same patient, with day-to-day intraindividual coefficients of variation as high as 50%.[3] Factors that can increase urinary albumin excretion include urinary tract infection, congestive heart failure, exercise, fever, poor glycemic control, and vaginal discharge.[3] By obtaining a first morning sample we can minimize at least the effect of exercise.

In view of all of these considerations, the American Diabetes Association and the National Kidney Foundation demand at least two elevated albumin-to-creatinine ratios separated by 3 or 6 months to make the diagnosis of microalbuminuria.[4]

There are several laboratory methods for measuring urinary albumin excretion. All of them appear to have similar sensitivity and specificity.[2] The intra-assay and interassay variations have been reported to be between 2% and 8%.[2] For every test, the final choice among proposed cutoff values needs to be based on large outcome studies.

Albumin in the urine is very stable at normal temperatures, so urine samples do not need to be frozen when sent to other laboratories, and the storage process and time do not increase the variations of the current techniques. Therefore, microalbuminuria can be easily measured in most patients.

MICROALBUMINURIA AND DIABETES

Viberti et al[5] in 1982 reported that microalbuminuria predicted clinical nephropathy and death in patients with type 1 diabetes.

Mogensen et al[6] in 1984 reported a significant increase in cardiovascular and total mortality in patients with type 2 diabetes who had microalbuminuria. In that pioneer study, the authors divided patients with type 2 diabetes into three groups according to urinary albumin concentrations (30–140 µg/mL, 16–29 µg/mL, and < 15 µg/mL) and also followed a group of normal controls. At 9 years, the highest total mortality rate was in the group with diabetes and the highest rate of albumin excretion.

Subsequently, several cross-sectional, retrospective, and prospective studies in patients with type 2 diabetes consistently demonstrated an increased incidence of cardiovascular disease and cardiovascular mortality in those with microalbuminuria.

Dinneen and Gerstein[7] confirmed these findings in a meta-analysis of 11 longitudinal

studies that included 2,138 patients with type 2 diabetes and microalbuminuria followed for a mean of 6.4 years. The overall odds ratio for cardiovascular morbidity or mortality was 2.0 (95% confidence interval [CI] 1.4–2.7), and the odds ratio for total mortality was 2.4 (95% CI 1.8–3.1).

In other words, microalbuminuria doubled the risk of having a cardiovascular event; the risk was similar to or even higher than that conferred by established atherosclerotic risk factors. These findings held even after adjustments for other cardiovascular risk factors frequently associated with microalbuminuria such as age, hypertension, current smoking, hyperlipidemia, left ventricular hypertrophy, abdominal obesity, and hyperglycemia.

Is the risk due to later overt nephropathy?

A substudy of the Heart Outcomes Prevention Evaluation (HOPE) study[8,9] found that microalbuminuria was a strong predictor of risk for cardiovascular disease even after adjustment for renal function. Thirty eight percent of the HOPE study patients had diabetes, mostly type 2.

This is noteworthy, because microalbuminuria has not yet been clearly demonstrated to predict overt nephropathy in type 2 diabetes. Hence, the main reason for the high frequency of cardiovascular disease in this population is not clearly related to the later development of diabetic nephropathy.

In type 1 diabetes, on the other hand, microalbuminuria is a good predictor of renal disease as well as cardiovascular disease.[10,11] In this population, microalbuminuria has also been found to be associated with high blood pressure, long-standing diabetes, and poor glycemic control.

In type 1 diabetes, in contrast to type 2 diabetes, the relation between microalbuminuria and cardiovascular morbidity and mortality has been mainly attributed to the later development of overt nephropathy. However, in adults with type 1 diabetes, microalbuminuria alone has been associated with excess cardiovascular mortality.[12,13]

For example, in a Scandinavian study[12] of 939 adults with type 1 diabetes followed for 10 years, the relative risk for cardiovascular death in patients presenting with microalbuminuria was 1.87 (95% CI 1.03–3.40); in those with overt nephropathy it was 2.97 (95% CI 1.68–5.24). (Microalbuminuria was defined as urinary albumin excretion of 31 to 299 mg/24 hours, and overt nephropathy was defined as excretion of more than 300 mg in at least two of three consecutive 24-hour urine samples.)

These findings were not confirmed, however, in the DCCT (Diabetes Control and Complications Trial),[14] the largest study of type 1 diabetes ever conducted in the United States and Canada, with 1,441 young patients who underwent either intensive or standard diabetic therapy. Even though the intensive therapy group had a 39% lower incidence of microalbuminuria and lower rates of hypertension, dyslipidemia, and overt nephropathy, their incidence of macrovascular events was not significantly different from that in the standard therapy group.

Nevertheless, the DCCT patients were not expected to have a significant number of macrovascular problems because their average age was only 27 ± 7 years and they had had diabetes for only 5.6 ± 4.1 years when the study began. In patients with type 1 diabetes, the cardiovascular consequences of microalbuminuria seem to become apparent only after about 10 years.

Urine samples for protein need not be frozen

Diabetes and microalbuminuria: Conclusions

In type 2 diabetes, microalbuminuria is strongly associated with traditional cardiovascular risk factors and is a harbinger of later cardiovascular complications. In type 1 diabetes, microalbuminuria *might* be an independent predictor of cardiovascular complications, particularly in patients older than 45 years.

MICROALBUMINURIA AND HYPERTENSION

Parving et al[15] in 1974 were the first to report microalbuminuria in hypertensive patients without diabetes. Since then, several studies suggested that microalbuminuria occurs in about 30% of patients with mild or moderate hypertension, ranging from 7% to 40% depending on age and ethnic group.[16,17]

The magnitude of albuminuria correlates

with the severity of hypertension, particularly with systolic pressure and pulse pressure.[18,19]

As in diabetic patients, microalbuminuria in hypertensive patients is associated with several traditional and nontraditional markers of cardiovascular disease.[17] For this reason, to accept microalbuminuria as a risk factor for atherosclerotic disease, adjustment for traditional and novel risk factors is mandatory. And indeed, microalbuminuria has been shown to be an independent risk factor for cardiovascular disease and death in hypertensive patients.

Retrospective and cross-sectional studies

Several retrospective and cross-sectional studies reported that the prevalence of cardiovascular disease is significantly higher among hypertensive patients with microalbuminuria than hypertensive patients without microalbuminuria.

In a large cross-sectional study[20] of 11,343 nondiabetic hypertensive patients, those with microalbuminuria had a significantly higher prevalence ($P < .001$) of:

- Coronary artery disease (31% vs 22%)
- Left ventricular hypertrophy (24% vs 14%)
- Previous stroke (6% vs 4%)
- Peripheral vascular disease (7% vs 5%).

In the patients with microalbuminuria and cardiovascular disease, the amount of albumin in the urine was also significantly higher than in those who did not present with cardiovascular disease ($P < .001$).

About 30% of patients with mild or moderate hypertension have microalbuminuria

Prospective studies

Few prospective studies have addressed whether microalbuminuria predicts cardiovascular disease and mortality in patients with hypertension. Nevertheless, these few studies tended to support this observation.

For example, a European prospective study[21] of 2,085 nondiabetic hypertensive patients followed for 10 years found that the relative risk of ischemic heart disease in patients with microalbuminuria was 2.3 (95% CI 1.3–3.9), independent of age, gender, total cholesterol level, high-density lipoprotein (HDL) cholesterol level, body mass index, smoking status, and blood pressure.

In addition, in the subgroup of 245 hypertensive patients followed for 5 years in the Hoorn study,[22] microalbuminuria was the best predictor of cardiovascular mortality, with an adjusted relative risk of 2.8 (95% CI 1.2–6.3).

However, not all the studies support the positive relation between microalbuminuria and cardiovascular disease in patients with hypertension.

The HARVEST study[23] compared three groups: patients up to 45 years old with sustained stage 1 hypertension (blood pressure 140/90–159/99 mm Hg), similar patients with "white coat" hypertension, and normotensive controls. The mean left ventricular wall thickness was greater in both groups of hypertensive patients than in controls, but the albumin excretion rate was higher only in those with sustained hypertension.

In the Risk Factor Intervention Study in Sweden,[24] microalbuminuria was an independent predictor of cardiovascular mortality in patients with diabetes and hypertension, but not in people without diabetes or hypertension. Surprisingly, the same study showed an increased risk of cardiovascular events in hypertensive patients without diabetes whose albumin excretion was higher than 200 mg/24 hours.

Microalbuminuria and hypertension: Conclusions

In people older than 45 years with stage 2 or higher hypertension (blood pressure ≥ 160/100 mm Hg), microalbuminuria seems to be strongly associated with several traditional and nontraditional cardiovascular risk factors and with target-organ damage. The increased cardiovascular risk may be due to microalbuminuria per se, its associated conditions, or both. Moreover, the higher the level of urinary albumin excretion, the higher the likelihood of cardiovascular disease and cardiovascular mortality.

Whether microalbuminuria is a good predictor of cardiovascular disease in people with well-controlled essential hypertension remains to be determined. Antihypertensive therapy can lower the albumin-creatinine ratio, thus modifying the level of the risk indicator and confounding the relationship between microalbuminuria and cardiovascular disease.

POSSIBLE MECHANISMS OF DAMAGE

Microalbuminuria may be related to cardiovascular damage by several biological pathways (TABLE 2).

Renal dysfunction. The amount of albumin in the urine is traditionally thought to depend on the electrochemical characteristics of the glomerular membrane barrier, the intraglomerular pressure, and tubular reabsorption. In this view, changes in any of these may translate into an excess of urinary albumin excretion.

However, nondiabetic people with hypertension and microalbuminuria were found to have normal urinary excretion of beta-2 microglobulin, a marker of tubular protein transport.[15] This suggests that microalbuminuria results from an increased filtered albumin load rather from decreased tubular reabsorption.

Systemic blood pressure, on the other hand, correlates with intraglomerular pressure and microalbuminuria.[18,25] Moreover, systolic blood pressure is one of the most relevant determinants of microalbuminuria.[17] However, microalbuminuria continues to be an independent risk factor for cardiovascular disease even after adjustment for blood pressure.

In hypertensive patients, microalbuminuria is related to salt sensitivity, absence of a nocturnal dip in blood pressure, and higher mean 24-hour blood pressure measurements. All of these factors have been related to a high prevalence of cardiovascular disease in hypertensive populations.[25,26]

Metabolic syndrome. Microalbuminuria is also associated with the metabolic syndrome, which includes insulin resistance, low HDL cholesterol levels, high triglyceride levels, and truncal obesity.

Current evidence strongly suggests that hyperinsulinemia is associated with a greater risk for cardiovascular disease.[27] Patients with type 1 and type 2 diabetes mellitus with microalbuminuria are more insulin-resistant than those without microalbuminuria.

Insulin per se could lead to arteriosclerosis, renal damage, and microalbuminuria, either directly by its trophic actions, or indirectly by its effects on blood pressure and lipid metabolism.[17]

TABLE 2

Factors that cluster with microalbuminuria

- Insulin resistance
- Central obesity
- Low levels of high-density lipoprotein cholesterol
- High triglyceride levels
- Systolic hypertension
- Lack of nocturnal dip in blood pressure on 24-hour monitoring
- Salt sensitivity
- Endothelial dysfunction
- Hypercoagulability
- Impaired fibrinolysis
- Renal dysfunction

Endothelial dysfunction. Microalbuminuria has also been proposed as a marker of endothelial dysfunction, as microalbuminuria has been related to elevated concentrations of accepted markers of endothelial dysfunction such as von Willebrand factor, thrombomodulin, and activated factor VII.[28] However, the results from small studies that assessed endothelial function through forearm blood flow using plethysmography or flow-mediated dilation of the coronary or brachial arteries have been controversial.[29–31]

Whether endothelial dysfunction detected by vasodilatation techniques is an earlier marker of subclinical atherosclerotic disease than microalbuminuria (or vice versa) warrants further consideration.

Inflammation. Microalbuminuria could also be considered a marker of inflammation in multiple inflammatory processes such as sepsis, trauma, acute pancreatitis, and acute respiratory distress syndrome.[32]

Two recent studies reported on the association of microalbuminuria with markers of chronic inflammation.[33,34] In the larger study,[33] mean levels of C-reactive protein and fibrinogen were higher in microalbuminuric type 2 diabetic patients than in nonmicroalbuminuric subjects; however, C-reactive protein was not related to microalbuminuria

Several pathways may link microalbuminuria and cardiovascular disease

independently of traditional risk factors.

The relation between C-reactive protein and other inflammatory markers of cardiovascular risk and microalbuminuria in other high-risk populations deserves additional investigation.

Transvascular escape of albumin. Finally, there is some evidence that microalbuminuria reflects a generalized increase in transvascular escape of albumin.[17] In animals, increased transvascular albumin transport is associated with increased transport of lipoproteins into the arterial wall.[17] Whether this induces or enhances the development of atherosclerotic plaque in the vessel wall, and therefore could be the link between microalbuminuria and atherosclerotic disease, is unknown.

In this regard, microalbuminuria correlates with the thickness of the intima of the common carotid artery, a sonographic and quantitative surrogate measurement of systemic atherosclerosis.[35]

MICROALBUMINURIA: PRACTICAL PERSPECTIVE

Enough proof has been collected to support the role of microalbuminuria as a predictor of cardiovascular events in high-risk populations. Therefore, in the clinical setting, microalbuminuria could be a valuable tool in cardiovascular risk assessment in:

- Patients with type 2 diabetes
- Older patients with type 1 diabetes
- Older patients with hypertension, stage 2 or higher.

Screening for microalbuminuria on a regular basis may help to identify a subgroup of patients with a cluster of proven and modifiable risk factors who are at high risk for cardiovascular disease and need more intensive therapy and closer follow-up because they could benefit from early intervention and treatment.

Screening for microalbuminuria might identify a group at high risk

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