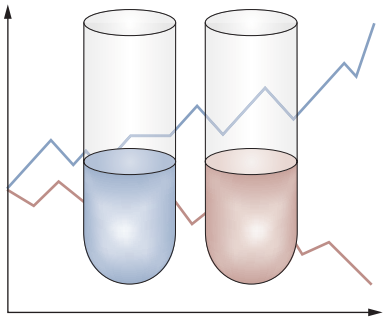
CHRONIC KIDNEY DISEASE

Use of urine albumin and cystatin C levels improves risk stratification in chronic kidney disease

The addition of serum cystatin C level to the combination of serum creatinine level and urine albumin-to-creatinine ratio (ACR) for the classification of chronic kidney disease (CKD) improves the prediction of risks of all-cause mortality and end-stage renal disease (ESRD), according to a study published in *JAMA*.

"The cornerstone of detection of CKD has been a serum test of creatinine level," explains researcher Carmen Peralta at the University of California, San Francisco. "However, as creatinine is made by muscle it can be inaccurate as a marker of kidney function in persons with unpredictable muscle mass, such as the very elderly. Cystatin C is an alternative marker of kidney function and has been shown to be a stronger predictor of death and cardiovascular disease; urinary albumin level has also been shown to be useful in identifying people at high risk of CKD complications. We thought that combining these variables in a triple-marker approach would improve the accuracy of predicting which individuals are at high risk of CKD complications."

Peralta *et al.* designed a prospective cohort study to determine whether the addition of urine ACR and serum cystatin C measurements in the classification of CKD improves risk prediction compared with use of creatinine-based estimates of glomerular filtration rate (GFR) alone. The study involved 26,643 black and white US adults aged ≥45 years who were enrolled in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study and for whom renal function data were available. After a baseline examination, participants were followed up by telephone every 6 months. Death reports (up to 30th June 2010) were confirmed by linkage to the social security death index or by review of death certificates, and incident ESRD (up to 31st August 2009) was



determined through the US Renal Data System database.

The researchers categorized participants into eight groups on the basis of their baseline GFR estimated by serum creatinine level (<60 ml/min/1.73 m^2 and ≥60 ml/min/1.73 m^2), baseline GFR estimated by serum cystatin C level (<60 ml/min/1.73 m^2 and ≥60 ml/min/1.73 m^2) and baseline urine ACR (<30 mg/g and ≥30 mg/g). These cutoff points are known risk thresholds for CKD complications. As CKD is defined as an estimated $GFR_{creatinine}$ of <60 ml/min/1.73 m^2 in most general clinical settings, the researchers first stratified analyses by the presence or absence of CKD by creatinine. The mean age of participants was 65 years; 40% of participants were black and 54% were female. Over a median follow-up period of 4.6 years, 1,940 individuals died and 177 developed incident ESRD.

"We found that using a triple-marker approach was more accurate in identifying people who were at higher risk for death or development of ESRD than was creatinine alone," reports Peralta. "Among 2,904 individuals who were labeled as having CKD by creatinine alone, 24% did not have CKD by either cystatin C level or urine albumin level. These individuals were not at increased risk of death or ESRD despite being labeled as having CKD by their serum creatinine level. Conversely, among people labeled as not having CKD by creatinine level, 16% were found to have occult CKD by cystatin C and/or albumin in the urine."

In multivariate analyses, the researchers found that the risk of death was higher among patients with CKD defined by creatinine plus urine ACR or cystatin C than among those with CKD defined by creatinine alone (hazard ratio for death was 5.6 for those with CKD defined by all three biomarkers, 3.2 for those with CKD defined by creatinine and cystatin C, and 3.3 for those with CKD defined by creatinine and urine ACR).

The risk of incident ESRD was highest in individuals with CKD defined by all three markers. The second highest rate of ESRD occurred in individuals who did not have CKD according to their creatinine level but did have CKD as defined by both urine ACR and serum cystatin C level.

Adding cystatin-C-based estimates of GFR to fully adjusted models with creatinine-based GFR estimates and ACR was associated with net reclassification improvements of 13.3% for death and 6.4% for ESRD.

"Our findings confirm prior reports that albuminuria quantification and cystatin C can improve risk stratification among those with CKD detected by creatinine," state the authors. "It is important to replicate these findings in other populations, such as the young, the elderly, and ethnic minorities," notes Peralta. "Our approach has important implications for future research because it shows that using a combination of markers to detect kidney disease is better than using one. How best to implement this information in clinical practice is a task for the future."

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Original article Peralta, C. A. *et al.* Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *JAMA* **305**, 1545–1552 (2011)