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COMMENTARY

Albuminuria in hypertension

Yao-Ping Lin

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Chronic kidney disease (CKD) is on its way to becoming a global public health issue, and hypertension ranks among the leading causes of CKD. Screening for kidney disease is crucial among those with hypertension. In essence, CKD can be identified by kidney damage ascertained from albuminuria and kidney function according to the glomerular filtration rate (GFR). The estimated GFR (eGFR) ($ml\,min^{-1}$ per $1.73\,m^2$) can be calculated as $186 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 0.742$ (if female) based on the equation from the Modification of Diet in Renal Disease (MDRD) study.[1] On the basis of an international consensus of the United States NKF-KDOQI (National Kidney Foundation-Kidney Disease Quality Outcome Initiative) in 2002 and the KDIGO (Kidney Disease: Improving Global Outcomes) in 2005, CKD staging was modified in 2009 with the addition of albuminuria stages (stages 1 to 3 with urine albumin/creatinine ratios of <30, 30–300 and $>300\,mg\,g^{-1}$, respectively) to the GFR stages (stages 1 to 5 with GFR $\geqslant 90$, 60–89, 30–59, 15–29 and $<15\,ml\,min^{-1}$ per $1.73\,m^2$, respectively).

Under normal conditions, the blood albumin is filtered through the renal glomerulus and retrieved from the renal tubular lumen by the renal proximal tubular cells to enter the peritubular blood microcirculation. The filtered albumin that is not retrieved by the proximal tubular cells then undergoes lysosomal degradation into small peptide fragments. An increased pressure load from an elevated aortic pulse pressure, an increased peripheral resistance and an augmented volume load from increased flow pulsation could alter the renal hemodynamics and consequently damage the renal microvasculature. Therefore, the albumin is filtered to an extent that exceeds the retrieval capacity of the proximal tubules. Moreover, the elevated angiotensin II and transforming growth factor-β1 in hypertension could disturb the lysosomal degradation pathway and consequently lead to albuminuria.[2] In addition, as a kidney damage marker, albuminuria could also reflect systemic vascular damage.

In this issue of *Hypertension Research*, Kim *et al.*[3] conducted a large-scale, cross-sectional study that enrolled 40 473 hypertensive patients in Korea to determine the prevalence and determinants of albuminuria and microalbuminuria in this population. The prevalence of albuminuria was determined using a positive dipstick test and was 13.4%. The prevalence rates of elevated Urine Albumin-to-Creatinine Ratio (UACR) and microalbuminuria were 6.6% and 5.4%, respectively. Up to 17.64% of the studied population presented diabetes, and 40.76% were obese, defined as body mass index $\geqslant 25\,kg\,m^{-2}$. It is well known that metabolic syndrome is defined by three of the following traits: high blood pressure (BP $>130/85$ mm Hg), hyperglycemia (fasting blood sugar $>100\,mg\,dl^{-1}$), abdominal obesity, high triglycerides ($>150\,mg\,dl^{-1}$) and abnormal high-density lipoprotein cholesterol.

There is a strong association between metabolic syndrome and CKD. In a cohort of the National Health and Nutrition Examination Survey (NHANES) III, which included 7800 participants with normal renal function at baseline who were followed for 21 years, a twofold increase in the risk for microalbuminuria was observed that correlated with the number of metabolic syndrome traits that were present.[4] In a meta-analysis of 11 prospective observational studies that included a total of 30 146 participants who fulfilled the criteria of metabolic syndrome,[5] metabolic syndrome had an odds ratio (OR) of 1.55 (95% confidence interval, CI 1.34–1.80) for the development of eGFR $<60\,ml\,min^{-1}$ per $1.73\,m^2$. Regarding the individual components of metabolic syndrome, elevated BP had an OR of 1.61 (95% CI 1.29–2.01). Given the complex interactions among these components of metabolic syndrome and their individual effects on CKD, it would be difficult to determine the prevalence of albuminuria/microalbuminuria in this heterogeneous population.

In the present study, kidney-related disease is considered to be a comorbid condition that is related to elevated UACR. Besides evaluating kidney damage by the presence of albuminuria, measuring eGFR as a renal functional assessment is indispensable as a screen for kidney disease. The importance of eGFR measurement in screening CKD can be exemplified from the NHANES, in which only ~65% of the diabetic and 30% of the nondiabetic individuals with decreased GFR presented a urine albumin–creatinine ratio $>30\,mg\,g^{-1}$.[6]

In hypertensive patients, it is essential to use simultaneous albuminuria/proteinuria and eGFR assessments to properly evaluate the cardiovascular risks. Current guidelines recommend that eGFR $<60\,ml\,min^{-1}$ or the presence of microalbuminuria should be considered as equivalents of cardiovascular disease.[7] In a collaborative meta-analysis of 10 cohorts with a total of 266 975 patients with a history of hypertension, diabetes or cardiovascular disease,[8] the all-cause mortality increased progressively at eGFR $<60\,ml\,min^{-1}$. Albuminuria was associated with the all-cause mortality without thresholds. When albuminuria and eGFR were considered together, they were

Dr Y-P Lin is at the Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan and School of Medicine, National Yang-Ming University, Taipei, Taiwan
E-mail: linyp@vghtpe.gov.tw

multiplicatively associated with the all-cause and cardiovascular mortality. Moreover, compromised renal function, as defined by a low eGFR, could lead to poor BP control due to sympathetic overactivity and renin–angiotensin activation. The patients also presented dyslipidemia, insulin resistance, chronic inflammation, abnormal body composition, accelerated atherosclerosis and arteriosclerosis and increased comorbidities. These conditions could act as potential confounders for analyzing the determinants of UACR.

Immunoassay using polyclonal sera has been proposed as the gold standard for quantifying urine albumin by the National Kidney Disease Education Program—IFCC (International Federation of Clinical Chemistry) Working Group on Standardization of Albumin in Urine. Urine dipstick tests, such as the immunometric dipstick Micral-test used in the present study, offer a cost-effective means of screening for albuminuria. However, variations in the urine volume applied to the dipstick strip might render biased results due to variations in the urine albumin concentration. Because the urine creatinine excretion rate remains constant, it can be used as a reference to counteract the confounding due to urine volume. Several large-scale epidemiology studies have applied dipstick tests that were designed to simultaneously measure urine albumin and creatinine. It would be useful to explore the prevalence rates of albuminuria obtained from various screening modalities. Furthermore, there are multiple structural variants of urine albumin and albumin fragments that might be undetectable using immuno methods. Given that albumin is the most abundant antioxidant in circulation, post-translational modification owing to oxidative stress could enhance the albumin fragmentation and carbonylation, which would lead to a loss of the immunoreactivity of urinary albumin when assessed by immunoblotting.[9] Whether the increased oxidative stress in CKD would increase the immuno-unreactive albumins in the urine and the significance of these albumins in predicting the prognosis remain to be elucidated.

Genetic factors should be considered when interpreting the wide variations observed in the prevalence of albuminuria in hypertension across various ethnic population studies. As comprehensively reviewed by Martineza *et al.*,[10] the candidate gene approach reported in the literature regarding urinary albumin excretion and hypertension was relevant to the renin–angiotensin–aldosterone system, natriuretic peptides, adrenergic system, inflammation, oxidative stress, intracellular signaling, lipid metabolism, regulation of the extracellular matrix and fibrinolysis. Polymorphisms in the protein coding genes relevant to these systems might affect the prevalence of albuminuria. Novel genetic susceptibility loci could be discovered by *data mining* several publicly accessible genome consortiums, including ICBP (International Consortium for Blood Pressure), hyperGen, CKDGen, CARe (Candidate-gene Association Resource) and KidneyGen. In a meta-analysis of data from 63 153 individuals from the CKDGen and CARe Consortiums, Boger *et al.*[11] identified an association between microalbuminuria and a missense variant (I2984V) of the *CUBN* gene encoding cubilin, which is essential for albumin reabsorption by the renal proximal tubule cells. Identifying these genetic traits for albuminuria might explain the variations in the prevalence rate and facilitate tailored therapies for the early prevention of CKD progression.

It remains unclear whether microalbuminuria should be considered a marker of kidney damage or a treatment target. Actually, the association between the albuminuria magnitude and the clinical outcomes might be different in patients with other comorbidities. In a cohort analysis of 298 875 US veterans,[12] very low levels of the urine albumin–creatinine ratio were linearly associated with decreased mortality and less deterioration of the eGFR in all subgroups, including those with and without diabetes, hypertension, cardiovascular disease and congestive heart failure. Strikingly, there is a U-shaped association in the CKD patients, and the lowest levels of urine ACR are associated with higher mortality and the rapid progression of CKD. The ROADMAP (Randomized Olmesartan and Diabetes Microalbuminuria Prevention Trial)[13] further posed the important issue of whether microalbuminuria is a treatment target. It was a double-blinded, randomized controlled trial that enrolled 4447 patients with diabetes and normoalbuminuria and followed them up for a median of 3.2 years. The primary outcome was the time to the first onset of microalbuminuria, and the secondary end points were the time to the onset of renal and cardiovascular events. Although angiotensin receptor blockade by olmesartan could slow the progression of microalbuminuria, there were unexpectedly a greater number of fatal cardiovascular events in those treated by olmesartan. More randomized controlled trials targeted at microalbuminuria as a surrogate endpoint are anticipated in the future to elucidate the optimal intervention time point in the albuminuria continuum for superior outcomes.

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