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Original Investigation

Estimated Albumin Excretion Rate Versus Urine Albumin-Creatinine Ratio for the Estimation of Measured Albumin Excretion Rate: Derivation and Validation of an Estimated Albumin Excretion Rate Equation

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Background: Glomerular filtration rate estimation equations use demographic variables to account for predicted differences in creatinine generation rate. In contrast, assessment of albuminuria from urine albumin-creatinine ratio (ACR) does not account for these demographic variables, potentially distorting albuminuria prevalence estimates and clinical decision making.

Study Design: Polynomial regression was used to derive an age-, sex-, and race-based equation for estimation of urine creatinine excretion rate, suitable for use in automated estimated albumin excretion rate (eAER) reporting.

Setting & Participants: The MDRD (Modification of Diet in Renal Disease) Study cohort (N = 1,693) was used for equation derivation. Validation populations were the CRIC (Chronic Renal Insufficiency Cohort; N = 3,645) and the DCCT (Diabetes Control and Complications Trial; N = 1,179).

Index Test: eAER, calculated by multiplying ACR by estimated creatinine excretion rate, and ACR.

Reference Test: Measured albumin excretion rate (mAER) from timed 24-hour urine collection.

Results: eAER estimated mAER more accurately than ACR; the percentages of CRIC participants with eAER within 15% and 30% of mAER were 33% and 60%, respectively, versus 24% and 39% for ACR. Equivalent proportions in DCCT were 52% and 86% versus 15% and 38%. The median bias of ACR was −20.1% and −37.5% in CRIC and DCCT, respectively, whereas that of eAER was +3.8% and −9.7%. Performance of eAER also was more consistent across age and sex categories than ACR.

Limitations: Single timed urine specimens used for mAER, ACR, and eAER.

Conclusions: Automated eAER reporting potentially is a useful approach to improve the accuracy and consistency of clinical albuminuria assessment.

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INDEX WORDS: Albuminuria; proteinuria; chronic kidney disease; creatinine; albumin-creatinine ratio (ACR) correction; creatinine excretion rate (CER) prediction; urine albumin-creatinine ratio.

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Because creatinine generation rate is determined largely by muscle mass,[1] creatinine-based glomerular filtration rate (GFR) estimation equations use demographic predictors of muscle mass (ie, age, sex, and race) to account for associated differences in creatinine generation rates.[2,3] In the steady state, urinary creatinine excretion rate (CER) is approximately equal to creatinine generation rate, so urine albumin-creatinine ratio (ACR) is a measure of albumin excretion rate (AER) per unit of muscle mass. Sex-specific ACR cutpoints for albuminuria categorization previously have been recommended,[4] but recent international guidelines recommend the application of ACR in milligrams per gram to approximate AER without adjustment for sex, age, or race.[5] Some previous studies correlated ACR with AER per 1.73 m^2 estimated body surface area (BSA) or protein-creatinine ratio (PCR) with protein excretion rate (PER) per 1.73 m^2, inferring CER is proportional to BSA.[6,7] However, in clinical practice, ACR is interpreted without reference to BSA. Failure to account for differences in muscle mass may distort albuminuria prevalence estimates and compromise the diagnostic performance of ACR.

The introduction of multiple age-, sex-, and race-specific cutpoints would make ACR interpretation complicated; a logical alternative is the application of

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a demographic-based equation to calculate estimated CER (eCER). Multiplying ACR (milligrams per gram) by eCER (grams per 24 hours) gives an estimated AER (eAER, in milligrams per 24 hours).[8] Such an approach could be applied in an automated fashion to laboratory ACR reporting, analogous to the current approach to estimated GFR (eGFR). A number of CER estimation equations previously have been derived,[9-13] but all incorporate weight as a predictor variable and thus cannot be applied automatically to laboratory reports. We therefore sought to derive and validate a CER estimation equation based solely on age, sex, and race in order to assess the merits of eAER reporting. Data from the Modification of Diet in Renal Disease (MDRD) Study regarding measured CER (mCER) were used for derivation of the CER estimation equation. The performance of eAER then was validated compared to measured AER (mAER) independently using data sets from the CRIC (Chronic Renal Insufficiency Cohort) Study and DCCT (Diabetes Control and Complications Trial). Comparison also was made with the performance of a weight-, age-, sex-, and race-based CER estimation equation recently derived by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) for the purpose of evaluating the completeness of timed urine collections.[9]

METHODS

Participants

The eligibility criteria, recruitment procedures, and measurement methods of the MDRD, CRIC, and DCCT-EDIC (Epidemiology of Diabetes Interventions and Complications) studies have been published previously.[14-16] Briefly, the MDRD Study was a randomized trial of the effects of dietary protein restriction and intensive blood pressure control on CKD progression.[14] Patients with insulin-dependent diabetes were excluded. Data from the first baseline assessment visit prior to randomization were used for equation derivation, excluding participants (n = 4) with mCER < 350 or >3,500 mg/24 h (considered likely to have inaccurate urine collection).[9] This left a total of 1,693 participants with results available for age, sex, race, and mCER.

The CRIC Study recruited participants aged 21-74 years with CKD to investigate risk factors for CKD progression and cardiovascular disease in patients with CKD.[15] Patients with polycystic kidney disease or on immunosuppression therapy for glomerulonephritis were excluded. Data from the baseline assessment visit were used for equation validation, including 3,645 participants with results available for age, sex, race, mCER, mAER, and measured PER in 24-hour urine samples (excluding n = 56 with mCER < 350 or >3,500 mg/24 h). Unlike the MDRD Study and DCCT cohorts, the CRIC Study did not form part of the data set used for derivation of the CKD-EPI CER estimation equation ($eCER_{CKD\text{-}EPI}$),[9] thus allowing comparison of eAER derived by the method described here versus that calculated using $eCER_{CKD\text{-}EPI}$ ($eAER_{CKD\text{-}EPI}$).

The DCCT recruited white participants aged 13-39 years with type 1 diabetes mellitus and preserved excretory function to assess the micro-/macrovascular benefits of more intensive glycemic control.[16] Timed 4-hour urine collection albumin and creatinine results from the closeout assessment visit were used for further equation validation, including a total of 1,179 participants with age, sex, race, and urine biochemistry data (excluding n = 7 with CER < 350 or >3,500 mg/24 h).

Data sets from these studies were provided by the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository[17] following institutional review board approval.

Equation Derivation

Urine CER estimation equations were derived in the MDRD Study cohort using least squares regression. Age, sex, and race were included a priori in the models as known determinants of creatinine generation rate.[9] Predictive models were limited to these variables in order to produce an equation suitable for widespread automated laboratory application, as currently applied for eGFR. BSA indexing was not applied prior to equation derivation, but the relationship of BSA (estimated by the formula of Dubois[18]) to mCER was examined using linear regression.

Based on the appearances of LOWESS (locally weighted scatterplot smoothing) curves relating mCER to age across sex and black/nonblack race groups, a quadratic term for age was included in regression analyses performed separately within these groups. Standard linear regression of mCER and log-transformed mCER also was performed. Equation performance was assessed by R^2 and root mean squared error, and the best performing equation was carried forward for independent validation of eAER.

Test and Reference Measures

eAER was calculated by multiplying ACR and eCER. In the CRIC cohort, the reference standard was mAER from a 24-hour urine collection. In the DCCT cohort, the reference standard was mAER extrapolated from a 4-hour urine collection.[19] Albuminuria was not measured in the MDRD Study cohort, so internal assessment of equation performance within this cohort was based on estimated PER with reference to 24-hour urine protein results. ACR, eAER, and estimated PCR values were obtained from the same timed urine collections that served as the reference measures in all cohorts.

The performance of eAER calculated from eCER was compared to that of ACR with/without sex-specific cutpoints and to eAER calculated using the $eCER_{CKD\text{-}EPI}$ formula[9] ($eAER_{CKD\text{-}EPI}$). $eCER_{CKD\text{-}EPI}$ is calculated as eCER (mg/24 h) = 879.89 + 12.51 × weight (kg) − 6.19 × age + (34.51 if black) − (379.42 if female). Threshold definitions of moderately increased[5] (previously micro-) albuminuria and severely increased (previously macro-) albuminuria applied were as follows: 30 and 300 mg/g for ACR, 17 and 250 mg/g for male-specific ACR cutpoints, 25 and 355 mg/g for female-specific ACR cutpoints, 30 and 300 mg/24 h for eAER, and 30 and 300 mg/24 h for mAER.

Equation Performance

Because an advantage of the eAER approach is that it is not confined to arbitrary cutpoint definitions, eAER performance was assessed using the same approach as that used to validate eGFR equations[3,20] (ie, consideration of bias, accuracy, and precision). Bias was assessed as the median difference between mAER and eAER, with precision expressed as the interquartile range of this difference. Accuracy was measured in terms of the percentages of individuals with eAER within 15% (P_{15}), 20% (P_{20}), or 30% (P_{30}) of the mAER. Bootstrap methods were used to compute 95% confidence intervals (CIs) for the median difference (2,000 bootstraps) and an adjusted Wald polynomial approximation[21] was used to estimate CIs for P_{15}, P_{20}, and P_{30}. Equation performance was assessed across sex, age, and race categories and strata of eGFR calculated using the 4-variable MDRD Study equation.[22] Weighted Cohen κ[23] was used to measure agreement in the categorization of normal, moderately increased, and severely increased albuminuria among CRIC participants. Due to the small