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Original Investigation

Comparison of Urinary Albumin and Urinary Total Protein as Predictors of Patient Outcomes in CKD

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Background: Proteinuria is common and is associated with adverse patient outcomes. The optimal test of proteinuria to identify those at risk is uncertain. This study assessed albuminuria and total proteinuria as predictors of 3 patient outcomes: all-cause mortality, start of renal replacement therapy (RRT), and doubling of serum creatinine level.

Study Design: Retrospective longitudinal cohort study.

Setting & Participants: Nephrology clinic of a city hospital in Scotland; 5,586 patients with chronic kidney disease (CKD) and proteinuria measured in random urine samples (n = 3,378) or timed urine collections (n = 1,808).

Predictors: Baseline measurements of albumin-creatinine ratio (ACR), total protein–creatinine ratio (PCR), 24-hour albuminuria, and total proteinuria.

Outcomes: All-cause mortality, start of RRT, and doubling of serum creatinine level were assessed using receiver operating characteristic curves and Cox proportional hazards models.

Measurements: Blood pressure, serum creatinine level, ACR, PCR, date of death, date of starting RRT.

Results: Patients were followed up for a median of 3.5 (25th-75th percentile, 2.1-6.0) years. For all outcomes, adjusted HRs were similar for PCR and ACR (derived from random urine samples and timed collections): death, 1.41 (95% CI, 1.31-1.53) vs 1.38 (95% CI, 1.28-1.50); RRT, 1.96 (95% CI, 1.76-2.18) vs 2.33 (95% CI, 2.06-3.01); and doubling of serum creatinine level, 2.03 (95% CI, 1.87-2.19) vs 1.92 (95% CI, 1.78-2.08). Receiver operating characteristic curves showed almost identical performance for ACR and PCR for the 3 outcome measures. Adjusted HRs for ACR and PCR were similar when derived from random urine samples or timed collections and compared with 24-hour total protein and albumin excretion for each outcome measure.

Limitations: This is a retrospective study.

Conclusions: Total proteinuria and albuminuria perform equally as predictors of renal outcomes and mortality in patients with CKD. ACR and PCR were as effective as 24-hour urine samples at predicting outcomes and are more convenient for patients, clinicians, and laboratories. Both ACR and PCR stratify risk in patients with CKD.

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Editorial, p. 1

Proteinuria is common, with a prevalence of 1.3% (frank proteinuria) to 8.2% (microalbuminuria) in the US general population,[1] and is associated with adverse patient outcomes.

Total proteinuria is the single strongest predictor of renal risk, predicting progressive kidney disease and end-stage kidney disease.[2-4] In patients with diabetes mellitus, albuminuria predicts progressive kidney disease,[5] but the importance of albuminuria (as opposed to total proteinuria) in those with nondiabetic kidney disease is less well established. It predicts progression to end-stage renal disease in those with decreased estimated glomerular filtration rate (eGFR)[6] and de novo decreases in kidney function in the general population.[7]

Albuminuria also is associated with increased risk of cardiovascular disease and death in both diabetic and nondiabetic populations,[8,9] even at levels less than microalbuminuria.[10,11] Proteinuria assessed using dipstick urinalysis is associated with increased cardiovascular risk[12]; however, dipsticks mainly mea-

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sure albumin. The impact of total proteinuria on mortality has been less well characterized.

Quantification of proteinuria therefore is essential to stratify risk, but should it be measured as total proteinuria or albuminuria? Some guidelines recommend using albumin-creatinine ratio (ACR) for all patients with chronic kidney disease (CKD),[13,14] whereas others recommend restricting ACR to patients with diabetes mellitus and using total protein–creatinine ratio (PCR) for all others.[15,16]

The biochemistry laboratory in Glasgow Royal Infirmary routinely analyzes urine samples for both albumin and total protein. We assessed which was the superior predictor of renal outcomes and mortality in patients with CKD attending our clinic.

METHODS

Participants and Setting

Since 1987, clinical details of all patients attending the renal clinic at Glasgow Royal Infirmary have been entered into an electronic patient record (Proton; Clinical Computing UK Ltd, www.ccl.com), which also receives laboratory data electronically. Urine albumin, total protein, and creatinine quantification is requested routinely for all patients. Twenty-four–hour urine collections are obtained on request by individual clinicians. We retrospectively searched our database for all patients who had total protein, albumin, and creatinine measured on a urine sample on the same date. For most patients, this was measured in a spot sample. However, for the minority who performed a 24-hour urine collection, ACR and PCR were calculated from an aliquot of the 24-hour urine collection. The earliest available paired results for ACR and PCR were used. Samples from 1999 onward were used because details of laboratory assays before this date were not available. Patients were excluded from analysis if they were younger than 18 years, on renal replacement therapy (RRT), or had less than 1 year of follow-up available (on the basis that there was insufficient exposure to the variable of interest). The following baseline data also were obtained: sex, age at time of urine sample, primary kidney disease, use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, weight, height, blood pressure, serum creatinine level, eGFR, and contemporaneous 24-hour urine protein excretion (if available). Subsequent measurements of serum creatinine and eGFR were obtained. The following outcomes also were recorded: date of death and date of starting RRT for established kidney failure (RRT for acute kidney injury was excluded from this analysis).

For the last decade, written consent for use of the electronic patient record has been obtained from patients, and the consent specifically states that the data will be used for purposes of audit and research in addition to routine clinical care. Data were downloaded with patient identifiers removed before further analysis. The National Health Service National Research Ethics Service confirmed that ethical approval was not required for this analysis.

Laboratory Assays

The biochemistry laboratory measures ACR and PCR in all samples from the renal service and has done so consistently since November 29, 1999. Twenty-four–hour urine collections are assayed for volume, protein, albumin, and creatinine concentrations. Other investigations usually include serum creatinine. The electronic patient record calculates eGFR using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[17,18] No modification is made for race to the eGFR calculation; however, race is relatively homogeneous in our population (95.5%-98.9% white, 0.74%-3.71% Indo-Asian, 0.09%-0.23% black, and 0.3%-0.59% from other minority ethnic groups).[19]

Before August 2006, urine albumin was measured on an Advia 1650 analyzer (Siemens [formerly Bayer Diagnostics]; www.siemens.com) using an immunoturbidimetric method with anti–human albumin antiserum. Mean between-batch coefficient of variation (CV) was 4.4% at a concentration of 54 mg/L. The urine total protein assay was performed on the same analyzer using the pyrogallol red colorimetric method, with a mean between-batch CV of 8.32% at a concentration of 0.56 g/L. In August 2006, the analyzer was replaced by an Abbott Architect 2000 (www.abbott.com). Subsequently, urinary albumin was measured with an immunoturbidimetric method using anti–human albumin antiserum, with mean between-batch CVs of 3.65% at 29.9 mg/L and 1.65% at 127 mg/L. The lower limit of detection for urine albumin is <3 mg/L. Patients with urine albumin excretion <3 mg/L were analyzed as 3 mg/L.

Urinary total protein was analyzed using a turbidimetric method with benzethonium precipitation. This assay runs with a mean between-batch CV of 3.4% at a concentration of 0.16 g/L and CV of 1.7% at 0.59 g/L. Urine creatinine was assayed using a reaction rate Jaffé method with Abbott reagents. Mean between-batch CVs are 3.4% at a concentration of 5.9 mmol/L and 3.0% at 13.2 mmol/L. In-house comparison was made between results obtained using the Bayer Advia 1650 and the Abbott Architect 2000, and no significant differences were found in precision and accuracy between results obtained before and after the change in instrumentation for these analytes. Returns to the UK External Quality Assurance Scheme showed no change in accuracy, precision, or bias in the laboratory's results during this period. The laboratory is fully accredited by Clinical Pathology Accreditation (UK) Ltd.

Statistical Analyses

Data were analyzed using SPSS 16.0 for Windows (SPSS Inc, www.spss.com). All data were assessed for normality, and appropriate summary statistics are presented. Urine creatinine results were reported by the laboratory in millimoles per liter, which were converted to grams per liter to aid interpretation of results.

A hierarchical Cox regression survival analysis was constructed for the outcomes of all-cause mortality, start of RRT, and doubling of serum creatinine level. The covariates of age, sex, blood pressure, and serum creatinine level were entered in the first block, and either ACR, PCR, 24-hour urine albumin excretion, or 24-hour urine total protein excretion was entered in the second block. PCR, ACR, 24-hour urine total protein excretion, and 24-hour urine albumin excretion were converted to a log scale, and ACR and PCR were standardized. The hazard ratios presented for ACR and PCR are for 1-SD (standard deviation) difference. Cases were excluded from the Cox regression survival analysis if any variables were missing (mostly blood pressure). Analyses were repeated with missing variables imputed using regression to ensure there was no influence on the model.

The linearity of each continous predictor was tested by calculating martingale residuals for the Cox regression model without the predictor and then plotting these against the predictor using LOWESS (locally weighted scatterplot smoothing). The proportional hazards assumption was tested by creating time-dependent covariates for each predictor and including them in the model if the interaction was significant. The albumin assay changed in August 2006; therefore, sensitivity analysis was performed for samples before the assay change in 2006.