terminal differentiation of the tubule. Most mechanistic insights into renal tubule formation are based on in vitro studies with MDCK cells and to a lesser extent, collecting duct cells, because the phenotypes of mice, where proteins are often selectively deleted and/or overexpressed in specific nephron segments, are usually assessed by standard histology, which fails to provide information and/or details on tubule morphogenesis. This shortcoming may be changed by new imaging technologies similar to those technologies described in the work by Kao et al., which can verify whether observations made in vitro are recapitulated in mammals. For example, the work by Kao et al. shows that the distal metanephric mesenchyme cells that invade the ureteric bud do not express occludin, zona occludens-1, and activated β-catenin, suggesting that they acquire mesenchymal features compared with the epithelial features found in other cells of the S-shaped body. These observations differ from the MDCK cell model of tubule and lumen formation, where there are tight connections between the cells and high expression of tight junction proteins.

Another key finding in the paper by Kao et al. is that the invasive phenotype is highly dependent on Notch signaling. In addition to Notch, many molecular pathways have been shown to be critical for tubule lumen formation in MDCK and collecting duct cell models; however, whether the same mechanisms and/or pathways that occur in vitro also work in vivo is unclear. Functional disruption of integrin β1, the key molecule that regulates epithelial cell interactions with extracellular matrix, is a good example of this situation. Inhibition of the integrin β1 subunit in either MDCK or collecting duct cells in three-dimensional gels results in cyst formation with poorly formed lumens. In contrast, selective deletion of this subunit in the ureteric bud primarily results in decreased branching, whereas tubular lumens seem to form normally as assessed by histologic examination. These mice develop severe collecting duct dilatation after birth. It is possible that the tubular dilatation was caused by incomplete lumen formation, which could be assessed by the new imaging techniques and the state of the art tools described in the work by Kao et al.

In conclusion, the rapid advances of sophisticated imaging techniques combined with the generation of transgenic mice expressing differentially fluorescently labeled cells allows us to visualize morphogenesis in vivo with improved resolution. These tools will help cross the wide gap that exists between in vivo and in vitro model systems by enabling us to verify whether the mechanisms controlling tubule formation in vivo are the same as those mechanisms identified in cell culture models. Understanding one of the most complex morphogenetic processes in metazoans will help define basic mechanisms of abnormal tubule formation in pathologic conditions.

DISCLOSURES

None.

REFERENCES


Urinary Albumin: How Low Is Normal?

Jiang He and Jing Chen
Department of Epidemiology and Medicine, Tulane University School of Public Health and Tropical Medicine, and Tulane University School of Medicine, New Orleans, Louisiana


CKD is not only a major cause of ESRD but also cardiovascular disease and premature death.1–3 Prospective cohort studies document that macroalbuminuria (urinary albumin >300 mg/24 h or >200 μg/min) and microalbuminuria (urinary albumin 0–300 mg/24 h) are associated with increased risk of cardiovascular disease and mortality.4–7 The relationship between microalbuminuria and cardiovascular disease risk is uncertain.8–10 Prospective cohort studies with sufficient power and follow-up are needed to determine the association between microalbuminuria and cardiovascular disease risk.
albumin 30–300 mg/24 h or 20–200 μg/min) associate with increased risk of cardiovascular disease in the general population\textsuperscript{3–5} and in patients with diabetes.\textsuperscript{6,7} Furthermore, prospective cohort studies indicate that the association between urinary albumin and risk of cardiovascular disease is continuous without threshold effects, and is independent from other cardiovascular disease risk factors.\textsuperscript{4,6–8}

The Chronic Kidney Disease Prognosis Consortium pooled data from 105,872 participants (730,577 person-years) from 14 studies to examine the association between urinary albumin/creatinine ratios (ACRs) and mortality from cardiovascular disease and all causes.\textsuperscript{8} Compared with an ACR of 5 mg/g, hazard ratios (HRs) and 95% confidence intervals (95% CIs) were 1.20 (1.15–1.26), 1.63 (1.50–1.77), and 2.22 (1.97–2.51) for all-cause mortality at ACRs of 10, 30, and 300 mg/g, and 1.13 (1.07–1.20), 1.55 (1.30–1.86), and 2.59 (1.95–3.44) for cardiovascular mortality, respectively, after adjusting for age, sex, race, history of cardiovascular disease, systolic BP, serum total cholesterol, diabetes, cigarette smoking, and estimated GFR.\textsuperscript{8,9}

This issue of JASN presents a report by Piero Ruggenenti and the Bergamo Nephrologic Diabetes Complication Trial (BENEDICT) study investigators on the relationships between urinary albumin and long-term cardiovascular events in 1208 hypertensive type 2 diabetic patients with normal urinary albumin who participated in the BENEDICT trial.\textsuperscript{10} This study is unique because all study participants had a urinary albumin <20 μg/min (30 mg/24 h) in two of three overnight urine collections at the baseline examination. A continuous nonlinear relationship between urinary albumin and combined cardiovascular events was observed without thresholds.\textsuperscript{10} A one-unit increase in urinary albumin (1 μg/min or 1.44 mg/24 h) was independently associated with a 5% increase in cardiovascular events (HR, 1.05; 95% CI, 1.02–1.08) after adjusting for age, sex, duration of diabetes, cigarette smoking, history of cardiovascular disease, body mass index, hemoglobin A1c, randomization to angiotensin converting enzyme (ACE) inhibitor therapy during the trial, mean arterial pressure, serum creatinine, LDL/HDL cholesterol ratio, triglycerides and uric acid levels, and treatment with lipid lowering therapy. Furthermore, the excess risk of cardiovascular disease (HR, 1.02; 95% CI, 1.01–1.04) was observed in individuals with a urinary albumin of 1–2 μg/min (1.44–2.88 mg/24 h) compared with those with a urinary albumin <1 μg/min (<1.44 mg/24 h).

These data confirm a continuous association between urinary albumin and increased risk of cardiovascular disease. Moreover, this study indicates that any degree of measurable urinary albumin increases risk of cardiovascular disease. Therefore, there is no normal measurable urinary albumin. However, one must bear in mind that these data are from an observational study conducted in patients with hypertension and diabetes. It is possible that measurable urinary albumin reflects residual and unmeasured confounding effects. In addition, repeated measures of urinary albumin were not available, and the longitudinal relationship between changes in urinary albumin and risk of cardiovascular disease cannot be investigated. Finally, it remains unknown whether this relationship between urinary albumin and risk of cardiovascular disease is the same in the normotensive nondiabetic population.

Another interesting finding from this study is that the association between urinary albumin and risk of cardiovascular disease disappeared among the trial participants who were originally assigned to ACE inhibitor therapy.\textsuperscript{10} This finding is not entirely expected because all trial participants received ACE inhibitor therapy during the average 9.2 years of posttrial follow-up. A statistical test for interaction between initial treatment assignments in the BENEDICT trial and urinary albumin on the risk of cardiovascular events was not performed. Therefore, one cannot exclude the possibility that this observation was due to chance alone.

There is strong evidence that treatment of microalbuminuria and macroalbuminuria with ACE inhibitors or angiotensin II–receptor blockers slows the progression of kidney disease.\textsuperscript{11,12} In a meta-analysis of 85 randomized controlled trials (21,708 patients), there is a significant reduction in the development of ESRD, progression of microalbuminuria to macroalbuminuria, and risk of nonfatal cardiovascular disease with ACE inhibitors versus placebo.\textsuperscript{11} However, there was no significant reduction in deaths from all-cause mortality or cardiovascular disease with ACE inhibitors versus placebo.\textsuperscript{11} The recent US Preventive Services Task Force Report indicates that ACE inhibitors (relative risk [RR], 0.65; 95% CI, 0.49–0.88) and angiotensin II–receptor blockers (RR, 0.77; 95% CI, 0.66–0.90) reduce ESRD versus placebo in stage 1–3 diabetic patients with CKD and macroalbuminuria.\textsuperscript{12} ACE inhibitors reduce mortality versus placebo (RR, 0.79; 95% CI, 0.66–0.86) in patients with microalbuminuria and cardiovascular disease or high-risk diabetes.\textsuperscript{12}

Given the observational design, this study cannot recommend treating patients with a measurable urinary albumin within normal range (<30 mg/24 h). However, this study can generate hypotheses for further clinical trials. Cost-effectiveness must be taken into account if a randomized controlled trial is to tackle this issue.

DISCLOSURES
None.

REFERENCES
How Benign Is IgA Nephropathy with Minimal Proteinuria?

Benjamin J. Freda and Gregory L. Braden
Division of Nephrology, Baystate Medical Center, Springfield, Massachusetts; and Tufts University School of Medicine, Boston, Massachusetts

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IgA nephropathy (IgAN) is the most common primary GN in the world.1 Although IgAN is characterized by dominant mesangial IgA deposits, the overall histologic features and clinical course are highly variable, resulting in controversy regarding optimal approaches to guide assessment of prognosis and treatment.2,3 The natural history of IgAN can range from clinically silent urinary abnormalities and preserved renal function over many decades to ESRD. Progression to ESRD occurs in 10%–50% of patients, usually developing slowly over 20 years.4,5 Ten-year survival rates (62%–98%) are also highly variable.6,7

In regions where renal biopsies are routinely performed for isolated urinary abnormalities (microscopic hematuria, minimal proteinuria <0.5 g/d), the incidence of IgAN is higher, and the estimates of renal survival are affected by lead-time bias. A more fully informed understanding of the natural history of IgAN across its entire clinical and histologic spectrum could assist clinicians in assessing prognosis and implementing treatment.

Much has been learned over the last 20–30 years regarding risk stratification of IgAN.3 Clinical parameters that correlate with increased risk of progression of disease include proteinuria >1 g/d, hypertension, and reduced GFR. The impact of these variables on prognosis is strengthened when they are followed over time. In contrast to other glomerular diseases, proteinuria in IgAN at an excretion rate of even 0.5–1.0 g/d is associated with risk of ESRD.3

Histologically, two of the strongest pathologic predictors of progression of IgAN have been the degree of tubulo-interstitial fibrosis/tubular atrophy and glomerulosclerosis.3 Previous histologic scoring systems focused on glomerular lesions and have not been conclusively shown to offer prognostic information independent of clinical factors.8 Recently, the Oxford Classification of IgAN was published describing reproducible histologic parameters in 265 patients from 17 centers in Asia, Europe, North America, and South America with IgAN and proteinuria >0.5 g/d.9 Mesangial hypercellularity, endocapillary

See related article, “Measurable Urinary Albumin Predicts Cardiovascular Risk among Normoalbuminuric Patients with Type 2 Diabetes,” on pages 1717–1724.

References


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Correspondence: Dr. Gregory Braden, Baystate Medical Center/Tufts University School of Medicine, 100 Wason Avenue, Suite 200, Springfield, MA 01108. Email: Benjamin.freda@bhs.org

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