AJKD
Original Investigation

Urine Albumin-Creatinine Ratio Versus Albumin Excretion for Albuminuria Staging: A Prospective Longitudinal Cohort Study

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Background: New guidelines advocate the use of albumin-creatinine ratio (ACR) in a urine sample instead of 24-hour urinary albumin excretion (UAE) for staging albuminuria. Concern has been expressed that this may result in misclassification for reasons including interindividual differences in urinary creatinine excretion.

Study Design: Prospective longitudinal cohort study.

Setting & Participants: We examined 7,623 participants of the PREVEND and RENAAL studies for reclassified when using ACR instead of 24-hour UAE, the characteristics of reclassified participants, and their outcomes. Albuminuria was categorized into 3 ACR and UAE categories: <30, 30 to 300, and >300 mg/g or mg/24 h, respectively.

Predictors: Baseline ACR and 24-hour UAE.

Outcomes: Cardiovascular (CV) morbidity and mortality and all-cause mortality.

Results: When using ACR in the early morning void instead of 24-hour UAE, 88% of participants were classified in corresponding albuminuria categories. 307 (4.0%) participants were reclassified to a higher, and 603 (7.9%), to a lower category. Participants who were reclassified to a higher ACR category in general had a worse CV risk profile compared with nonreclassified participants, whereas the reverse was true for participants reclassified to a lower ACR category. Similarly, Cox proportional hazards regression analyses showed that reclassification to a higher ACR category was associated with a tendency for increased risk for CV morbidity and mortality and all-cause mortality, whereas reclassification to a lower ACR category was associated with a tendency for lower risk. Net reclassification improvement, adjusted for age, sex, and duration of follow-up, was 0.107 ($P = 0.002$) for CV events and 0.089 ($P < 0.001$) for all-cause mortality.

Limitations: Early morning void urine collection instead of spot urine collection.

Conclusions: Our results indicate that there is high agreement between early morning void ACR and 24-hour UAE categories. Reclassification is therefore limited, but when present, is generally indicative of the presence of CV risk factors and prognosis.

Am J Kidney Dis. 67(1):70-78.

INDEX WORDS: Albuminuria; albumin-creatinine ratio (ACR); urinary albumin excretion (UAE); cardiovascular outcome; mortality; risk categorization; albuminuria staging; PREVEND (Prevention of Renal and Vascular Endstage Disease); RENAAL (Reduction of Endpoints in Non−Insulin-Dependent Diabetes With the Angiotensin II Antagonist Losartan).

It has been established that elevated albuminuria is a valuable risk marker for renal and cardiovascular (CV) complications.[1-5] Albuminuria can be assessed in several ways, of which 24-hour urinary albumin excretion (UAE) measurement was long considered the gold standard. However, recent guidelines advocate the use of albumin-creatinine ratio (ACR) in a urine sample from an early morning void.[6] Opponents of the use of ACR to assess albuminuria argue that individuals identified as having increased albuminuria based on ACR may have no evidence of increased albuminuria by 24-hour urine collection.[7,8]

One reason for discrepancy in albuminuria staging based on ACR versus 24-hour UAE is that an increased ACR may be due not only to an increase in albuminuria, but also to a decrease in urinary creatinine concentration. Creatinine, as waste product of muscle catabolism, is dependent on muscle mass and consequently differs by, among other factors, age and sex. Another reason is that albuminuria is subject to a circadian rhythm, whereas urinary creatinine excretion is fairly stable during the day.[9] Assessment of ACR in an early morning urine sample may therefore differ from the ACR in a 24-hour urine collection. A third reason is that 24-hour UAE is subject to collection errors, and reclassification

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Received January 15, 2015. Accepted in revised form May 26, 2015. Originally published online July 15, 2015.

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0272-6386
http://dx.doi.org/10.1053/j.ajkd.2015.05.025

to another risk category based on spot urine ACR may be due to incorrect 24-hour urine collection.

The aim of this study was to analyze the importance of misclassification when evaluating albuminuria by ACR in an early morning urine sample instead of 24-hour UAE. Importance is assessed by calculating the percentage of participants in which it occurs, as well as by studying whether reclassification reflects clinical characteristics and prognosis in these participants. For these analyses, we used data from 2 studies in which 24-hour urine and early morning urine samples were available and allowed calculation of 24-hour UAE and ACR.

METHODS

Study Overview

This study is a collaboration between the investigators of the PREVEND (Prevention of Renal and Vascular Endstage Disease) Study and the RENAAL (Reduction of Endpoints in Non−Insulin-Dependent Diabetes with the Angiotensin II Antagonist Losartan) Study. This collaboration was established to ensure sufficient participants in all 3 albuminuria classes of the present chronic kidney disease (CKD) staging system for analyses.

Study Design and Population

The PREVEND Study is a prospective cohort study that investigates the natural course of albuminuria and its relation to kidney and CV disease (CVD). Details of the study protocol have been published elsewhere.[10,11] In brief, participants in the PREVEND Study were selected in 1997 from individuals aged 28 to 75 years in the general population in Groningen. Pregnancy and insulin use were exclusion criteria. In total, 8,592 individuals participated in the first screening (1997-1998), of whom 6,000 had urinary albumin concentrations $>$ 10 mg/L in the spot morning urine sample and 2,592 participants had urinary albumin concentrations $<$ 10 mg/L. This screening consisted of 2 outpatient clinic visits, at which baseline measurements were performed. Part of this screening was that participants collected two 24-hour urine samples, of which the first sample was used for the present analyses.

The RENAAL Study is a multinational, double-blind, randomized, placebo-controlled study that evaluated the renal protective effects of the angiotensin II blocker losartan in patients with type 2 diabetes and nephropathy. The study was initiated in 1996, and patient enrollment was completed in 1998. The study design and results have been reported elsewhere.[12-14] In brief, inclusion criteria for the RENAAL Study were as follows: type 2 diabetes (assessed as age $>$ 30 years at time of diagnosis, no history of ketoacidosis, and not using insulin therapy within 6 months after diagnosis), serum creatinine level of 1.3 to 3.0 mg/dL (1.5-3.0 mg/dL for males heavier than 60 kg), urinary ACR from a first morning specimen of at least 300 mg/g, hemoglobin A_{1c} level $<$ 12%, and aged 31 to 70 years. All patients collected at baseline a first morning void urine sample for albumin and creatinine assessment. In addition, a random sample of 701 patients collected 24-hour urine samples for UAE quantification.

Both studies were approved by medical ethics committees, conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines, and adhere to the ethical principles that have their origin in the Declaration of Helsinki.

For the present analyses, we use data from participants (N = 7,623) in the 2 studies for whom 24-hour and early morning urine samples were available and allowed calculation of 24-hour UAE and ACR in an early morning sample (6,922 of 8,592 PREVEND participants and 701 of 1,513 RENAAL participants). There were too few participants in the PREVEND Study with severely increased albuminuria (ie, albumin excretion $>$ 300 mg/g or $>$300 mg/24 h) and too few participants in the RENAAL Study with normal to mildly increased albuminuria (albumin excretion $<$ 30 mg/g or $<$30 mg/24 h) to allow separate analysis of the effect of reclassification when using an early morning void ACR instead of 24-hour UAE according to KDIGO (Kidney Disease: Improving Global Outcomes) albuminuria stages. Therefore, we combined the PREVEND and RENAAL studies to study with sufficient power the effect of reclassification when using early morning void ACR− instead of 24-hour UAE–defined albuminuria categories.

Measurements and Definitions

At the baseline visit, anthropometric measurements were performed, blood pressure was measured, and fasting blood and urine samples were taken in which analytes were measured using routine methodologies. Urinary albumin was measured by nephelometry (PREVEND: BNII; Dade Behring Diagnostic; RENAAL: Beckman Array; Beckman).

CVD history was defined by self-report. Hypertension was defined in accordance with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) criteria as systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg or use of antihypertensive medication. Diabetes was defined in accordance with American Diabetes Association (ADA) criteria as fasting glucose level $>$ 7.0 mmol/L or nonfasting glucose level $>$ 11.1 mmol/L or use of antidiabetic medication. Body mass index was calculated as the ratio between weight and the square of height.

Albuminuria Measures

The 24-hour UAE (in mg/24 h) is given as urinary albumin concentration times volume of one 24-hour urine collection. ACR (in mg/g) was calculated by dividing urinary albumin concentration (mg/L) by urinary creatinine concentration (g/L). Cutoff values indicating normoalbuminuria and moderately and severely increased albuminuria were defined in accordance with the prevailing KDIGO CKD guideline[6]: for ACR and 24-hour UAE, $<$30, 30 to 300, and $>$300 mg/g or mg/24 h, respectively.

Outcomes

The outcomes assessed were CV morbidity and mortality and all-cause mortality during follow-up. In the PREVEND Study, information for date and cause of death were obtained by record linkage with the Dutch Central Bureau of Statistics. Information for hospitalization for CV morbidity was obtained from Prismant, the Dutch national registry of hospital discharge diagnoses. In the RENAAL Study, information for CV morbidity and mortality were collected prospectively. For this study, incident CV morbidity was defined according major adverse cardiac event criteria.[13]

Statistical Analysis

To assess reclassification, we created 3 $\times$ 3 cross-tabulations using the mentioned clinically relevant cutoff values for 24-hour UAE and ACR. In these tables, the proportion of reclassified participants was calculated. McNemar test, a nonparametric test for comparing 2 related samples, was used to test the significance of the ratios of up- and downclassification between 24-hour UAE versus ACR. Differences in characteristics between nonreclassified and reclassified participants were calculated with χ^2 test for categorical data and analysis of variance (in case of normally distributed data) or Mann-Whitney test (in case of nonparametric data) for continuous data.