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Original Investigation

Comparison of Concurrent Complications of CKD by 2 Risk Categorization Systems

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Background: Using both estimated glomerular filtration rate (eGFR) and proteinuria to classify the severity of chronic kidney disease (CKD) has been proposed. The utility of a staging system incorporating both eGFR and proteinuria for guiding the evaluation of concurrent CKD complications is not known.

Study Design: Cross-sectional analysis.

Setting & Participants: 30,528 participants in the US National Health and Nutrition Examination Survey conducted in 1988-1994 and 1999-2006 (n = 8,242 for hyperparathyroidism).

Predictors: Classification system that uses both eGFR and proteinuria (alternative) and a system that primarily uses eGFR (NKF-KDOQI [National Kidney Foundation's Kidney Disease Outcomes Quality Initiative]).

Outcomes: Prevalence of anemia, acidosis, hyperphosphatemia, hypoalbuminemia, hyperparathyroidism, and hypertension.

Measurements: GFR estimated from the CKD Epidemiology Collaboration (CKD-EPI) equation and proteinuria assessed using urine albumin-creatinine ratio.

Results: Prevalences of hypoalbuminemia, hypertension, and hyperparathyroidism increased with more severe CKD using the NKF-KDOQI system. For example, the prevalence of hyperparathyroidism was 9.1%, 11.1%, 28.2%, and 72.5% for stages 1, 2, 3 and 4, respectively. Similarly, prevalences of anemia, acidosis, and hyperphosphatemia increased progressively from stage 2 through 4. With the alternative system, prevalences of anemia, hyperphosphatemia, hypertension, and hyperparathyroidism were lower in stage 3 than in stage 2. For example, the prevalence of hyperparathyroidism was 13.5%, 40.3%, 22.2%, and 63.4% for stages 1, 2, 3 and 4, respectively. Applying the alternative system, participants without each complication were more likely to be reclassified appropriately to lower stages (eg, overall net reclassification index of −6.5% for hyperparathyroidism). However, participants with complications (except for hypoalbuminemia) were more likely to be reclassified inappropriately to lower stages.

Limitations: Use of a single creatinine measurement to estimate GFR and single measurement to assess albumin-creatinine ratio. Small number of participants with CKD stage 4.

Conclusions: The NKF-KDOQI system may better identify patients with certain concurrent CKD complications compared with systems using eGFR and proteinuria.

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INDEX WORDS: Chronic kidney disease; glomerular filtration rate; albuminuria; anemia; acidosis; hyperphosphatemia; hyperparathyroidism; hypoalbuminemia; hypertension.

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) defines chronic kidney disease (CKD) as the presence of decreased estimated glomerular filtration rate (eGFR) or markers of kidney damage, generally determined by elevated proteinuria. However, the severity of CKD has been classified primarily by level of eGFR.[1,2] Although this classification system led to improved awareness of CKD,[3-5] it has been criticized on the grounds that it does not sufficiently differentiate between patients who are and are not likely to have adverse outcomes.[6] Recently, a KDIGO (Kidney Disease: Improving Global Outcomes) consensus conference proposed that CKD be classified using both proteinuria and eGFR.[7] The potential advantages of such an alternative system include improved specificity for classifying people at low risk of adverse outcomes, including progressive kidney disease and mortality, into lower CKD stages.[8]

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Although a system using both proteinuria and eGFR may more accurately stage individuals with respect to risk of future adverse outcomes, it is unknown whether such an approach would classify people with concurrent CKD complications better than eGFR alone. We previously showed in a general population sample that albuminuria, a specific type of proteinuria, and eGFR are associated differentially with certain concurrent CKD complications (anemia, acidosis, hyperphosphatemia, hypoalbuminemia, hyperparathyroidism, and hypertension), and that other than hypoalbuminemia, eGFR had a stronger association with each of these CKD complications than albuminuria.[9] We sought to evaluate the effect of using both eGFR and proteinuria to classify patients with respect to concurrent complications of CKD. Therefore, we calculated the prevalence of these complications of CKD across categories of a recently published CKD risk stratification system that incorporates both eGFR and proteinuria using data from the US National Health and Nutrition Examination Survey (NHANES).[8] For comparison, the prevalence of these 6 complications was calculated by CKD stage defined using the NKF-KDOQI classification system.

METHODS

Study Population

The NHANES are cross-sectional, multistage, stratified, clustered probability samples of the US civilian noninstitutionalized population conducted by the National Center for Health Statistics. The NHANES included in the present analysis were conducted in 1988-1994 in 2 phases (1988-1991 and 1991-1994) and 1999-2006 in 4 phases (1999-2000, 2001-2002, 2003-2004, and 2005-2006). Data from all phases were combined here following National Center for Health Statistics recommendations.[10] The present analysis was restricted to participants 20 years or older who completed both an interview and medical evaluation (n = 39,136). Those who were pregnant or missing measurements of urinary albumin or creatinine excretion, serum creatinine, phosphorus, hemoglobin, bicarbonate, serum albumin, or blood pressure were excluded from the present analyses. Participants with eGFR <15 mL/min/1.73 m^2 also were excluded because of the small number of individuals available in this group. After these exclusions, data for 30,528 participants were available for the analysis of anemia, acidosis, hyperphosphatemia, hypoalbuminemia, and hypertension. Intact parathyroid hormone (iPTH) was measured in only NHANES 2003-2004 and NHANES 2005-2006. Data were available for 8,242 participants for the analysis of iPTH.

Information for age, sex, and race/ethnicity (categorized as non-Hispanic white, non-Hispanic black, Mexican American, or all other) was based on self-report collected during the interview portion of the survey. Participants who reported having smoked 100 or more cigarettes during their lifetime were classified as current smokers if they reported currently smoking in NHANES III or smoking "some days" or "most days" in NHANES 1999-2006. Diabetes mellitus was defined as self-report of a previous diagnosis, not during pregnancy, with concurrent use of insulin or oral hypoglycemic medication or blood glucose level ≥126 mg/dL in participants who fasted 9 or more hours before their study visit or ≥200 mg/dL in nonfasting participants.

Measures of Kidney Function and Damage

Serum creatinine was assayed using the Synchron AS/Astra Analyzer (Beckman Coulter, www.beckmancoulter.com) in NHANES III and an LX20 analyzer (Beckman Coulter) in NHANES 1999-2006 and was recalibrated to standardized creatinine measurements.[11] eGFR was calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation.[12] Urine albumin and creatinine were measured on random spot urine samples obtained using a clean-catch technique and sterile containers in the same laboratory during each phase of NHANES. Urine albumin was measured by solid-phase fluorescence immunoassay and urine creatinine was measured by the modified kinetic Jaffé method using a Synchron AS/Astra Analyzer in NHANES III and a CX3 analyzer (Beckman Coulter) in NHANES 1999-2006. Urinary albumin-creatinine ratio (ACR) was computed and is reported in milligrams per gram (1 mg/g = 0.131 mg/mmol). Participants were classified according to NKF-KDOQI CKD staging, which primarily uses level of eGFR, and an alternative classification system, which uses level of both eGFR and ACR (Fig 1A).[2,8]

Assessment of CKD Complications

Complications that reflect different biological mechanisms were included. Hemoglobin was measured by Coulter Splus J in NHANES III and Beckman Coulter MAXM in the later surveys. Anemia was defined as hemoglobin level <12 g/dL for women and <13.5 g/dL for men.[13-15] Bicarbonate, phosphate, and serum albumin were assayed using Hitachi 737 (Roche Diagnositcs, www.roche.com/diagnostics) in NHANES III, Hitachi 704 (Roche Diagnostics) in NHANES 1999-2000, and Beckman-Synchron LX20 in the NHANES 2001-2006.[16,17] Acidosis was defined as serum bicarbonate level <22 mEq/L. Hyperphosphatemia was defined as serum phosphate level ≥4.5 mg/dL.[16] Hypoalbuminemia was defined as serum albumin level <3.5 g/dL. Serum iPTH was measured at the University of Washington, Seattle, WA, on an Elecsys 1010 autoanalyzer (Roche Diagnostics, www.roche.de), using an electrochemiluminescent process. This second-generation method uses a biotinylated monoclonal PTH-specific antibody and monoclonal PTH-specific antibody labeled with a ruthenium complex to form a sandwich complex. Hyperparathyroidism was defined as iPTH level ≥70 pg/mL.[18,19] To standardize laboratory values across all NHANES phases, age-, sex-, and race/ethnicity-adjusted differences in mean levels for hemoglobin, bicarbonate, phosphate, serum albumin, and iPTH for participants aged 20-39 years without diabetes and hypertension and with eGFR >60 mL/min/1.73 m^2 and ACR <10 mg/g for each survey were calculated. Differences from the mean values for NHANES 2005-2006 then were added/subtracted for values for all participants in the other NHANES phases. This approach has been used in prior analyses of NHANES data.[20] Blood pressure was measured 6 times in NHANES III and 3 times in NHANES 1999-2006. Using the average of all available blood pressure measurements, hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or self-reported use of antihypertensive medication.

Statistical Analyses

Demographic and clinical characteristics were summarized as mean values or proportions by each stage in the NKF-KDOQI classification system and the alternative classification system, separately. For each system, prevalences of anemia, acidosis, hyperphosphatemia, hyperparathyroidism, hypoalbuminemia, and hypertension were calculated by CKD stage. Additionally, using log-linear generalized estimating equations, prevalence ratios for all 6 complications were calculated for each stage; participants without CKD served as the referent.[21] Prevalence ratios were adjusted for age, race-ethnicity, sex, body mass index, total and high-density lipoprotein cholesterol levels, diabetes mellitus, his-