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Microalbuminuria
A Useful Marker of Cardiovascular Disease

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Review

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Leakage of small amounts of proteins in urine has been considered since 1980s a crucial sign of early kidney disease, especially in diabetic patients. An increasing interest in microalbuminuria as a cardiovascular risk marker has been more recently considered. Many studies linked microalbuminuria to early cardiovascular disease, as a marker of endothelial dysfunction, not only in diabetic patients, but also in hypertensive patients and in general population. Microalbuminuria is considered nowadays by guidelines as a cost-effective marker of subclinical organ damage in hypertensive patients and should be checked routinely in hypertensive patients. Assessing subclinical organ damage is recommended not only at the level of screening, but also during treatment. Microalbuminuria is also considered as a treatment outcome marker and useful for understanding the ability of a given therapeutic intervention to regress organ damage or slow down its progression.

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INTRODUCTION

Leakage of large amounts of proteins in urine has been considered a crucial sign of kidney disease for centuries. In the early 1980s, with the development of biotechnology, medical community was able to detect small amounts of albumin in urine nondetectable with previous colorimetric techniques. This condition was confusingly named microalbuminuria meaning "micro" amounts of albumin and not a smaller albumin size.

Microalbuminuria was first proposed by diabetologists as a marker of early stage of diabetic nephropathy.[1] Since then, our knowledge of albumin leakage has expended. It was proposed as a marker of kidney disease and more recently as a predictor marker of cardiovascular morbidity and mortality, not only in diabetic patients, but also in hypertensive nondiabetic patients.[2] Microalbuminuria is strongly associated with risk for cardiovascular disease[3]; however, this link remains somewhat controversial and poorly understood. It is not clear whether microalbuminuria is a risk factor for cardiovascular disease, a risk marker or indicator for cardiovascular disease, or a marker of endothelial dysfunction. In fact, a risk factor must be a variable that are causally related to cardiovascular disease, whereas risk marker is indirectly associated with cardiovascular disease. It reflects pathophysiologic mechanism that causes atherosclerosis.

There is no direct evidence that microalbuminuria can cause cardiovascular disease (ie atherosclerosis), but the possibility that, for example, increased renal protein trafficking through glomerular basement membrane and tubules elicits a renal response that enhances the atherothrombotic process have to be well considered; otherwise, microalbuminuria is a widely recognized, strong, and independent risk marker of cardiovascular disease among hypertensive individuals, with or without diabetes mellitus. Microalbuminuria was recently proposed

by the European Society of Hypertension guidelines as one of the best cost-effective tools to diagnose target organ damage in hypertensive patients.[2]

DEFINITION AND MEASUREMENT

Microalbuminuria is defined as a small amount of urine leakage of albumin not detected by available techniques usually used as colorimetric techniques. The dipstick techniques could detect concentrations only above 300 mg/L. Levels of albumin excretion below the sensitivity of the dipstick have been referred as microalbuminuria. It has become possible to measure microalbuminuria using new more sensitive techniques; those commercially available are immune-based techniques such as immunoturbidimetry, immunonephelometry and enzyme-linked immunosorbent assays. These methods appear to have similar sensitivity and provide similar results.[4] Using these methods, the lower limit of microalbuminuria has been defined as the upper boundary of the 95% confidence interval (CI) of the distribution of urinary albumin concentration in the normal population, fixed at 30 mg/d (Table). However, it is important to standardize the measurement of microalbuminuria and the urine collection technique to have comparative results between studies.[5]

Semi-quantitative measurement of micro-albuminuria were later developed with sensitive urine dipstick techniques such as the Micral® test strip (Roche Laboratories, Basel, Switzerland). Recently, an accurately and rapidly measurement of albumin was proposed using desktop machines (HemoCue Urine Albumin, Bayer DCA 2000, Bayer Diagnostics, Tarrytown, NY, USA), which is extremely valuable in the setting in which the practicing physician needs to diagnose the presence of microalbuminuria, especially where no central laboratory facilities are available or in remote areas.

Although the 24-hour urine collection sample remains the "gold standard" for measuring microalbuminuria, the procedure of collecting is cumbersome for patients and inadequate for large trials. Other urine sample collections are proposed such as the first urine void in the morning or a random urine sample. For the urine spot collection, microalbuminuria is influenced by variation in urinary volume and higher albumin concentration when urine is more concentrated and vice versa. That is why it is preferable to use the albumin-creatinine ratio, correcting for the variations in urinary volume. There is no difference between 24-hour urinary albumin concentration and albumin-creatinine ratio in their ability to estimate microalbuminuria as shown by the study of Gansvoort and colleagues.[6]

Since no worldwide standardisation of urine sample collections for microalbuminuria is available, it makes the choice quite confusion for the practicing doctor. Moreover, urinary albumin concentration can be falsely high in the presence of urinary tract infection or genital leakage and it depends on physical activity, age, and sex, as well.

MICROALBUMINURIA AS A MARKER

Microalbuminuria and Organ Damage

It has been suggested that microalbuminuria is simply a marker of generalized atherosclerosis and that this explains its association with clinical cardiovascular disease. Microalbuminuria and cardiovascular disease may be linked not by a common risk factor, but rather by a common pathophysiologic process. In fact, it have been proposed that dysfunction of the vascular endothelium causes both microalbuminuria and cardiovascular disease.[7] Generalized endothelial dysfunction is now considered a transducer of atherogenic risk factors and is thought to play an important role in both the initiation and the

Definitions and Classification of Albuminuria

Category	24-hour Urine Albumin (mg/24 h)	Timed Overnight Albumin (µg/min)	Spot Morning Sample		
			Albumin (mg/L)	Albumin-creatinine ratio (mg/mmol)	Albumin-creatinine ratio (mg/g)
Normal range	< 30	< 20	< 20	< 2.5 (males) < 3.5 (females)	< 20 < 30
Microalbuminuria	30 - 300	20 - 200	20 - 200	2.5 - 25 (males) 3.5 - 35 (females)	20 - 200 (males) 30 - 300 (females)
Macroalbuminuria	> 300	> 200	> 200	> 25 (males) > 35 (females)	> 200 (males) > 300 (females)

progression of atherosclerosis. Therefore, an association of microalbuminuria with generalized endothelial dysfunction, if exists, could explain why microalbuminuria strongly predicts cardiovascular disease.

These findings support the concept that impaired endothelial nitric oxide synthesis plays a role in the association of microalbuminuria with cardiovascular disease risk regardless of whether diabetes is present or not. Recent large population-based studies illustrate this. It was shown that endothelial nitric oxide synthesis, as estimated from ultrasonically measured brachial artery endothelium-dependent, flow-mediated dilation, was impaired in individuals with diabetes mellitus as compared with those without and also was impaired in individuals with microalbuminuria as compared with those without, regardless of whether they had diabetes or not.[8,9] After adjustment for age, sex, baseline arterial diameter, and other potential confounders, flow-mediated dilation was 0.038 mm (95% CI, 0.001 to 0.075) lower in the presence of microalbuminuria ($P = .04$) and decreased linearly across microalbuminuria categories (by 0.027 mm [95% CI, 0.007 to 0.046] per category [< 2, ≥ 2 to 5, ≥ 5 to 10, and ≥10 mg/mmol] increase of microalbuminuria; $P = .007$).[9] Endothelium-independent nitroglycerin-induced vasodilatation was similar in individuals with and without microalbuminuria. All results were similar in individuals without and with diabetes mellitus. Microalbuminuria is then and since 1989 was considered as a mirror of generalized endothelial dysfunction, the so called "steno-hypothesis.[10]"

Variability of the vascular state as determined by microalbuminuria may be associated with susceptibility to subsequent organ damage.[11] As target organ damage, changing of vascular compliance is a strong predictor of cardiovascular disease. The carotid-femoral pulse wave velocity is the gold standard in the evaluation of arterial compliance and stiffness. In 70 newly diagnosed patients with hypertension, higher values of pulse wave velocity was demonstrated in those with microalbuminuria, even after correction for 24-hour systolic and diastolic blood pressure and body mass index. Moreover, a tight correlation was found between urinary albumin excretion and pulse wave velocity.[12] Similar findings were noted in type 1 diabetic patients.[13]

Microalbuminuria as a Cardiovascular Risk Marker in General Population

The prevalence of microalbuminuria has been established by numerous studies between 7% and 10% in the general population.[14,15] The development of microalbuminuria is usually linked to a kidney disease[16]; however, it is not a specific renal marker.

Apart from patients with diabetes mellitus and hypertension, microalbuminuria seems to be associated with all-cause and cardiovascular mortality in the general population. This was shown in PREVEND (Prevention of Renal and Vascular End-Stage Disease) study which was designed to investigate the natural course of increased levels of urinary albumin and the relationship with renal and cardiovascular disease in the general population.[17] The results provide compelling evidence that microalbuminuria is a strong predictor of cardiovascular mortality, independent of other cardiovascular risk factors.[18] The relative risk increased by 1.5 in the normal high range of albuminuria, and by 2 in microalbuminuria, and 2 in macroalbuminuric patients. This was confirmed by the Framingham Heart Study where low level of albuminuria, well below the currently recommended threshold, conferred an increased risk for cardiovascular events in normotensive individuals without diabetes mellitus and with normal kidney function.[19]

The assumption is supported by a recent meta-analysis where the link between albuminuria and cardiovascular disease was analyzed in a total of 26 cohort studies with more than 169 000 individuals and 7117 coronary events. Patients with microalbuminuria had a 50% greater risk of coronary heart disease than those without it (risk ratio, 1.47; 95% CI, 1.30 to 1.66). In those with macroalbuminuria, the risk was more than doubled (risk ratio, 2.12; 95% CI, 1.87 to 2.52).[20]

Microalbuminuria as a Cardiovascular Risk Marker in Hypertensive Diabetic Patients

Dinneen and Gerstein[21] reported in a systematic review that microalbuminuria among individuals with type 2 diabetes mellitus was associated with a 2.4-fold (95% CI, 1.8 to 3.1) increased risk for cardiovascular death as compared with normoalbuminuria. As shown by Miettinen and coworkers, microalbuminuria is closely related, level dependent, to major cardiovascular events

(stroke and coronary heart disease) and mortality in type2 diabetic patients.[3] The same findings were reported in type 1 diabetic patients. A study that involved 64 asymptomatic patients with type 1 diabetes revealed a higher incidence of myocardial ischemia, detected by stress echocardiography, and electrocardiography, in the presence of microalbuminuria versus normoalbuminuria (25 versus 6.3%; OR 6.3; 95% CI, 1.2 to 37.8; P = .03).[22]

Microalbuminuria is independently associated with inflammatory markers in early type 2 diabetic nephropathy.[23,24] If it is linked to the development of diabetic renal damage, it can also be attributed to the endothelial dysfunction and atheroma formation, since atherosclerosis is an inflammatory disease as proposed by Ross.[25]

Taking in mind microalbuminuria as a marker of generalized vascular dysfunction, it seems confusingly to link prevention of occurrence, reduction, or normalization of microalbuminuria as a marker of kidney improvement under treatment generally using angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Microalbuminuria can simply be related to the improvement of the vascular state.

Microalbuminuria as a Cardiovascular Risk Marker in Hypertensive Nondiabetic Patients

Parving and colleagues first described the essential hypertension and microalbuminuria associations in 1974.[26] They observed that the presence of elevated levels of urinary excretion of albumin in patients who were unsatisfactory treated for hypertension was directly correlated with blood pressure values and tended to be reduced whenever a better control of blood pressure was obtained. These results were later confirmed by various series.[27] In fact, microalbuminuria is detectable in up to 40% of hypertensive population, predominantly in those patients inadequately controlled with treatment. The prevalence of microalbuminuria is associated with the duration and severity of hypertension.[28]

The HARVEST study (Hypertension and Ambulatory Recording Venetia Study) examined the association between microalbuminuria and office and ambulatory blood pressure and their relationship with other recognized cardiovascular risk factors in hypertensive stage 1 middle-aged patients. A 24-hour systolic blood pressure profile was higher in patients with microalbuminuria than it was in those with normal albuminuria (levels < 16 mg/24 h), emerging as the only determinant of microalbuminuria in the logistic regression analysis.[29]

The correlation between microalbuminuria and mortality was apparent from studies that involved high-risk patients.[30] In a HOPE (Heart Outcomes Prevention Evaluation) substudy, urinary albumin excretion predicted mortality in patients who were at a high cardiovascular risk (≥ 55 years of age with cardiovascular disease or diabetes plus at least one other cardiovascular risk factor).[31] In a prospective study that involved individuals who were aged 50 to 75 years, microalbuminuria was associated with an increased risk for cardiovascular death after adjustment for other risk factors (risk ratio, 3.22; 95% CI, 1.28 to 8.06).[32] The risk for all-cause mortality in patients with microalbuminuria was also elevated (risk ratio, 1.70; 95% CI, 0.86 to 3.34), especially among those with concomitant hypertension (risk ratio, 2.87; 95% CI, 1.22 to 6.33).

It was reported that patients with microalbuminuria are characterized by signs of diffuse vascular and organ damage as left ventricular hypertrophy,[33] supporting the statement that microalbuminuria is a marker of early organ damage and cardiovascular changes in patients with essential hypertension.[34]

Microalbuminuria as a Cardiovascular Risk Marker: Threshold?

The association between urinary albumin excretion and the risk for cardiovascular disease does not begin at the traditional thresholds for defining microalbuminuria, but instead has a much lower threshold, starting at 1 mg/mmol creatinine or even less.[19,35]

Gerstein and coworkers[31] demonstrated a continuous positive relationship between urinary albumin excretion and adverse clinical outcomes. Epidemiological and experimental data show that microalbuminuria is associated with an increased risk for all-cause and cardiovascular mortality, cardiac abnormalities, cerebrovascular disease, and possibly, peripheral arterial disease. The association between urinary albumin excretion and adverse clinical outcomes is observed at levels below the current microalbuminuria threshold.[19,31,36] For example, in a 6-year examination of 1568 seemingly healthy individuals (without hypertension, diabetes mellitus, or cardiovascular

disease), the risk for cardiovascular events increased continuously with the level of urinary albumin excretion not only in the whole study population, but also in the subgroup of patients with albuminuria below the threshold for a definition of microalbuminuria.[19]

GUIDELINES

The National Kidney Foundation guidelines recommend a front-end urinary albumin excretion screening in all patients who are at risk for kidney disease, including those with diabetes mellitus, hypertension, family history of chronic kidney disease, age over 60 years, and racial and ethnic minorities.[37] The American Diabetes Association recommends an annual urinary albumin excretion test in all patients with type 1 diabetes of more than 5 years' duration and in all patients with type 2 diabetes mellitus starting at time of diagnosis as a prognostic indicator of cardiovascular risk.[36]

The reappraised European Society of Hypertension 2007 guidelines[38,39] consider microalbuminuria as one of the most cost-effective means to predict target organ damage that should be measured in all hypertensive patients, to adjust cardiovascular risk and adapt treatment.

TREATMENT OF MICROALBUMINURIA

A Treatable Marker

The presence of albuminuria serves as a powerful tool to identify those patients requiring an integrated intervention on cardiovascular risk factors. The PREVEND 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 cardiovascular events in microalbuminuric subjects. Treatment with fosinopril had a significant effect on urinary albumin excretion and a trend in reducing cardiovascular events with a 40% lower incidence (hazard ratio, 0.60; 95% CI, 0.33 to 1.10; $P = .10$).[40] In fact, reduction in microalbuminuria translates to a reduction in cardiovascular events in hypertensive patients. This was reported by many substudies, as the LIFE (Losartan Intervention for End-point Reduction in Hypertension) study.[41] The rate of primary cardiovascular composite end-point was studied according to the 4 levels of baseline and in-treatment value of urinary albumin excretion, presented as albumin-creatinine ratio ($\leq$ 0.5 mg/mmol, 0.5 mg/mmol to 1 mg/mmol, 1 mg/mmol to 3 mg/mmol, and > 3 mg/mmol). The risk for a subsequent cardiovascular end-point increases 3- to 4-fold from the lowest ($\leq$ 0.5 mg/mmol) to the highest (> 3mg/mmol) strata.

Controlling blood pressure per se is the most important strategy to reduce urinary albumin excretion. In the IRMA2 (Irbesartan Microalbuminuria-2) trial, normalization of microalbuminuria in patients with type 2 diabetes mellitus and hypertension occurred in approximately 20% of patients who attained traditional blood pressure goals of 140/90 mm Hg with medications such as diuretics, -blockers, and vasodilators.[42] An improvement of the normalization rate to approximately 33% occurred when the full dosage (300 mg) of irbesartan was used as part of the blood pressure lowering regimen to 140/90 mm Hg. However, even lower blood pressure goals may be advantageous for reducing urinary albumin excretion, and both the American Diabetes Association and the Joint National Committee 7 recommend a lower blood pressure goal of less than 130/80 mm Hg in patients with diabetes mellitus.[38,43] Such a target is revised by the reappraisal of the European Society of Hypertension guidelines for patients with concomitant coronary heart disease; the target systolic blood pressure should be ranged from 130 mm Hg to 140 mm Hg,[36] based on a meta-analysis by Zanchetti and coworkers.[44]

Recent data from the ROADMAP (Randomized Olmesartan and Diabetes Microalbuminuria Prevention) trial can be seen as conflicting.[45] In this study, type2 diabetic patients with normal urinary albumin excretion were treated by olmesartan to prevent microalbuminuria occurrence and therefore reduce cardiovascular morbidity and mortality. This study is considered as positive since the primary end-point was attempted with a significant risk reduction of microalbuminuria occurrence by 23% in favor of olmesartan. However, this microalbuminuria reduction was not associated with cardiovascular morbidity or mortality reduction; the secondary end-point composite of death from cardiovascular causes was significantly in favor of placebo with death 5 times more likely in the olmesartan group. This result, however, can be explained by the ACCORD (Action to Control Cardiovascular Risk in Diabetes)

study,[46] showing a high blood pressure reduction with treatment in older patients with potential coronary ischemic heart disease. In these patients, low blood pressure (< 120/70 mm Hg) can cancel the benefit of microalbuminuria reduction on the occurrence on cardiovascular disease. Patients dead in the ROADMAP had coronary artery disease and blood pressures less than 120 mm Hg. Such results are duplicated in the IDNT (Irbesartan Diabetic Nephropathy Trial).[47]

The use of a combination of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with microalbuminuria and high cardiovascular risk is not effective and should not be recommended. These are the conclusion of the IMPROVE (Irbesartan in the Management of PROteinuric patients at high risk for Vascular Events) study which failed to demonstrate that dual rennin angiotensin system blockade with irbesartan, and ramipril over 20 weeks provided better albuminuria reduction than ramipril alone.[48] These findings suggest that patients with cardiovascular risk and relatively low albumin excretion rate in early-stage disease may only require monotherapy with renin-angiotensin-aldosterone system blocking agents. These conclusions are confirmed by the more recently another clinical trial.[40,50]

Strict glycemic control also delays the onset of microalbuminuria, the progression of microalbuminuria to clinical proteinuria, and the development of nephropathy in patients with either type 1 or type 2 diabetes.[51] Glycosaminoglycans have also been demonstrated to reduce albuminuria.[52] Whether these specific therapeutic strategies will prevent progression of cardiovascular disease because they reduce microalbuminuria is unknown.

There is some debate in the literature as to whether statins reduce urinary albumin excretion.[53-55] According to the results reported in a late-breaking trials session at the XLVII European Renal Association-European Dialysis and Transplant Association Congress by de Zeeuw (not yet published), investigating the effects of statins on urinary protein excretion and kidney function, atorvastatin (80 mg) was protective and rosuvastatin (10 mg or 40 mg) unprotective, and possibly harmful, in diabetic and nondiabetic patients, suggesting that statins are not equivalent on renal features. High-dose atorvastatin significantly reduced proteinuria and did not affect kidney function, whereas rosuvastatin was associated with a significant decline in kidney function and had no effect on proteinuria.[56] Regardless, these drugs are important given the cardiovascular risk. Currently, most guidelines recommend a low-density lipoprotein cholesterol goal of less than 1 g/L for patients with advanced kidney disease or diabetes mellitus and less than 0.7 g/L for patients with diabetes mellitus and cardiovascular disease. Disturbances in triglyceride, high-density lipoprotein cholesterol, and non-high-density lipoprotein cholesterol levels should also be addressed.[57] Moreover, strategies to improve diet by reducing dietary salt, smoking avoidance, and proper exercise are quite important to consider.

MICROALBUMINURIA: BEYOND

Although microalbuminuria is considered nowadays as a marker of high cardiovascular risk and endothelium dysfunction, this biomarker is not specific, since it is increased with both kidney disease and cardiovascular disease, nor well measured. In fact, all available immunoassays underestimate microalbuminuria because intact albumin presents in urine in two types of immune and non-immune reactive.[58]

As reported by Comper and colleagues,[59] microalbuminuria can be detected 3.9 and 2.4 years earlier by high-performance liquid chromatography than "conventional" detection respectively in type I and II diabetic patients. Moreover, the Australian Diabetes, Obesity, and Lifestyle Cohort reported a prevalence of microalbuminuria detected by high-performance liquid chromatography in 20% of patients, more than the 5.5% detected at the same time by immunonephelometry. More than 17% considered normoalbuminuric by immunonephelometry were microalbuminuric if microalbuminuria is detected by high-performance liquid chromatography.[60]

In the near feature, urine proteomic era will surely propose more sensitive and specific urine biomarkers than microalbuminuria for cardiovascular risk evaluation.

CONCLUSIONS

Microalbuminuria is currently a marker of both kidney disease and cardiovascular disease.

Because of its high cost-effective ratio and wide availability, it is recommended for evaluation of hypertensive patients, not necessarily diabetic, to detect subclinical target organ damage that increases the cardiovascular risk level, and to adjust therapeutic strategy. Microalbuminuria can be considered as a treatable marker to evaluate therapeutic efficiency.

CONFLICT OF INTEREST

None declared.

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