In 1963, Keen and Chlouverakis published a new immunoassay that detected urine albumin at low concentrations and subsequently showed that urine (micro)albumin was elevated in patients with diabetes after a glucose load (1). In the early 1980s, several small longitudinal observational studies suggested that the presence of microalbuminuria (e.g., 15-150 μg/min) nearly uniformly predicted the development of overt diabetic nephropathy (DN) and an increase in mortality in patients with type 1 diabetes mellitus (T1DM) (2-4). Mogensen (3) subsequently proposed in 1984 the five stages of DN in T1DM beginning with hyperfiltration marked by an elevated GFR followed by a clinically silent phase, in which many patients may remain throughout their lives. In the third phase, the development of incipient nephropathy, characterized by the onset of microalbuminuria, serves as a harbinger for the fourth stage of macroalbuminuria (overt DN) and ultimately, a drop in GFR leading to ESRD (5). In contrast to T1DM, patients with type 2 diabetes mellitus (T2DM) are usually at a later stage, often with microalbuminuria or established overt DN. Only about 25%-40% of patients with T1DM and 5%-40% of patients with T2DM ultimately develop DN. Although this paradigm of DN is still used, it has been refined by the results of numerous studies. Many if not the majority (21%-64%) of patients with T1DM or T2DM who develop microalbuminuria will revert to normoalbuminuria, and only a minority (17%-34%) progress to macroalbuminuria (6). Reversion of microalbuminuria often occurs in the absence of treatment with renin-angiotensin system blockers. DN can also occur without evidence of elevation in urine albumin (6).

Despite these caveats, an increase in albuminuria has been found to be a strong predictor of a more rapid decline in renal function as well as an increase in cardiovascular and all-cause mortality in both patients with diabetes as well as the general population (7,8). The CKD Prognosis Consortium performed a meta-analysis of over 1 million participants (12.5% had diabetes) in 43 different cohorts and found a graded increase in the hazard ratio (HR) for all-cause and cardiovascular mortality and progression to ESRD with urine albumin-to-creatinine ratios (ACRs) over 10 mg/g (8). Compared with an ACR<10 mg/g, ACRs of 10-29, 30-299, and >300 mg/g were associated with statistically significant HRs (95% confidence intervals) of 1.35 (1.27 to 1.44), 1.73 (1.61 to 1.86), 2.67 (2.31 to 3.08), respectively, for all-cause mortality and 1.6 (0.85 to 3.02), 3.55 (2.89 to 4.36), 6.79 (4.36 to 10.6), respectively, for ESRD in patients with diabetes, and they were not different from those in nondiabetic patients. On the basis of studies such as this, the Kidney Disease Improving Global Outcomes in 2009 modified the original National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification of kidney disease by adding three levels of albuminuria to the preexisting five stages (now modified to six stages) of GFR to better reflect the independent prognostic significance of increases in albuminuria (7).

Although the biologic link between microalbuminuria and cardiovascular disease (CVD) is not known, it is postulated that microalbuminuria is a marker for generalized endothelial dysfunction (the Steno hypothesis) (9). Microalbuminuria is associated with multiple cardiovascular risk factors, including elevated systolic BP, hemoglobin A1c, and atherogenic lipoprotein abnormalities including elevated cholesterol and triglycerides, which may regress with remission of microalbuminuria (10-12).

Although the absolute level of albuminuria is unquestionably an important prognostic factor, uncertainty remains whether changes in albuminuria, particularly in the microalbuminuric range, are a reliable predictor of patient prognosis and can be used as a surrogate marker for clinical outcomes, such as ESRD or mortality (13-15). For patients with macroalbuminuria associated with either T1DM or T2DM, treatment-induced reduction in urine protein excretion is frequently but not universally associated with a slower rate of progression of kidney disease and improved cardiovascular mortality (6,15,16). However, for patients with microalbuminuria, particularly with T1DM, the answer is less clear (6).

In this context, the study by DeBoer et al. (17) examined the relationship between albuminuria and the development of reduced GFR or cardiovascular outcomes in 1441 patients with T1DM initially randomized between 1983 and 1989 into the Diabetes Control and Complications Trial (DCCT). The DCCT examined the effect of intensive versus conventional blood sugar control on diabetic complications (18). After completion of the DCCT in 1993, 1375 of the surviving patients had albuminuria measured, and ESRD was defined as a doubling of serum creatinine or initiation of dialysis treatment. The 14-year follow-up of the DCCT showed that an increase in urinary albumin excretion was associated with an increase in cardiovascular and all-cause mortality and a decreased GFR in patients with diabetes. In addition, other studies have shown that an increase in urinary albumin excretion is associated with an increased cardiovascular mortality rate in nondiabetic patients with chronic kidney disease (21).

In conclusion, the relationship between albuminuria and cardiovascular and all-cause mortality in patients with diabetes is well established. The relative importance of albuminuria as a surrogate marker for cardiovascular disease outcomes needs further study.
participants were subsequently enrolled in the long-term longitudinal, observational follow-up study known as the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Urine albumin excretion rate (AER) was measured yearly in the DCCT and every 2 years during the EDIC Study. Baseline urine AER was 12±8 mg/dl in the 726 patients randomized into the primary prevention group and 20±24 mg/dl in the 715 patients randomized in the secondary prevention group. At the time of each follow-up measurement of urine AER, patients were classified into four mutually exclusive groups: normoalbuminuria (sustained urine AER <30 mg/dl), sustained microalbuminuria (AER=30–299 mg/dl on two or more consecutive urine samples), sustained macroalbuminuria (AER>300 mg/dl), or remitted microalbuminuria (urine AER <30 mg/dl on two occasions after achieving sustained microalbuminuria or macroalbuminuria). The primary CVD and renal outcomes were those used in the DCTC and the EDIC Study. The primary outcome of any CVD was defined as the first occurrence of either nonfatal myocardial infarction or stroke, death from CVD, subclinical myocardial infarction on electrocardiogram, confirmed angina, or the need for coronary artery revascularization. Renal disease was defined as an eGFR<60 ml/min per 1.73m² on two consecutive visits, initiation of dialysis, or kidney transplantation. Albuminuria status was used as a time-dependent variable in unadjusted and adjusted Cox proportional hazards models to test the association with CVD and renal outcomes.

Over a mean follow-up of 24.6 years, at least one cardiovascular event occurred in 184 participants, and 98 participants developed a reduced GFR. Consistent with prior studies, increased urine AER was associated with a higher risk of cardiovascular events and reduced GFR. Compared with sustained normoalbuminuria, patients with sustained microalbuminuria, remitted microalbuminuria, and macroalbuminuria had adjusted HRs (95% confidence intervals) of 1.79 (1.13 to 2.85), 2.62 (1.68 to 4.07), 2.65 (1.68 to 4.19) for CVD events, respectively, and 5.26 (2.43 to 11.41), 4.36 (1.80 to 10.57), 54.4 (30.8 to 95.9) for reduced GFR, respectively. Notably, the HRs for CVD events and reduced GFR were not lower for patients with remitted microalbuminuria compared with sustained microalbuminuria. Moreover, carotid-intima thickness was also similarly increased in patients with sustained or remitted albuminuria compared with normoalbuminuria. Interestingly, the introduction of a 4-year time lag in the model between measurement of urine AER and assessment of the clinical outcome did not materially change the increased risk of sustained or remitted albuminuria for CVD. However, introduction of the time lag attenuated the association of remitted microalbuminuria with reduced GFR, which was no longer statistically different compared with normoalbuminuria. By contrast, addition of the time lag did not attenuate the association between sustained microalbuminuria or macroalbuminuria and reduced GFR. The authors conclude that the study supports the association between increased albuminuria and adverse cardiovascular and renal outcomes in T1DM, but remission of microalbuminuria, which often occurred in the absence of treatment, does not seem to improve outcomes.

In contrast to this study, treatment-induced remission of microalbuminuria to normoalbuminuria has previously been associated with both a slowed rate of decline of eGFR and reduced cardiovascular end points in T2DM (19–21) and a trend toward reducing cardiovascular end points in nondiabetics (22). However, the beneficial effects of treatment in these studies may have been independent of changes in albuminuria.

This important study raises questions about the use of changes in microalbuminuria as a surrogate outcome for progression of CVD or decline in GFR in T1DM. It may be that microalbuminuria is a marker for generalized vascular dysfunction but that remission of albuminuria is mediated by (unknown) factors unrelated to progression of CVD or renal disease. Alternatively, a true association between changes in microalbuminuria and improved cardiovascular and renal outcomes may have been missed. The number of clinical end points per group was small, and therefore, the robustness of the study results is a concern. Patients who develop microalbuminuria, even if it remits, have higher baseline levels of albuminuria compared with those with sustained normoalbuminuria (23). Remission of sustained microalbuminuria does not mean complete normalization of urine albumin excretion, and therefore, the change in urine albumin between sustained microalbuminuria and remitted microalbuminuria in absolute terms is small and may not be sufficient to show a clinically significant outcome—even with relatively long follow-up. Moreover, it is known that structural changes of DN, such as thickening of the glomerular basement membrane, antedate the development of microalbuminuria by many years (23). It is possible that it also takes many years before remission of albuminuria leads to improvement in clinical outcomes. The observation by DeBoer et al. (17) that introduction of a 4-year delay between remission of microalbuminuria and assessment of clinical outcome markedly attenuated the HR for decline in GFR for patients who remitted compared with those who had sustained microalbuminuria is consistent with this hypothesis. In conclusion, despite the many strengths of this study, it is simply not possible to conclude with certainty whether a change in microalbuminuria is (or is not) a surrogate marker for cardiovascular or renal outcomes in T1DM.

Disclosures

B.S.D. reports grants and consulting fees from Proteon Therapeutics (Waltham, MA), consulting fees from Humacyte Inc. (Morrissville, NC), consulting fees and equity interest in Flow Forward Medical (Olathe, KS), and equity interest in Metative Medical (Olathe, KS). B.S.D. reports research grants for clinical trials in diabetic nephropathy from AbbVie Inc. (North Chicago, IL) and Bayer (Leverkusen, Germany).

References


Published online ahead of print. Publication date available at www.cjasn.org.