A s one reviews the epidemiologic evidence linking microalbuminuria as a measure of increased cardiovascular morbidity and mortality, one is struck by the consistency of the data in diabetic and nondiabetic populations. Given that this test is simple to obtain, relatively inexpensive, and provides enormous predictive value relative to many other clinical cardiovascular testing measures, why is it not used more frequently in the general population to screen for cardiovascular disease?

Traditionally in clinical medicine, we have focused on blood pressure, cholesterol, and glucose levels as a means of identifying those patients at risk for cardiovascular disease events. We have also used reduction of these clinical measures as an indicator of therapeutic success. Although there remains some debate as to how intensive the goals should be, in general, lower goals are recommended for those patients with more cardiovascular disease risks. Could longitudinal measurements of urine microalbumin add some objectivity to our estimation of treatment response to high blood pressure, dyslipidemia, or diabetes?

Why is a microvascular abnormality of the blood–urine interface within the glomeruli of the kidneys such a powerful tool for predicting macrovascular events such as stroke and myocardial infarction? This is an intriguing issue to consider. Which comes first? Is the microalbuminuria a reflection of a primary vascular disease, which has affected the kidneys, the brain, the heart and the rest of the circulation? Or might microalbuminuria be a biomarker for the amount of vascular disease in the body? Although there is not a simple answer to this question, one should consider the intriguing observations of the Ibsen study and other clinical trials, which suggest that the reduction of microalbuminuria or albuminuria/proteinuria are associated with fewer kidney and cardiovascular events. Ibsen et al evaluated the predictive value of microalbuminuria for cardiovascular events in >8000 patients with hypertension and left ventricular hypertrophy during 4.8 years of antihypertensive treatment. Not only did they show that a spot-urine albumin to creatinine ratio at baseline was predictive of events but that time varying albuminuria during follow-up was closely related to the risk for the primary composite end point of cardiovascular death or nonfatal stroke or myocardial infarction. If the albuminuria decreased during follow-up, so did the risk. Also significant were stepwise increases in risks seen for the composite end point if urinary albumin excretion increased during follow-up. These results are nearly identical to the observations of de Zeeuw et al, who noted in patients with diabetic kidney disease that baseline urinary protein excretion correlated with increased risk for kidney and cardiovascular events, and a stepwise reduction in proteinuria during 3.4 years of follow-up correlated with a reduced risk for kidney and cardiovascular events.

Is the reduction of albuminuria nothing more than just showing that these patients achieved better blood pressure, cholesterol, or glucose control? Or is there something about the therapeutic approach that results in lower levels of albuminuria, which is beneficial for the circulation?

The presence of albumin or protein in the urine is indicative of disease of the glomerular vascular beds. Could this also be reflective of injury to the afferent glomerular vascular vessels, which are important in autoregulating glomerular vascular blood supply? Might the level of blood pressure associated with a reduction of proteinuria by 50% be indicative of a more appropriate blood pressure goal for an individual patient? We all appreciate that lower blood pressure goals are important, but we also know that every patient is different.

Less albuminuria also could be reflective of a healthier diet. We know that increasing dietary salt can increase blood pressure in susceptible individuals. We also know that increasing dietary salt offsets the antihypertensive and antiproteinuric properties of renin-angiotensin system (RAS) blockers and other antihypertensive drugs. Might people with lower levels of albuminuria during treatment simply be eating less salt?

Of course, the other intriguing question is the type of antihypertensive drugs. RAS blockers, such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, reduce blood pressure and albuminuria more consistently than other antihypertensive agents largely through their combined effects of reducing systemic and glomerular capillary hydrostatic pressure. They also improve glycemic control and indirectly improve lipids by diminishing proteinuria. Might there be something about these specific drugs that is beneficial for the circulation if dosed in a way to reduce albuminuria? Should these drugs be dosed to reduce blood pressure or albuminuria? My supposition is that reduction of microalbuminuria or proteinuria might provide clinical clues about appropriate blood pressure, cholesterol, and glycemic and dietary goals in a given patient. However, the RAS blockers used in many of these trials may also provide additional vascular benefits.
However, one has to be careful in interpreting these data. As exciting and provocative as they are, they are all derived from post hoc analyses. Needless to say, a prospective clinical trial is needed to test the hypothesis that planned reduction in albuminuria will be associated with fewer kidney and cardiovascular events. Unfortunately, a microalbuminuria trial would likely take 10, if not 20, years to demonstrate impact on clinical cardiovascular events. An albuminuria trial could be completed in 3 to 5 years. However, it would need to be powered to be sure that a sufficient number of patients were treated so that the competing hazard of kidney events would not obscure differences in outcome based on cardiovascular events.

These new data highlight the need for screening for microalbuminuria in the patient with hypertension, dyslipidemia, or the metabolic syndrome so that clinicians can more objectively evaluate the need for cardiovascular risk reduction measures in a given patient. Patients with obesity-related metabolic syndrome will fuel the epidemic of kidney and cardiovascular disease of the next several decades. Early efforts to objectively identify those patients at risk are critical. Perhaps it will be shown someday that longitudinal measurements of albuminuria will assist us in the recognition of the achievement of appropriate cardiovascular risk reduction measures in a given patient.

References


Reduction in Microalbuminuria: A Biomeasure of Therapeutic Success?
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