Urine Creatinine Excretion and Clinical Outcomes in CKD

Lucia Di Micco, Robert Ross Quinn,† Paul Everett Ronksley,† Vincenzo Bellizzi,‡ Adriane Marlene Lewin,† Bruno Cianciaruso,§ and Pietro Ravani,† for the Alberta Kidney Disease Network (AKDN)*

Summary

Background and objectives Twenty-four–hour urine creatinine excretion is a reliable approximation of muscle mass. Whether changes in urine creatinine predict clinical outcomes in persons with CKD is unknown. This work studied the relationship between urine creatinine and patient and renal survival in people with CKD not requiring renal replacement therapy.

Design, setting, participants, & measurements This longitudinal cohort study included incident stages 3–5 CKD patients referred to the renal clinic at the University Federico II in Naples between January of 1995 and December of 2005. Clinical data and urine creatinine were updated at each visit. Main outcomes were all-cause mortality and kidney failure requiring dialysis.

Results This study enrolled 525 individuals and followed them for a median of 6 years (range of 4 months to 15 years). Urine creatinine excretion declined by 16 mg/d per year (95% confidence interval, 14 to 19) in participants with CKD stages 3a, 3b, and 4, and it remained stable in participants with stage 5 CKD. Per each 20 mg/d decline in urine creatinine, mortality increased by 3% (adjusted hazard ratio, 1.03; 95% confidence interval, 1.01 to 1.05), and the risk of initiating dialysis increased by 2% (adjusted hazard ratio, 1.02; 95% confidence interval, 1.01 to 1.03). These associations were independent of body mass index and GFR.

Conclusions In persons with CKD stages 3 and 4, urine creatinine declines at a rate of 16 mg/d per year. Lower urine creatinine excretion predicts greater risk of kidney failure and patient mortality.

Clin J Am Soc Nephrol 8: 1877–1883, 2013. doi: 10.2215/CJN.01350213

*Department of Medicine, Division of Nephrology, Hospital A. Landolfi, Solofra (AV), Italy; †Departments of Medicine and Community Health Sciences, University of Calgary, Calgary, Alberta, Canada; ‡Division of Nephrology, Dialysis and Transplantation, University Hospital San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy; and §Department of Nephrology, University of Naples "Federico II," Naples, Italy

Correspondence: Dr. Pietro Ravani, University of Calgary, Faculty of Medicine, Foothills Medical Centre, 1403 29th Street NW, Calgary, AB T2N 2T9, Canada. Email: pravani@ucalgary.ca

Introduction

Abnormalities of body composition and impaired nutritional status are common findings across all stages of CKD (1). Although malnutrition may be a modifiable risk factor for clinical outcomes (including death), limited information is available on how best to assess body composition in persons with CKD. International guidelines recommend the combined use of anthropometry, bioelectrical impedance analysis, and dual x-ray absorptiometry in patients receiving dialysis, but little information is available to guide clinical assessment of nutritional status in CKD patients not yet requiring dialysis (2–4). Although simple, inexpensive, and safe, anthropometric measures, such as body mass index (BMI), arm circumference, mid-arm muscle circumference, and skinfolds, have several limitations and therefore, are used in combination with other tools, such as bioelectrical impedance analysis (4). However, their interpretation is limited by interobserver variability (5) and changes in fluid status (6). Bioelectrical impedance analyses of lean and fat mass have been shown to provide inaccurate estimations in the presence of anomalies of hydration status (6).

Twenty-four–hour urine creatinine (UCr) excretion is widely available and accepted as a reliable approximation of muscle mass in healthy people and people with CKD (7,8). However, because extrarenal excretion increasingly contributes to the total creatinine excretion as renal function declines (up to one third of total creatinine excretion in stage 5 CKD), there is uncertainty as to whether UCr predicts clinical outcomes independently of kidney function (9). Interestingly, in incident patients with kidney failure treated with hemodialysis or peritoneal dialysis who have some degree of residual kidney function, high UCr is associated with better outcomes (10,11). In addition, reduced UCr has been found to be associated with major cardiovascular events and mortality in the general population (12), mortality and graft loss after renal transplant in renal transplant recipients (13), and mortality in coronary artery disease patients (14). Whether similar associations exist in CKD patients not yet treated with dialysis is unknown but could have implications for patient management and future research.

We hypothesized that UCr predicts patient and renal survival in persons with CKD. To test this hypothesis, we studied the relationship between baseline and time-varying levels of UCr and patient and renal survival in a cohort of incident patients with CKD

(stages 3–5), including persons with kidney failure not receiving dialysis, accounting for levels of kidney function and BMI.

Materials and Methods

Patients and Study Design

We performed a longitudinal cohort study of persons with incident CKD (stages 3–5) referred for the first time to the renal clinic at Federico II University in Naples between January of 1995 and December of 2005. Participants had to be 18 years or older, provide informed consent, have an estimated GFR (eGFR; four-variable Modification of Diet in Renal Disease study equation) of 10–60 ml/min per 1.73 m^2 on at least two consecutive occasions within 6 months of referral (15), and return to the clinic at least one time after they were deemed eligible to have at least three measurements of 24-hour UCr excretion. After patients were deemed eligible, we averaged these first three measurements to calculate a baseline measurement. The index date was the date of the last serum creatinine measurement during the eligibility assessment period. Exclusion criteria were anticipated inability to perform a correct 24-hour urine collection, presence of malignancy, pregnancy or breastfeeding, treatment with steroids or immunosuppressive drugs in the previous year, use of nonsteroidal anti-inflammatory drugs more often than one time per week, and proteinuria >3 g/d (because fluid retention may modify the reliability of BMI as an indicator of nutritional status). As per center practice, patients returned to the clinic for blood work and clinical evaluation every 3–6 months in CKD stages 3a (eGFR=45–59 ml/min per 1.73 m^2), 3b (eGFR=30–44 ml/min per 1.73 m^2), and 4 (eGFR=15–29 ml/min per 1.73 m^2) and monthly in CKD stage 5 (eGFR<15 ml/min per 1.73 m^2). Participants were followed until death, dialysis start, date of transfer to another center, or end of the study (September 30, 2010). All participants provided written informed consent. The ethics review board of Federico II University in Naples approved the study.

Data Collection

We collected information about patient demographics, primary kidney disease, and Charlson Comorbidity Index (16) at the time of referral. Clinical data (BMI [kg/m^2] and BP) were updated at each follow-up visit along with laboratory data, including serum urea nitrogen, electrolytes, bicarbonate, creatinine, cholesterol, hemoglobin, albumin, C-reactive protein, urine urea nitrogen and creatinine, and proteinuria. Protein intake was estimated using urinary urea nitrogen excretion. Details of serum and urine creatinine determinations, urine protein determination, and protein intake calculations are in Supplemental Material.

Exposure and Covariates

The exposure of interest was UCr measured at baseline and each visit. Dedicated renal nurses instructed patients on how to obtain a careful 24-hour urine collection during two to three educational sessions on management goals of CKD. Urine collection was considered inaccurate, discarded, and repeated if measured creatinine excretion rate was outside the 60%–140% range of the value estimated according to the work by Dwyer and Kenler (17) (Supplemental Material). BMI was categorized based on World Health Organization recommendations (18) into low (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), high (25–29.9 kg/m^2), and obese categories (≥30 kg/m^2).

Outcomes

The outcomes of interest were all-cause mortality and kidney failure requiring dialysis. In-hospital death was ascertained through medical records. We collected information regarding out-of-hospital death by contacting the family of patients who failed to return to the clinic or through the registry office. Dialysis was started in the presence of intractable fluid overload or hyperkalemia (values>6 mEq/L despite medical therapy), usually (but not necessarily) with eGFR<10 ml/min per 1.73 m^2.

Statistical Analyses

We used the *t* and chi-squared tests to compare means and frequencies across UCr category (below versus equal to or above the sample median). We used linear mixed models to study the relationship between UCr and other covariates. We built the linear model by determining if there was a change in UCr excretion over time (in years) across categories of BMI (low, normal, high, and obese) and CKD stages 3–5 (prespecified interactions) controlling for age, sex, Charlson Index, and markers of inflammation and protein intake. We planned to add diabetes as an independent covariate if the Charlson Comorbidity Index was not associated with UCr levels, because there is a known association between diabetes and kidney disease progression and levels of BMI. Patient identifier and time were treated as random covariates. We then used Cox regression to model time to dialysis initiation and death as a function of time-varying values of UCr while controlling for the same variables that we considered in the linear model. This type of analysis incorporates information from all UCr measurements in all individuals at all time points. In standard Cox regression, the hazard ratio (HR) estimates the change in hazard associated with a unit change in baseline UCr by comparing different individuals (for example, people in different CKD stages). In time-varying covariate analysis, the HR estimates the change in hazard associated with a unit change in UCr observed in different individuals at any time and the same individual over time. We then fitted a competing risk model stratified by failure type (dialysis and death) to acknowledge possible stratum specific effects (19). As with the linear model, we considered the overall model fit and assumptions, and we monitored variations of the exposure regression coefficient while manually removing nonsignificant potential confounders. We tested a prespecified modifying effect of BMI and CKD stage on the relationship between UCr and survival outcomes. We conducted several sensitivity analyses, which are summarized in Supplemental Material. Model specification, assumptions, and overall fit were checked using formal and graphical tests based on residuals. We planned to recruit at least 500 patients and follow them until approximately 20% died. Even if the covariates in the model were highly correlated

Table 1. Baseline characteristics of study participants

Characteristics	All (*n*=525)	UCr<1085 mg/24 h (*n*=262)	UCr≥1085 mg/24 h (*n*=263)	*P* Value
Men (%)	304 (57.9)	94 (35.9)	210 (79.8)	<0.001
Age, yr (mean± SD)	56.9±15.7	61.2±15.1	52.7±15.1	<0.001
Urine volume/d (ml)	2090±630	1910±570	2270±630	<0.001
Diabetes (%)	96 (18.3)	57 (21.8)	39 (14.8)	0.04
Charlson Comorbidity Index	3.9±1.58	4.3±1.6	3.5±1.4	<0.001
Primary renal disease, *N* (%)				
GN	64 (12.2)	26 (9.9)	38 (14.4)	0.11
Diabetic nephropathy	40 (7.6)	21 (8)	19 (7.2)	0.73
Tubulointerstitial diseases[a]	136 (25.9)	68 (26)	68 (25.9)	0.98
Multisystem diseases[b]	42 (8.0)	22 (8.4)	20 (7.6)	0.74
Hypertension	50 (9.5)	25 (9.5)	25 (9.5)	0.99
Not known or other	193 (36.8)	100 (38.2)	93 (35.4)	0.51
SBP (mmHg)	137.8±21.9	139.6±24.5	135.9±18.7	0.06
DBP (mmHg)	79.5±11.1	78.6±12.0	80.5±10.1	0.07
CRP (mg/dl)	0.7±1.5	0.8±1.5	0.6±1.5	0.45
Albumin (g/dl)	4.2±0.5	4.1±0.5	4.2±0.4	0.004
Hemoglobin (g/dl)	12.9±1.9	12.3±1.8	13.5±1.9	<0.001
BMI (kg/m^2)	26.7±4.6	26.2±4.3	27.2±4.8	0.02
Bicarbonate (mEq/L)	24.4±3.6	24.1±3.8	24.7±3.3	0.11
Protein intake (g/24 h)	66.0±22.1	54.4±16.1	66.0±22.1	<0.001
Proteinuria (g/24 h)	1.2±1.2	1.1±1.2	1.3±1.3	0.14
Years of follow-up, median	6.18	5.9	6.9	<0.001
CKD stage 3a, *N* (%)	86 (16.4)	25 (9.5)	61 (23.2)	<0.001
CKD stage 3b, *N* (%)	167 (31.8)	75 (28.6)	92 (35)	0.12
CKD stage 4, *N* (%)	192 (36.6)	99 (37.8)	93 (35.4)	0.33
CKD stage 5, *N* (%)	80 (15.2)	63 (24)	17 (6.5)	<0.001

UCr, 24-hour urinary creatinine; SBP, systolic BP; DBP, diastolic BP; CPR, C-reactive protein; BMI, body mass index.
[a]Tubulointerstitial diseases include pyelonephritis, interstitial nephropathies, and cystic diseases.
[b]Multisystemic diseases include lupus, cryoglobulineamia, vasculitides, myeloma, and amyloidosis.

(*e.g.*, ρ>0.5), we estimated that, after 20% of the participants experienced an event, our study would have had enough power (>90%; with two-sided α<0.01) to detect small effects associated with a change in UCr (*e.g.*, HR from 1.15 to 1.20 per 0.1 g/d). We used Stata version 12.0 (www.stata.com) and R (http://cran.r-project.org) for analysis.

Results

Patient Characteristics

We screened 627 individuals and excluded 102 individuals from the study for the following reasons: 47 patients had proteinuria>3 g/d, 4 patients had the first visit before 1995, 15 patients had a GFR>60 ml/min, 11 patients did not provide consent, and 25 patients were unable to reliably collect a 24-hour urine sample. Study participants (*n*=525) were, on average, 57 years (SD=15.7 years), and 58% were men (Table 1). Mean BMI was 26.7 (SD=4.5), and BMI was greater than 30 in 107 patients (20.4%); 16% of patients were in stage 3a CKD, 32% of patients were in stage 3b CKD, 37% of patients were in stage 4 CKD, and 15% of patients were in stage 5 CKD. Study participants had a median of eight 24-hour UCr measurements (interquartile range [IQR]=4–14) over the study period. Participants with baseline UCr equal to or above the median (1085 mg/24 h) tended to be younger, men, and nondiabetic and have greater eGFR, higher albumin, hemoglobin, and protein intake, and lower C-reactive protein (Table 1). None of the patients had abnormal values of bilirubin or ketones or received drugs interfering with UCr excretion (*e.g.*, anti-H_2 receptor blockers or cephalosporins).

Associations with UCr

Baseline UCr correlated inversely with age (r=0.34; *P*<0.001) and directly with eGFR (r=0.32; *P*<0.001), hemoglobin (r=0.38; *P*<0.001), serum albumin (r=0.16; *P*<0.001), protein intake (r=0.68; *P*<0.001), and BMI (r=0.12; *P*<0.001). Figure 1 shows the relationship between baseline CKD stage and UCr excretion (mg/d). On average, UCr declined by 20 mg/d for every year of follow-up (95% confidence interval [95% CI], 18 to 22 mg/yr) in crude analysis; this decline was independent of the annual eGFR decline of the cohort as a whole (1.4 ml/min per 1.73 m^2 per year; 95% CI, 1.3 to 1.5 ml/min per 1.73 m^2 per year). We did not find an association between the Charlson Index and UCr excretion rate. Table 2 summarizes the adjusted model of baseline levels and annual change in UCr excretion. Baseline values were greater in men and tended to be lower in diabetic patients and patients with more severe CKD. Older age, smaller body size, and lower protein intake were also associated with significantly lower UCr at baseline. Daily UCr declined by 16 mg/yr in participants in

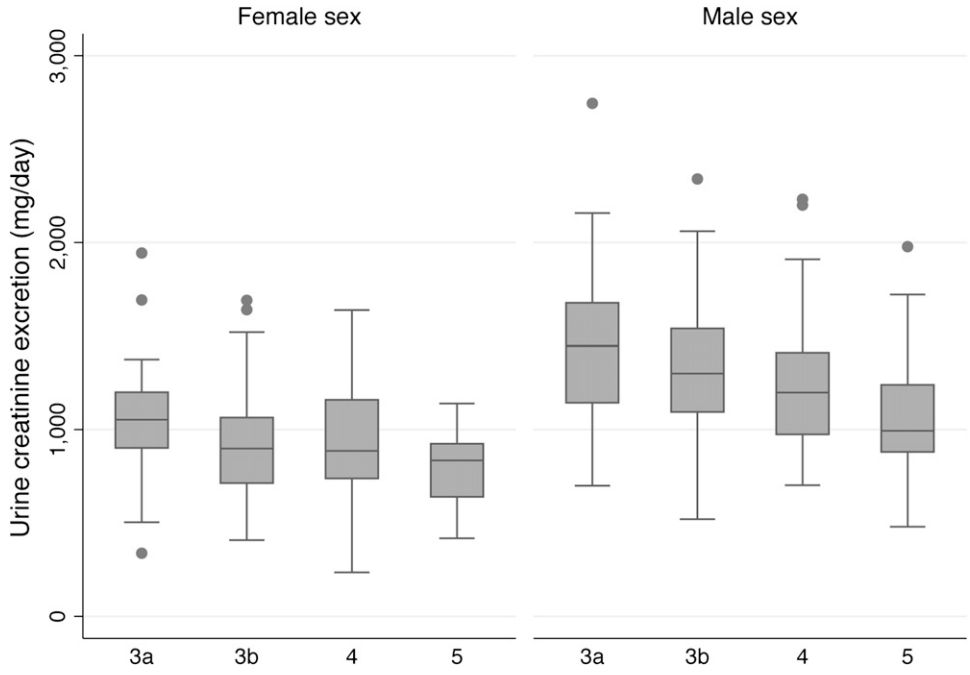

Figure 1. | **Relationship between urine creatinine (UCr) excretion rate (mg/d) and CKD stage at study entry by sex.** The line across the boxes is the median value of UCr excretion, the lower and upper edges of the box represent the 25th and 75th percentiles, respectively, and the dots represent observations beyond 1.5 times the interquartile range (outliers).

CKD stages 3a, 3b, and 4 and did not change in participants in stage 5 CKD. There was no difference in UCr decline between stages 3a, 3b, and 4. A sensitivity analysis limited to observations between the 5th and 95th percentiles of urine volume is reported in Supplemental Material (Supplemental Table 1).

Kidney and Patient Survival

During a median follow-up of 6 years (range of 4 months to 15 years), 93 patients died, and 200 patients required dialysis; 42 patients were censored when they transferred to another center, and 190 patients were censored at the end of the study period. In unadjusted analysis, per 20 mg/d

Table 2. Predictors of baseline urine creatinine and rate of change of urine creatinine over time in years (linear mixed model)

Predictors	Average Difference on UCr	95% Confidence Intervals
Variables associated with baseline UCr (mg/d)		
Intercept[a] (CKD stage 3a)	1025	985 to 1065
CKD stage 3b versus CKD stage 3a	−16	−55 to 24
CKD stage 4 versus CKD stage 3a	−34	−73 to 5
CKD stage 5 versus CKD stage 3a	−105	−158 to −52
Men (versus women)	281	253 to 308
Diabetes (present versus absent)	−34	−71 to 1.6
Age (10 yr)	−63	−72 to −54
Protein intake (10 g/24 h)	81	78 to 85
BMI (10 kg/m^2)	62	39 to 84
Variables associated with the rate of change of UCr (mg/d per year)		
Time (yearly change in CKD stage 3a to 4)	−16	−19 to −14
Time (yearly change in CKD stage 5)	1.4	−10 to 13

UCr, 24-hour urinary creatinine; BMI, body mass index.
[a]The model intercept estimates the mean UCr excretion for a 57-year-old nondiabetic woman with CKD stage 3a (reference category), a BMI of 26.5 kg/m^2, and a protein intake of 65.6 g/d (mean values of continuous covariates included in the models). Average effects on UCr are the regression coefficients or average effects on the baseline excretion rate in milligrams per day (the model intercept) and the rate of change of UCr in milligrams per day per year (the model slope) associated with the covariates in the model. The slope was not affected by age, BMI, current values of estimated GFR, or individual estimated GFR intercept and slope (estimated using linear mixed models). Results of sensitivity analysis are reported in Supplemental Material (Supplemental Table 2).

reduction in UCr (a value close to the upper 95% confidence limit of the adjusted average annual decline in this cohort), the HR for kidney failure requiring dialysis was 1.02 (95% CI, 1.01 to 1.03), and the HR for mortality was 1.05 (95% CI, 1.03 to 1.07). There was no relationship between BMI and patient survival. In a fully adjusted model including age, diabetes, current serum albumin, current daily protein intake, current proteinuria, and current eGFR (Supplemental Table 2), results remained significant, although there was a small attenuation of the effects (HR for kidney failure, 1.02 [95% CI, 1.01 to 1.03]; HR for mortality, 1.03 [95% CI, 1.01 to 1.05]). Figure 2 shows the HRs for a larger decline in UCr excretion (100 mg/d) associated with different patient characteristics (Table 2) or within-person UCr decline over time (*e.g.*, constant decline of 20 mg/d per year for 5 years). Although eGFR is a stronger predictor for both patient events, UCr decline provides additional prognostic information (Figure 2). Results of the sensitivity analyses are reported in Supplemental Material (Supplemental Tables 3–7).

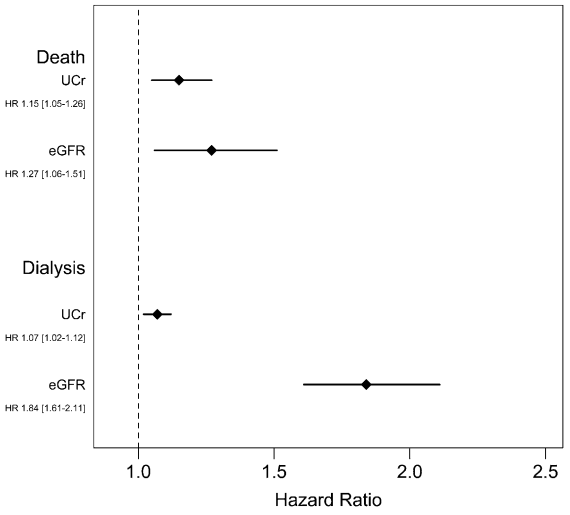

Figure 2. | Forest plot of the hazard ratios (HRs) for dialysis initiation and death associated with a 100 mg/d decrease in urine creatinine (UCr), which may be seen, for example, in a person in CKD stage 5 relative to another person in CKD stage 3a (Table 2) or after an annual decline of 20 mg/d for 5 years within the same person. For comparison, the plot shows the HRs associated with a 10 ml/min per 1.73 m^2 decline in estimated GFR (eGFR; resulting, for example, from an annual decline of 2 ml/min per 1.73 m^2 for 5 years). Supplemental Material has details and sensitivity analyses (Supplemental Tables 2–4).

Discussion

Our study is the first to report long-term data on the rate of decline of UCr in patients with CKD stages 3–5 and its association with clinical outcomes. Key findings of our study are twofold. First, in patients with CKD stages 3 and 4 but not stage 5, daily UCr declines by a predictable amount (about 16 mg/yr), independent of the annual decline in eGFR. Second, both low baseline UCr and more rapid decline in UCr are associated with decreased renal function and patient survival, independent of levels of eGFR and BMI.

The association between UCr and sex, age, and BMI is consistent with its role as an approximation of muscle mass in patients with CKD. However, the association of UCr with mortality was independent of BMI. Assuming that UCr is a marker of muscle mass and nutritional status, we can speculate that lean body mass may be a stronger predictor of mortality than BMI. Like in people without CKD, muscle mass tends to decline with age and comorbidities associated with activation of catabolic processes, reduced dietary intake, and lesser physical activity. Even in early stages of CKD, hormonal alterations after the loss of renal parenchyma result in metabolic and nutritional derangements with protein catabolism and reduction of lean body mass. Such complex alterations include abnormalities of carbohydrate metabolism, insulin resistance, dyslipidemia, and hypoalbuminemia. We found, in patients followed in a CKD clinic, that these metabolic and nutritional derangements are associated with a decline in UCr in the range of 15–20 mg/d per year in CKD stages 3 and 4, irrespective of current eGFR and individual eGFR decline, and that the decline in UCr is independently associated with increased risk of kidney failure and patient mortality (*i.e.*, by 2% and 3%, respectively, per each 20 mg/d decline in UCr). For example, we estimated that the risk of death increases by approximately 15% (and the risk of kidney failure increases by 7%) in 5 years in an individual whose UCr declines at a rate of 20 mg/d per year or UCr excretion is 100 mg/d lower at baseline than the UCr excretion of another person. Conversely, UCr did not change in CKD stage 5, where baseline levels of UCr were lowest. Considering that, in stage 5 CKD, the excretory function is almost completely lost, we speculate that people with stage 5 CKD are more likely to experience initiation of dialysis or death than a further decline in UCr excretion. Alternatively, our study may have been underpowered to detect these changes in UCr excretion as well as differences in rates of change between CKD stages 3 and 4.

Other works have found a direct relationship between levels of kidney function and UCr (20). However, longitudinal data on the rate of change in UCr in people with CKD and its impact on patient outcomes are lacking. A PUBMED search of publications with the term urine creatinine in the title identifies 37 citations as of March of 2013, of which 12 citations were published in the last 10 years; however, none of the publications investigated the relationship between UCr and clinical outcomes. Most available studies focus on the relationship between clinical indicators of nutritional status and outcomes with conflicting results. For example, larger body size was associated with longer survival (21–23) and lower rates of coronary events (24) in some cohorts but not others (25), indicating the uncertain prognostic use of BMI alone. Studies assessing the relative role of UCr and BMI have been conducted in individuals treated with hemodialysis or peritoneal dialysis but not persons with CKD not yet receiving dialysis. Some studies found longer survival in patients with normal or high BMI and high UCr and increased mortality in patients with high BMI and low UCr (10). In our study, UCr was an independent predictor of renal failure and patient death, but there was no significant interaction between UCr and BMI. Considering the small variation of

BMI in this European cohort (only one of five patients had a BMI>30 kg/m^2), our study may be underpowered to detect differences in the strength of the association between UCr and mortality across categories of BMI.

There are several limitations to our study. First, we acknowledge the lack of a direct measure of body tissue components to confirm the hypothesis that UCr is a direct marker of muscle mass. Although not routinely used in clinical practice, several reliable tools for the assessment of body composition exist (*e.g.*, dual-energy x-ray absorptiometry, air-displacement plethysmography, computerized tomography, and magnetic resonance imaging). However, a precise assessment of body composition was beyond the scope of this study. Second, we measured UCr in 24-hour samples. This method is prone to collection error and can only be used in patients who can adequately collect 24-hour urine. However, after few education sessions, only 4% of otherwise eligible patients were excluded from the study for this reason. Third, given the observational nature of our study, we cannot exclude the possibility of residual confounding, preventing us from drawing conclusions about causality. For example, participants with lower UCr levels tended to be older and sicker than participants with higher UCr levels. Considering the attenuation of the relative risks of death associated with a 20 mg/d decrease in UCr in adjusted models, residual confounding could potentially eliminate the statistical significance of these associations. Although a matched design on key variables, such as diabetes, age, CKD stage, BMI, and follow-up duration, would have been preferable, such a study would have required a much larger sample size. Fourth, the relatively low rate of eGFR decline (1.4 ml/min per 1.73 m^2 per year) may be seen as a limitation in terms of result generalizability. However, as in any study design, patient selection was based on eligibility criteria that we defined with the intent to maximize the signal-to-noise ratio (*e.g.*, the likelihood of detecting an independent decline of UCr excretion irrespective of BMI and CKD stages and its potential association with clinical outcomes) in a relatively small sample. Although it remains possible that the associations that we found exist only in people with slowly progressive CKD, a much larger sample would be necessary to test such a hypothesis in patients with varying degrees of CKD progression. Overall, our longitudinal study of a relatively large number of individuals with CKD not receiving dialysis is the first association study conducted so far. Other strengths include prespecified inclusion criteria, standardized data collection, relatively long median follow-up of 6 years, careful regression analyses based on a large number of urine samples, close patient contact, and intense patient education during the entire study period.

Our study has implications for clinical practice and research. UCr declines in stages 3 and 4 CKD, suggesting that changes in body mass composition may occur relatively early in the course of CKD. However, additional studies are necessary to test whether levels of and changes in daily UCr may be used as a proxy of patient nutritional status to predict prognosis. Clinicians may evaluate the change in UCr to assess the effects of interventions aimed at improving physical performance and body mass composition. Clinical trials comparing different dietary interventions or the use of exercise programs may also test the validity and reliability of UCr as a surrogate of more distant patient outcomes.

In conclusion, daily UCr can be measured in the majority of patients with CKD. In patients in CKD stages 3 and 4, daily UCr declines in a stable fashion at a rate of approximately 16 mg/yr. Faster decline predicts greater risk of kidney failure and patient mortality. Clinical trials are necessary to confirm its use to monitor the effects of interventions on nutritional status and body composition.

Acknowledgments

The authors thank Ms. Deborah Treijs (Research Assistant) and Anita Kozinski (Research Manager) from the University of Calgary for assistance during the training of L.D.M. in Canada. This study is part of the thesis work of L.D.M.

This work has been supported by the fellowship hosting institution (Alberta Kidney Disease Network; www.AKDN.info/research), which provided infrastructure and analytical support, and an unrestricted educational grant from the Italian Society of Nephrology (SIN Outgoing International Fellowship Grant SIN 2009).

The funding sources had no role in any stage of the design and conduct of the study; collection, management, analysis, and interpretation of data in the study; or preparation, review, or approval of the manuscript.

Disclosures

None.

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Received: February 3, 2013 **Accepted:** June 15, 2013

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.01350213/-/DCSupplemental.

See related editorial, "A Good Reason to Measure 24-Hour Urine Creatinine Excretion, but Not to Assess Kidney Function," on pages 1847–1849.

Supplemental data

Methods

Sample collection and creatinine determination

All blood and urine samples were collected in the morning during the same week patients were assessed. Creatinine determination was performed using the colorimetric Jaffe method with a Roche-Hitachi analyzer. We used the abbreviated Modification of Diet in Renal Disease (MDRD) equation to estimate glomerular filtration rate(1) throughout the study until 2002, when the laboratory switched to an isotope dilution mass spectroscopy (IDMS)-calibrated reference standard, at which point we used the IDMS-traceable MDRD study equation(2). We repeated all analyses using the six-variable MDRD formula after correcting serum creatinine values by 0.94 (175/186) for samples collected after 2002 and obtained the same results.

Quality assessment of the creatinine assay and reference values

Serum variability (human serum samples and laboratory products):

- Within-sample coefficient of variation (CV):
  - CV = 0.7% (Human serum);
  - CV = 0.6% (Precinorm);
  - CV = 0.6% (Precipath);
- Between-sample coefficient of variation:
  - CV = 2.3% (Human serum);
  - CV = 1.5% (Precinorm);
  - CV = 1.7% (Precipath);

Urine variability (human urine samples):

- Within-sample coefficient of variation (CV):
  - CV = 2.1% (Human urine I);
  - CV = 1.3% (Human urine II);
  - CV = 1.1% (Human urine III);
- Between-sample coefficient of variation:
  - CV = 2.2% (Human urine I);
  - CV = 1.7% (Human urine II);
  - CV = 1.2% (Human urine III);

Reference values for serum creatinine:

- Men: 62-106 micromol/L (0.7-1.2 mg/dL);
- Women: 44-80 micromol/L (0.5-0.9 mg/dL).

Reference values for urine creatinine:

- Men: 9-21 mmol/day (1040-2350 mg/day);
- Women: 7-14 mmol/day (740-1570 mg/day).

Accuracy of urine collection

Urine collection was considered inaccurate, discarded and repeated if measured creatinine excretion rate was outside the 60-140% range of the value estimated according to Dwyer and Kenler(3), who state:

> "[…] *A simple method to check for completeness of urine collection is to compare measured and calculated creatinine excretion rates. If the value is outside the 60 to 140% of calculated value, the sample should be discarded*."

Formulas for calculating creatinine excretion are:
Males: ratio %=100 (24-hr creatinine in mg)/24(wt in kg)
Females: ratio %=100 (24-hr creatinine in mg)/21(wt in kg)

Protein intake calculation

Dietary protein intake was estimated using daily urinary excretion of urea nitrogen(4):
[0.031 x body weight (kg) + urea (g/L)/2.13 x urine volume (L)] x 6.25

Urine protein determination

Determination of urine protein was performed using a colorimetric method based on pyrogallol red-molybdenum complex with a Cobas Integra Total Protein Urine/CSF (TPU-C) analyzer.

Reference value for 24-hour urine in adults: 28 to 141 mg/dl.

Reproducibility (data based on three human urine controls):

Within sample CV = 2.5% (urine I); 0.99% (urine II); 0.65% (urine III);
Between samples CV = 2.9% (urine I); 1.6% (urine II); 1.6% (urine III).

Results: Sensitivity analyses

Linear model

eTable 1: Predictors of baseline urine creatinine and rate of change of urine creatinine (UCr) over time in years (linear mixed model)

Sensitivity analysis: limited to observations between the 5th and 95th percentile of urine volume. Results of the main analysis are reported in Table 2 of the manuscript.

	Average effect on UCr	*95% Confidence Intervals*
Variables associated with baseline UCr (mg/day)		
Intercept* (CKD stage 3a)	1030	990 to 1070
CKD stage 3b vs. CKD stage 3a	-19	-59 to 21
CKD stage 4 vs. CKD stage 3a	-39	-79 to 6
CKD stage 5 vs. CKD stage 3a	-110	-164 to -56
Male sex (vs. female)	276	249 to 304
Diabetes (present vs. absent)	-37	-73 to -1
Age (10 years)	-59	-68 to -50
Protein intake (10 g/24 hours)	82	78 to 85
BMI (10 kg/m^2)	53	30 to 76
Variables associated with the rate of change of UCr (mg/day per year)		
Time (yearly change in CKD stage 3a to 4)	-17	-20 to -14
Time (yearly change in CKD stage 5)	3	-9 to 16

*The model intercept estimates the mean urine creatinine (UCr) excretion at baseline for a 57-year-old non-diabetic female with chronic kidney disease (CKD) stage 3a (reference category), a body mass index (BMI) of 26.5 kg/m2 and a protein intake of 65.6 g/day (mean values of continues covariates included in the models). Further details are in the footnote of Table 2.

Survival analysis

Main result

eTable 2. Predictors of dialysis initiation and death (dual-event survival model of Lunn-McNeil)

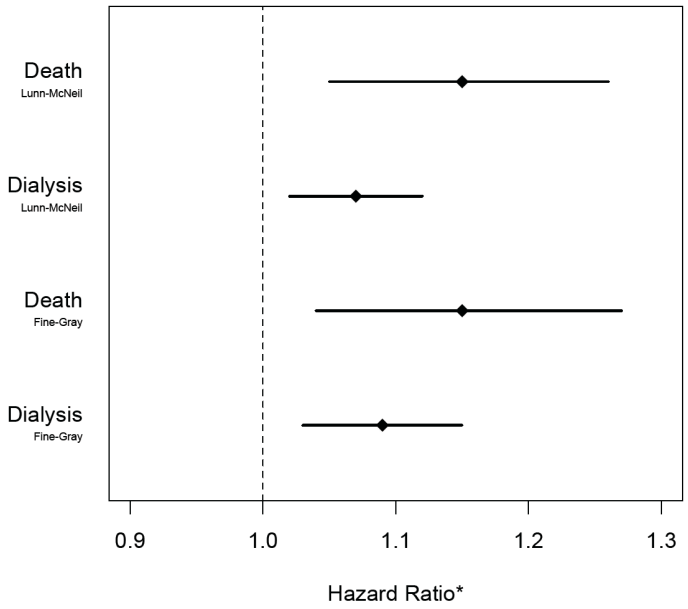
	HR (95% CI)
Predictors of dialysis initiation	
UCr (per 20 mg/day decline)*	1.02 (1.01, 1.03)
eGFR (per 2 ml/min/1.73 m^2 decline)*	1.13 (1.10, 1.16)
Proteinuria (per 1 g/24 h increase)	1.44 (1.32, 1.57)
Albumin (per 1 g/dl increase)	0.89 (0.62, 1.27)
Presence of diabetes	0.75 (0.51, 1.10)
Predictors of death	
UCr (per 20 mg/day decline)*	1.03 (1.01, 1.05)
eGFR (per 2 ml/min/1.73 m^2 decline)*	1.05 (1.01, 1.09)
Protein intake (10 g/day increase)	1.05 (0.92, 1.21)
Albumin (per 1 g/dl increase)	0.43 (0.27, 0.69)
Age (per year increase)	1.07 (1.05, 1.09)
Presence of diabetes	1.45 (0.95, 2.18)

Legend: UCr = urine creatinine; eGFR: estimated glomerular filtration rate; * the units chosen for UCr and eGFR approximate the average annual decline of UCr and eGFR in the present study cohort

Sensitivity analyses

In order to assess the appropriateness of standard survival analysis (i.e., censoring for death while studying the risk for dialysis and vice-versa), we conducted a sensitivity analysis using two competing risk approaches: the dual-event model of Lunn-McNeil for cause-specific hazards(5) which estimates both risks in the same model; and the sub-hazards model of Fine and Gray(6) with either dialysis as the outcome (with death as a competing risk) or death as the outcome (with dialysis start as a competing risk). The Lunn-McNeil model assumes independence of the competing risks; the Fine and Gray model relaxes this assumption and addresses the issue of potential informative censoring. Similarity of the sensitivity analysis results with those obtained by standard survival analysis is not consistent with informative censoring, supporting the validity of the Cox regression model reported in the main text.

eFigure 1: Urine creatinine decline (per 100 mg/day) and risk of dialysis and death



*Hazard ratios (Lunn-McNeil) and sub-hazard ratios (Fine and Gray) for dialysis and death associated with 100 mg/day decline in urinary creatinine (UCr) excretion.

eTable 3: The dual-event model of Lunn-McNeil and the Fine and Gray models:

	Lunn-McNeil model	Fine and Gray models
	Hazard Ratio (95% CI)	Sub-Hazard Ratio (95% CI)
Dialysis	1.07 (1.02, 1.12)	1.09 (1.03, 1.15)
Death	1.15 (1.05, 1.26)	1.15 (1.04, 1.27)

Both models are adjusted for levels of current (linear) eGFR, current proteinuria, current daily protein intake, current albumin, age and for diabetes. The dual-event model of Lunn-McNeil is stratified by event type: time to dialysis is censored for death; and time to death is censored for dialysis. In the renal survival model of Fine and Gray death is

treated as a competing risk; in the patient survival model of Fine and Gray dialysis is the competing risk.

Results of these models were the same using the following functions of eGFR and proteinuria: natural log, fractional polynomials and cubic splines. Also, results were the same adjusting for individual intercepts and slope predictions obtained respectively from the linear mixed model of proteinuria and from the linear mixed model of eGFR.

eTable 4: Reference models with additional adjustment for the *within-subject* percent change in UCr

	Lunn-McNeil	Fine and Gray
	Hazard Ratio (95% CI)	Sub-Hazard Ratio (95% CI)
Dialysis	1.08 (1.03, 1.13)	1.09 (1.04, 1.16)
Death	1.14 (1.03, 1.25)	1.14 (1.03, 1.27)

eTable 5: Survival results limited to observations between the 5^{th} and 95^{th} percentile of urine volume

	Lunn-McNeil	Fine and Gray
	Hazard Ratio (95% CI)	Sub-Hazard Ratio (95% CI)
Dialysis	1.08 (1.03, 1.14)	1.10 (1.04, 1.17)
Death	1.15 (1.03, 1.27)	1.13 (1.01, 1.26)

eTable 6. Survival results using baseline UCr as exposure (without updated UCr values)

	Lunn-McNeil	Fine and Gray
	Hazard Ratio (95% CI)	Sub-Hazard Ratio (95% CI)
Dialysis	1.05 (1.01, 1.09)	1.04 (1.01, 1.09)
Death	1.08 (1.01, 1.15)	1.08 (1.01, 1.16)

eTable 7. Survival results limited to study participants who survived at least 1 year (n=488), using change in UCr (individual slope of the linear mixed model) from baseline to year 1 as the exposure

	Lunn-McNeil	Fine and Gray
	Hazard Ratio (95% CI)	Sub-Hazard Ratio (95% CI)
Dialysis	1.12 (1.06, 1.19)	1.13 (1.07, 1.20)
Death	1.15 (1.04, 1.26)	1.14 (1.03, 1.27)

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