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Albuminuria in Renal and Cardiovascular Disease

By JULIE LIN, MD, MPH, FASN

Recent investigations have highlighted the importance of low urinary albumin excretion levels in predicting subsequent cardiovascular (CV) and kidney disease. Although increased albuminuria was recognized as associated with CV risk factors (eg, hypertension, diabetes mellitus [DM] or the metabolic syndrome, and obesity) for several years, it is now perceived to be an independent risk factor for incident CV disease, even after adjustment for these conditions. This issue of *Nephrology Rounds* presents key concepts in measuring albuminuria in human clinical and epidemiological studies and summarizes the published literature pertinent to microalbuminuria (MA) in renal, CV, and all-cause mortality. Finally, the emerging role of inflammation and diet in influencing albuminuria is discussed.

Measuring albuminuria

Defining proteinuria and albuminuria

Although the terms “proteinuria” and “albuminuria” are often used interchangeably, low levels of multiple distinct proteins are excreted in the urine in healthy humans, of which albumin is one subtype. The most abundant urinary protein is Tamm-Horsfall protein (MW 90 000 kDa) secreted by the thick ascending limb at 50 mg/24 hrs in healthy people.¹ This membrane protein located on the luminal surface of tubular cells provides the basic matrix for urinary casts observed in health and disease. While the function of Tamm-Horsfall protein is not entirely clear, scientists have hypothesized that it may serve an immunomodulatory role and protect against urinary-tract infections by binding some subtypes of *Escherichia coli*. Many of the proteins filtered in the kidney are avidly reabsorbed in the proximal tubules, which is why most urinary proteins (including light chains, trypsin, immunoglobulin [IgG], beta-2 microglobulin, retinol binding protein, cystatin C, and C-peptide) have a reported daily excretion rate of <5 mg/24 hrs in healthy individuals.¹

Urinary albumin excretion rate (AER)

A measurement comparison for proteinuria and albuminuria is shown in Table 1. Albumin has a molecular weight of 66 400 kDa and a urinary excretion level of <30 mg/24 hrs has traditionally been considered the upper limit of normal for healthy adults. MA has classically been defined as an AER of 30–300 mg over 24 hrs (or 20–200 µg/min), while macroalbuminuria has been defined as an AER of >300 mg/24 hrs.

Assays for albuminuria

There are multiple immunochemical assays for albuminuria and most measure intact urinary albumin using antialbumin antibodies (Table 1). Recently, high-performance liquid chromatography (HPLC) has been reported to detect urinary intact denatured albumin that is immunounreactive. Results with HPLC indicate higher urinary albumin concentrations as compared with traditional methods. However, the clinical significance of measurements of urinary albumin by HPLC versus traditional albumin measurements in the urine has not yet been established.²



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Table 1: Comparative measurements for proteinuria and albuminuria		
	Proteinuria	Albuminuria
Detected by standard clinical urine dipstick	No (if nonalbumin)	Yes
Clinical laboratory assay	Gel filtration, biuret method	Nephelometry, immunoturbidimetry, ELISA, radioimmunoassay, high-performance liquid chromatography
Traditional upper limit of normal in urine	150 mg/day	30 mg/day

ELISA = enzyme-linked immunosorbent assay

Urine protein electrophoresis

In the medical literature, the term “overt proteinuria” is often used to refer to higher albumin excretion rates (usually >300 mg or 1000 mg/day) in disease states. This term may often be appropriate because most nephropathies with heavy proteinuria have albumin as the component, but one important exception is multiple myeloma where Bence-Jones light chains may comprise a significant percentage of the urinary proteins. If dysproteinemia is clinically suspected, urine protein electrophoresis (UPEP) may be used for screening and then immunofixation can be employed to quantify the proportions of light chain versus albumin excretion.

Urinary dipstick

Urinary dipstick screening for albuminuria (often reported as “trace” to 4+) gives a semiquantitative assessment that may have significant intrapersonal variation, especially when the concentrating and diluting abilities of the kidney are intact. Dipstick screening, therefore, represents the least accurate and reproducible method for assessing albuminuria.

Timed urine collection

Measurement of urinary albumin concentration alone (mg/L) is also potentially subject to high intrapersonal variability. Quantification using a timed urine collection (eg, mg/24 hrs) has traditionally been considered the gold standard for assessing albuminuria. Timed urine collections, however, are cumbersome and may be fraught with collection errors.³ They are also considered to be impractical for large-scale epidemiological studies.

Albumin-to-creatinine ratio (ACR)

The ACR measured on a spot urine collection is widely used to quantify albuminuria in clinical practice and human research studies.

In the majority of proteinuric kidney diseases, albumin is the most abundant urinary protein; therefore, it may be suitable to extrapolate the total protein-to-creatinine ratio as a measure of the ACR in this situation.

A study by Ginsberg et al⁴ published in 1983 demonstrated that a spot protein-to-creatinine ratio appears to be a reasonable approximation of the urinary protein excretion rate over a wide range. An important assumption in using the ACR, however, is that urine creatinine excretion in steady state is approximately 1 g/day, thereby an ACR of 30–300 µg/mg would approximate an AER of 30–300 mg/24 hrs.

Sex-specific cutpoints

In the mid-1990s, investigators performed studies of repeated random versus timed urine samples in several hundred diabetic and nondiabetic participants and reported that sex-specific cutpoints to define ACR may be more appropriate than a single definition.^{5,6} This was based on the observation that daily urinary creatinine clearance may be as much as 55% higher in men than in women.⁵ Based on these data, an ACR defined as 17–249 µg/mg in men and 25–354 µg/mg in women was proposed as the sex-specific definition for MA.

The implication of using a sex-specific definition for MA was illustrated in an analysis of >15 000 participants in the National Health and Nutrition Examination Survey III (NHANES III) study where men had higher urine creatinine concentrations than women (mean ~150 mg/dL vs ~130 mg/dL) on spot urine samples, which presumably translates into higher daily urinary creatinine excretion rates for men.⁷ In contrast, urinary albumin concentrations appear to be equal in men and women at ~15 mg/dL. When a nonspecific ACR of 30–300 µg/mg was applied, women had an 8% prevalence of MA compared with 6% in men, whereas using sex-specific cutpoints for MA resulted in equal prevalences in both men and women.

Other influences on albumin measurement

Intrapersonal variation in ACR should also be acknowledged, although Warram and colleagues⁶ reported high intrapersonal correlation in repeated random ACR measurements taken 5 months apart in 1613 patients with type 1 DM and 218 healthy controls (Spearman coefficient $r=0.83$). Transient elevations in albuminuria can be seen with fever, urinary tract infections, vigorous exercise, and certain drugs. Therefore, clinicians should be mindful of the presence of these conditions at the time of urinary albumin assessment. A substudy of 241 people in the Prevention of REnal and Vascular ENdstage Disease (PREVEND) trial⁸ (mean AER 11.5 mg/24 hrs and mean ACR 5.7 µg/mg) who had 24-hr timed urines, first morning spot urines, and random spot urines measured on 3 separate occasions revealed that the first morning ACR had a lower intraindividual coefficient of variation than random spot ACRs (19% vs 34%). This suggests that the first morning ACR is preferable to a random ACR for assessment and longitudinal monitoring of albuminuria.

Epidemiology and history of microalbuminuria

In addition to the considerations of sex-specific cutpoints for MA, increasing age is directly associated with an increasing prevalence of MA in nondiabetic and nonhypertensive adults.⁹ Furthermore, non-Hispanic blacks and Mexican-Americans in the United States have a significant 22%–30% increased odds ratio for having MA when compared to non-Hispanic whites after adjustment for age, sex, blood pressure, body-mass index (BMI), DM, and current smoking.⁷

The overall prevalence of MA in the general population has been reported to be 7.2% in the PREVEND cohort from The Netherlands (n = 40 548)¹⁰ and 10.7% in the more racially diverse United States NHANES III study (N = 15 939).⁷ Notably, however, the PREVEND study defined MA as a urinary *concentration* of albumin of 20–200 mg/L, while the NHANES III study used sex-specific cutpoints for urinary ACR. Regardless, the prevalence of MA is not rare and raises the question of how its parameters were derived as a clinically important definition.

In 1982, in a study of 63 type 1 diabetic patients followed for 14 years, Viberti and colleagues¹¹ reported that those with a baseline AER >30 µg/min were significantly more likely to develop macroalbuminuria indicative of overt diabetic nephropathy (3.6% versus 88%), as well as experience death during the follow-up period (37.5% versus 9.1%). Since this initial report, MA has been defined as an AER of 30 mg/24 hrs. The absence of nondiabetic patients and the lack of studies on the distribution of albuminuria in large populations likely contributed to the development of these laboratory parameters that do not reflect the usual 5th and 95th percentile extremes often applied to define out-of-range values.

Albuminuria and kidney function decline

It is well established that untreated or persistent heavy albuminuria (excretion >1–3 g/24 hrs) is associated with progressive renal failure in DM, as well as with nondiabetic glomerular disease in multiple published studies. Moreover, most therapeutic trials of proteinuric renal diseases have identified the persistence of heavy albuminuria as one of the strongest predictors of poor renal outcomes. Therefore, it is important to examine the less well-researched area of MA in the progression of diabetic and nondiabetic kidney dysfunction.

MA has been considered the first sign of incipient nephropathy in type 1 and type 2 DM. Many diabetic patients with MA progress to “overt nephropathy” as marked by macroalbuminuria and renal function decline. For example, in type 1 DM, baseline MA was associated with a significantly faster rate of creatinine clearance decline in 634 patients followed for 10 years (relative risk [RR]=1.45, 95% confidence interval [CI], 1.11–1.88 for ≥ 3 mL/min/1.73 m²/year decline), compared with those

without MA.¹² Similarly, in another study in 108 Italians with type 2 DM followed for 4 years, the presence of baseline MA was associated with faster estimated glomerular filtration rate (eGFR) decline (-1.3 mL/min/1.73 m²/year, $P < 0.05$) compared with those without MA. As expected, those with baseline macroalbuminuria (proteinuria) experienced the fastest eGFR decline (-3.0 mL/min/1.73 m²/year, $P < 0.01$).¹³

Low levels of albuminuria appear to be associated with progression of renal insufficiency in the general population as well. In the PREVEND observational study, a 4-year follow-up of ~6500 inhabitants, investigators examined the incidence of *de novo* renal impairment defined as new eGFR <60 mL/min/1.73 m². Baseline AER was measured using an average of 2 24-hr urine collections. The authors reported a significantly higher rate of development of eGFR <60 mL/min/1.73 m² among those with AER 30–300 mg/24 hrs compared to the referent group with AER <2 mg/24 hrs. Furthermore, the association between AER and incident renal impairment appeared to be graded with a linearly increasing odds ratio between 10 mg/24 hrs and 300 mg/24 hrs.¹⁴ After adjustment for potential confounders, including baseline eGFR, age, sex, mean arterial blood pressure, BMI, plasma cholesterol, plasma glucose, smoking, hypertension medication, and DM, PREVEND investigators reported a statistically significant 30% odds ratio for developing new renal impairment per unit increase of log-transformed urinary AER.

Albuminuria in CV and mortality outcomes

The burden of CV morbidity and mortality in those with MA likely greatly exceeds that for progressive kidney failure. An analysis of Medicare patients by Collins et al¹⁵ demonstrated that people with either chronic kidney disease (CKD) or DM are 10–49 times more likely to die (presumably from CV disease) than reach dialysis dependency, respectively, whereas those with CKD and DM are 5 times more likely to die than reach end-stage renal disease (ESRD).

Albuminuria is considered a measure of systemic and renal vascular dysfunction and has been identified as an important predictor of CVD events both in patients with DM and in those without DM.¹⁶ Investigations in the Irbesartan in Diabetic Nephropathy Trial (IDNT) confirmed baseline urinary albuminuria to be a strong predictor of CVD in 1715 individuals with type 2 DM.¹⁷ A secondary analysis of the Reduction in Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial of 1513 subjects with type 2 DM and nephropathy (mean serum creatinine 1.9 mg/dL) also demonstrated that albuminuria reduction was the strongest independent predictor for decreasing subsequent CV events (18% reduction in the composite CV endpoint for each 50% reduction in albuminuria).¹⁸ The RENAAL investigators

Table 2: Notable studies of albuminuria and cardiovascular or mortality outcomes

	Study design	Study population	Albuminuria classification
HOPE (2001) ¹⁶	Secondary analysis of randomized trial (ramipril vs placebo)	N=5545 Diabetic or presence of at least 1 CVD risk factor	ACR >2 mg/mmol
LIFE (2003) ¹⁹	Secondary analysis of randomized trial (losartan vs atenolol)	N=8206 Hypertension and LVH	Deciles of ACR
PREVEND (2002) ¹⁰	Observational population cohort	N=40 548 Inhabitants of Groningen, Netherlands	Urinary albumin concentration >20 mg/L
Framingham Offspring (2005) ²⁰	Observational population cohort	N=1568 Nondiabetic, nonhypertensive, no prevalent CVD	Sex-specific median ACR for cohort (3.9 µg/mg for men, 7.5 µg/mg for women)
PEACE (2007) ²¹	Secondary analysis of randomized trial (trandolapril vs placebo)	N=2977 Stable CAD, ejection fraction >40%	Sex-specific ACR (>17 µg/mg for men, >25 µg/mg for women)

CVD = cardiovascular disease, LVH = left ventricular hypertrophy, CAD = coronary artery disease, ACR = albumin-to-creatinine ratio.

concluded that albuminuria was an important predictor of CV disease and that reducing albuminuria is an essential strategy in decreasing CV risk.

Multiple studies have demonstrated significant associations between higher levels of albuminuria (even at the traditional “normal range” of <30 mg/24 hrs AER or equivalent) and CV events and all-cause mortality. Data from both population-based observational studies and secondary analyses of clinical trials have consistently reported a significantly increased risk for adverse outcomes after adjustment for other factors, including age, BMI, blood pressure, and DM. A comparison of established and well-characterized studies is indicated in Table 2.^{10,16,19-21}

Although direct comparison of these data may not be possible because of the different albuminuria definitions used in the statistical analyses, all the investigations report increased risk at low levels of albuminuria at the traditional “normal range” in diverse study populations. Therefore, increasing albuminuria may represent a continuous risk since studies suggest there may not be an absolute threshold of albuminuria associated with CV and mortality risk. Moreover, although an eGFR of <60 mL/min/1.73 m² is an established independent predictor for CV disease and mortality, the presence of MA appears to provide an additional risk for all-cause mortality. In the Survival and Ventricular Enlargement (SAVE) study, the combination of albuminuria and an eGFR of <60 mL/min/1.73m² resulted in a nearly 3-fold increased risk of death (HR 2.74, 95% CI, 1.68–4.45) compared to having neither risk factor.²² Furthermore, both an eGFR <60 mL/min/1.73 m² and increasing albuminuria each remained as significant independent predictors of mortality in fully adjusted Cox proportional

hazards models in the Prevention of Events with ACE inhibition (PEACE) trial.²¹

Factors influencing albuminuria

Higher levels of albuminuria are associated with the presence and duration of DM, hypertension, and higher BMI in population-based studies.^{23,24} Because albuminuria – even at low levels – is a powerful and consistent predictor of poor renal, CV, and all-cause mortality outcomes, reduction of albuminuria may be a marker of decreased risk. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-2 receptor blockers (ARBs) are effective in reducing macroalbuminuria and the risk for progressive renal and CV disease, but the impact of these agents on low levels of albuminuria is not well defined. Therefore, besides renin-angiotensin system blockade, potentially modifiable risk factors that influence albuminuria are of interest as early intervention strategies.

Inflammation

The role of inflammation in albuminuria for instance, as it relates to CV risk and kidney-function decline is a growing area of research. Cross-sectional studies have reported significant direct associations between markers of inflammation and increased albuminuria. For example, C-reactive protein (CRP) levels were directly related to albuminuria in 1481 insulin-resistant and type 2 DM adults ($r=0.17$, $P<0.0001$). A statistically significant but markedly attenuated association remained after adjustment ($r=0.06$, $P<0.05$).²⁵ Another study in 202 patients with type 2 DM also reported modest but significant direct associations between CRP and ACR after adjustment for age, blood pressure, glycated hemoglobin (HbA_{1c}), presence of retino-

pathy, and insulin therapy. Each increase in CRP of 0.36 mg/L was associated with a 1-unit increase in ACR ($P=0.03$).²⁶ In a recent publication from NHANES 1999 to 2004, CRP was independently associated with increased odds for the presence of MA ($P=0.0003$) in this large, nationally representative dataset.²⁷ Furthermore, higher intercellular adhesion molecule 1 (ICAM-1) was also associated with progressive albuminuria in type 1 DM over 9 years in a longitudinal analysis.²⁸

Diet

Diet represents another potentially modifiable risk factor for albuminuria. An analysis of diet patterns and albuminuria in >5000 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) reported a direct association between animal food intake and ACR, but there was an inverse association between fruit and vegetable intake and ACR.²⁹ Consumption of animal fats has been reported to significantly alter kidney structure and function. Wistar rats fed a high animal fat diet of lard and egg yolk had decreased glomerular number and size (and the greatest increase in blood pressure) when compared with rats fed a high-fat diet of canola oil, which is high in monounsaturated fat.³⁰ In aging rats fed canola oil, fish oil, or butter, eGFR decline was greatest in the animals receiving the butter, which is high in saturated fat.³¹ Published literature on dietary fat and kidney function in humans, however, is currently very limited. One observational dietary study³² in 48 Australian patients with type 1 DM and MA compared with 130 patients with DM and no MA found an odds ratio of 4.9 (95% CI, 1.2–20.0) for MA when the highest to lowest quintile of saturated fat intake was compared. Further investigations in the area of diet and early kidney dysfunction deserve attention.

Summary

In the assessment of albuminuria, first morning spot urine and sex-specific ACR is the preferred method. MA appears to be an important predictor of overt nephropathy and kidney function decline in diabetics and nondiabetics. Recent evidence demonstrates that levels of albuminuria below the “traditional” MA range confer significantly elevated CV and mortality risk; therefore, the traditional definition of clinically relevant MA as being >30 mg/24 hrs should be revised. Additional work in examining changes in ACR over time and clinical outcomes, especially in nondiabetics, is needed to establish whether a decrease in ACR is a clinically appropriate effectiveness measure for medical therapy. Also, more studies are required to examine potentially modifi-

able risk factors for albuminuria (eg, inflammation and diet) and whether amelioration of these factors decreases not only albuminuria, but also subsequent renal, CV, and mortality risk.

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Abstracts of Interest

Screening for albuminuria identifies individuals at increased renal risk

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It is unknown whether screening for albuminuria in the general population identifies individuals at increased risk for renal replacement therapy (RRT) or accelerated loss of renal function. Here, in a general population-based cohort of 40,854 individuals aged 28 to 75 yr, we collected a first morning void for measurement of urinary albumin. In a subset of 6879 individuals, we measured 24-h urinary albumin excretion and estimated GFR at baseline and during 6 yr of follow-up. Linkage with the national RRT registry identified 45 individuals who started RRT during 9 yr of follow-up. The quantity of albuminuria was associated with increased renal risk: the higher the level of albuminuria, the higher the risk of need for renal replacement therapy and the more rapid renal function decline. A urinary albumin concentration of ≥ 20 mg/L identified individuals who started RRT during follow-up with 58% sensitivity and 92% specificity. Of the identified individuals, 39% were previously unknown to have impaired renal function, and 50% were not being medically treated. Restricting screening to high-risk groups (e.g, known hypertension, diabetes, cardiovascular disease [CVD], older age) reduced the sensitivity of the test only marginally but failed to

identify 45% of individuals with micro- and macroalbuminuria. In conclusion, individuals with elevated levels of urinary albumin are at increased risk for RRT and accelerated loss of renal function. Screening for albuminuria identifies patients at increased risk for progressive renal disease, 40 to 50% of whom were previously undiagnosed or untreated. *J Am Soc Nephrol.* 2009;20(4):852-862.

Should albuminuria be a focus of antihypertensive therapy goals?

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Albuminuria has been recognized as a risk marker for both chronic kidney disease and cardiovascular disease in large observational cohorts. In addition, *post hoc* analyses of many large randomized trials have found a positive relationship between albuminuria and adverse renal and cardiovascular outcomes, leading some to suggest that albuminuria may be a potential therapeutic target for antihypertensive treatment. However, direct clinical evidence linking albuminuria reduction to reduction in adverse renal and cardiovascular events is scarce. This paper reviews the evidence in the current literature to address whether albuminuria can be used as a credible predictor of risk for chronic kidney disease and cardiovascular disease and also reviews the clinical trial evidence to appraise the prospect of using albuminuria as a therapeutic target to prevent adverse renal and cardiovascular events. *Curr Hypertens Rep.* 2009;11(5):354-362.

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