Review Paper

Microalbuminuria: What Is It? Why Is It Important? What Should Be Done About It? An Update

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Microalbuminuria (MA) is defined as a persistent elevation of albumin in the urine of >30 to <300 mg/d (>20 to <200 μg/min). Use of the morning spot urine test for albumin-to-creatinine measurement (mg/g) is recommended as the preferred screening strategy for all patients with diabetes and with the metabolic syndrome and hypertension. MA should be assessed annually in all patients and every 6 months within the first year of treatment to monitor the impact of antihypertensive therapy. It is an established risk marker for the presence of cardiovascular disease and predicts progression of nephropathy when it increases to frank microalbuminuria >300 mg/d. Data support the concept that the presence of MA is the kidney's warning that there is a problem with the vasculature. The presence of MA is a marker of endothelial dysfunction and a predictor of increased cardiovascular risk. MA can be reduced, and progression to overt proteinuria prevented, by aggressive blood pressure reduction, especially with a regimen based on medications that block the renin-angiotensin-aldosterone system, and control of diabetes. The National Kidney Foundation recommends that blood pressure levels be maintained at or below 130/80 mm Hg in anyone with diabetes or kidney disease. (J Clin Hypertens. 2007;9:196–200) ©2007 Le Jacq

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The acceptable amount of albumin in the urine is <30 mg/d; values above 300 mg/d (200 μg/min) indicate overt proteinuria. Values between 30 mg/d and 300 mg/d (20–200 μg/min) measured on 2 or more separate occasions defines microalbuminuria (MA).[1] Current quantitative dipstick measurements for urine albumin are positive only when levels are above 300 mg/d. Specific laboratory methods of measurement are therefore necessary for the identification of MA.

MEASUREMENT OF MA

For many years, the gold standard for measurement of MA was protein quantification of a 24-hour urine collection. Collection errors and inconvenience have eliminated this approach for screening purposes.[2] The use of an early morning "spot" albumin-creatinine measurement (expressed as mg of albumin per gram creatinine) performed 3 times within a few weeks has been validated as an appropriate way to assess whether MA is present.[3,4] The National Kidney Foundation Disease Outcomes Quality Initiative (DOQI) guidelines recommend an untimed spot urine sample, with a preference for first morning samples.[5]

Dehydration; fever; exercise; heart failure; poor glycemic control; inflammatory states, such as small injuries and toothaches; along with increases in dietary sodium and protein can increase urinary albumin levels.[6,7] Values may also not be reliable in patients with greater muscle mass,

Table. Newer Methods of Albuminuria Detection

Method	Interassay Coefficients of Variation	Detection Limit for Albumin	False-Negative vs HPLC, %	False-Positive vs HPLC, %
HPLC	2.4% at 95.8 mg/L	2 mg/L	ND	ND
Immunonephelometry (Beckman Array Analyzer; Global Medical Instrumentation, Inc, Ramsey, MN)	4.2% at 12.1 mg/L and 5.3% at 45 mg/L	2 mg/L	ND	ND
Immunoturbidity (Dade-Behring Turbimeter; Dade Behring, Inc, Deerfield, IL)	4.1% at 10.6 mg/L and 2.2% at 77.9 mg/L	6 mg/L	36	0
Radioimmunoassay	9.2% at 12.2 mg/dL	16 μg/L	23	0

HPLC indicates high performance liquid chromatography; ND, not determined. From Busby and Bakris.[4]

African Americans, and men with higher levels of creatinine excretion.[8] Vigorous exercise may result in MA. Due to the variability of this value, it is recommended that at least 3 urine samples be assessed during a period of 2 to 3 months before the diagnosis of MA is established.[9]

Measurements Methods

The accuracy of dipstick methodologies such as the Micral-Test II (Boehringer Mannheim GmbH, Mannheim, Germany) to measure MA was recently assessed in a clinical trial of patients with hypertension. The results demonstrated a sensitivity of 88%, a specificity of 80%, a positive predictive value of 69%, and a negative predictive value of 92%.[10] Much debate continues regarding the superiority of dipsticks over the spot albumin-creatinine value. The issue was recently revisited in a study in 287 patients that compared the accuracy of urinary albumin concentration, albumin-creatinine ratios, and the Micral-Test II strips. A significant difference favoring the albumin concentration method was demonstrated. The first cutoff point with 100% sensitivity was 14.4 mg/L for urine albumin-creatinine (specificity, 77.2%) and 15.7 mg/g for urine albumin-creatinine ratio (specificity, 73.0%). In addition, the Micral-Test II sensitivity and specificity for the 20 mg/L cutoff point were 90.0% and 46.0%, respectively. The cost of diagnosing MA according to this trial was approximately $2 for the albumin-creatinine ratio and $4 for the Micral-Test II.[11] While the Micral-Test II may be easier, the spot urine test has greater sensitivity and specificity and most large laboratories provide the necessary equipment to make it easy for the patient to comply with the specimen collection.

Analyses of other methods for assessing MA are summarized in the Table. Recently, a high performance liquid chromatography (HPLC) method was developed and promoted as sensitive and specific for the detection of MA.[12] The use of HPLC-obtained albumin levels for the prediction of future cardiovascular (CV) events, however, has yet to be validated.

MA: ESTABLISHED AND EMERGING RISK MARKER

CV Risk Assessment

Yudkin and associates[13] concluded from cross-sectional studies that an association exists between MA and CV risk, an observation confirmed by other post hoc analyses of large prospective cohort studies such as the Heart Outcomes Prevention Evaluation (HOPE) trial. In this trial, MA was associated with an adjusted relative risk of 1.83 for major CV events (myocardial infarction, stroke, or CV death), 2.09 for all-cause mortality, and 3.23 for hospitalization for congestive heart failure.[14] Every 0.4 mg/mmoL increase in the albumin-creatinine level conferred a 5.9% increase in the adjusted hazard of major CV events. A post hoc analysis of the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study[15] indicated similar results. The risk for primary end point outcomes increased at levels of MA lower than currently accepted cutoff values. In patients without diabetes, hazard ratios for the composite endpoint increased by 57%, for CV mortality by 97.7%, for all-cause mortality by 75.2%, for stroke by 51.0%, and for myocardial infarction by 45% with every 10-fold increase in the urinary albumin-creatinine ratio.

Additional analyses from a subpopulation of the NHANES II study demonstrated that adjusted relative hazard ratios for CV mortality were 1.57 for subjects with urinary protein levels 30 mg/dL to 299 mg/dL and 1.77 for those with urinary protein levels ≥300 mg/dL compared with individuals with <30 mg/dL excretion.[16] The European

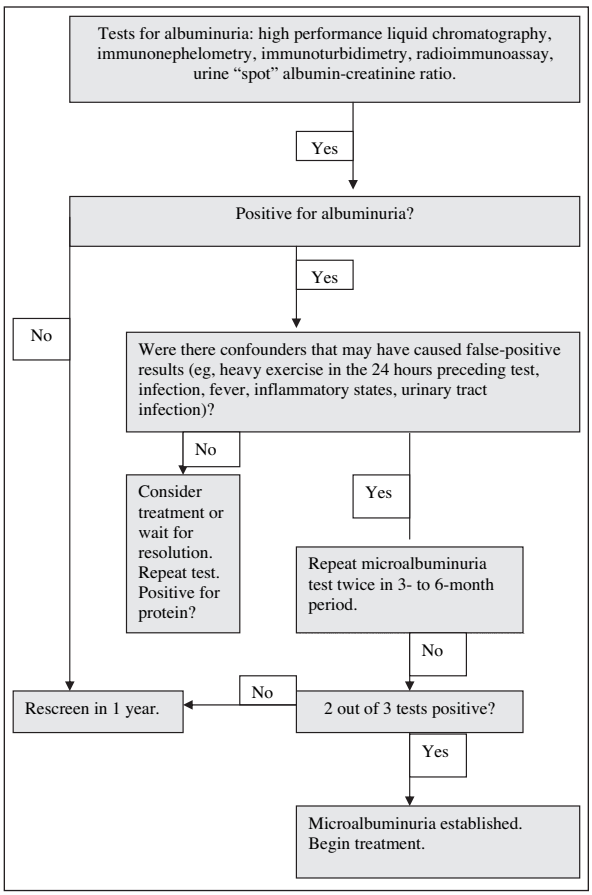

Figure. Guidelines for albuminuria detection and treatment. Adapted from Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines.[39]

Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) study results further support these findings, with the observation that MA at baseline conferred a 36% higher risk for incident CHD,[17] 49% for stroke,[18] and 103% for CV mortality at 7 years of follow-up.[19] In a recent study, similar observations were noted in a follow-up period of 42.5 months.[20]

Reduction in MA: Reduction in CV Events? Should a reduction in MA be part of the treatment goal in addition to achieving goal blood pressure? The MARPLE trial[20] included hypertensive patients without diabetes who received ramipril and other blood pressure–lowering medications, when needed, to achieve blood pressure goal. In these patients, a reduction in albumin excretion toward normal was associated with a nonsignificant trend in cerebrovascular end point reduction (*P*=.055). More conclusively, the LIFE trial showed that the subjects with the lowest CV event rate also had the statistically greatest reduction from baseline in urinary albumin excretion associated with a losartan-based treatment program.[21] The Prevention of Renal and Vascular End-Stage Disease Intervention Trial (PREVEND IT)[22] enrolled patients with baseline MA and randomized them to the angiotensin-converting enzyme inhibitor fosinopril or matching placebo and pravastatin or matching placebo. The study noted that the fosinopril-treated subjects had a 26% reduction in albumin excretion, an amount less than in the LIFE trial; this did not correlate with a reduction in CV mortality or hospitalization.

How Does MA Compare With Other Risk Markers? MA has been validated as a marker of CV risk in multiple epidemiologic studies when compared with conventional CV risk factors (age, hypertension, hyperglycemia, obesity, high total and low-density lipoprotein cholesterol, high triglycerides, low high-density lipoprotein cholesterol, smoking) as well as newer CV surrogate markers of CV risk such as C-reactive protein, hyperhomocysteinemia, and high fibrinogen levels.[23–31] Moreover, a recent follow-up of the HOPE study examined which markers would be most predictive of future myocardial infarction, stroke, or CV death during 4.5 years of follow-up. It was noted that only N-terminal pro-brain-natriuretic peptide yielded a higher hazard ratio than MA for these end points.[32]

COST-EFFECTIVENESS OF SCREENING

The American Diabetes Association, National Kidney Foundation (NKF), and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) have recommended screening for MA in all patients with diabetes.[33–35] A modification of the NKF approach for screening is shown in the Figure.[39] Screening can be deferred for 5 years after the diagnosis of type 1 diabetes, but should be done annually in persons with type 2 diabetes.

Screening for MA in people with diabetes has been shown to be cost-effective.[36] With older methods of screening, cost data for screening of persons without diabetes are less clear-cut.[37] Newer, more sensitive methods of detection from public screening programs support the concept of broader screening especially, among individuals with the metabolic syndrome and hypertension.[38]

SUMMARY

MA is a reliable marker of CV risk. Present guidelines call for screening of diabetics and people with hypertension who also have the metabolic syndrome. Completion of trials like ACCOMPLISH

will help clarify the importance of MA screening in the context of CV risk reduction among individuals in high CV risk groups.[40]

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