Estimating residual kidney function in dialysis patients without urine collection

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Residual kidney function contributes substantially to solute clearance in dialysis patients but cannot be assessed without urine collection. We used serum filtration markers to develop dialysis-specific equations to estimate urinary urea clearance without the need for urine collection. In our development cohort, we measured 24-hour urine clearances under close supervision in 44 patients and validated these equations in 826 patients from the Netherlands Cooperative Study on the Adequacy of Dialysis. For the development and validation cohorts, median urinary urea clearance was 2.6 and 2.4 ml/min, respectively. During the 24-hour visit in the development cohort, serum β-trace protein concentrations remained in steady state but concentrations of all other markers increased. In the validation cohort, bias (median measured minus estimated clearance) was low for all equations. Precision was significantly better for β-trace protein and β2-microglobulin equations and the accuracy was significantly greater for β-trace protein, β2-microglobulin, and cystatin C equations, compared with the urea plus creatinine equation. Area under the receiver operator characteristic curve for detecting measured urinary urea clearance by equation-estimated urinary urea clearance (both 2 ml/min or more) were 0.821, 0.850, and 0.796 for β-trace protein, β2-microglobulin, and cystatin C equations, respectively; significantly greater than the 0.663 for the urea plus creatinine equation. Thus, residual renal function can be estimated in dialysis patients without urine collections.

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Residual kidney function (RKF) is associated with improved survival in dialysis patients.[1–4] Even at the low levels of glomerular filtration rate (GFR) in dialysis patients, RKF is a major contributor to solute and volume clearance.[5–7] Dialysis patients with preserved RKF also have lower concentrations of uremic toxins, less volume overload, lower left ventricular mass, less inflammation, lower requirements for erythropoietin, and better quality of life.[4,8,9] Consequently, loss of RKF after starting dialysis is associated with increased risk of death.[10]

RKF is generally expressed as urinary clearance of urea (CL_{UREA}) or the average of urea and creatinine ($CL_{UREA, CREAT}$). Current guidelines recommend assessment of RKF at regular intervals for adjustment of the dialysis prescription and including CL_{UREA} in hemodialysis adequacy if it is ≥2 ml/min.[7,11,12] However, there are no simple methods for assessing RKF that are similar to GFR estimation from serum creatinine in nondialysis patients. In clinical practice, RKF is assessed by timed 24- to 48-hour urine collection with calculation of urea and creatinine clearance.[7] Urine collections, however, are cumbersome for the patients and the dialysis unit staff and prone to errors leading to overestimation or underestimation of RKF.[7] Serum concentrations of low molecular weight proteins, such as β-trace protein (BTP), β2-microglobulin (B2M), and cystatin C are highly correlated with measured GFR.[13–16] Hemodialysis clearance during conventional (diffusive) high-flux hemodialysis is minimal for BTP (~25,000 Da)[17–19] and partial for B2M (11,600 Da)[18,20] and cystatin C (13,300 Da).[18,21] Peritoneal dialysis clearance of B2M and cystatin C is lower than that of urea and creatinine,[22–26] whereas that of BTP has not been reported. High correlation with measured GFR and low or no removal by dialysis makes these markers attractive candidates for assessment of RKF.

The goal of our study was to use serum endogenous filtration markers to develop dialysis-specific equations to assess RKF and replace timed-urine collections. We developed these equations in a cohort of dialysis patients in Baltimore, Maryland, that underwent careful, closely supervised and

monitored 24-hour urine clearance measurements designed to minimize measurement error. We then validated the equations in an external cohort, the NECOSAD (Netherland Cooperative Study on Adequacy of Dialysis).

RESULTS

Clinical characteristics

In the development cohort (RKF Study; $n = 44$), mean age was 55 years, 64% were male and 21% white (Table 1). None of the patients were vegetarian or had undergone limb amputation. Urinary clearance measurements in the RKF Study were performed on an interdialytic day with the following distribution of the study visit days: Monday, 8 (13.1%); Tuesday, 23 (37.7%); Wednesday, 11 (18%); Thursday, 15 (24.6%); Friday, 2 (3.3%); and Sunday, 2 (3.3%). Patients in the validation cohort (NECOSAD; $n = 826$) were older and more likely to be white. In the development and validation cohorts, median 24-hour urine volume was 799 ml and 720 ml, median CL_{UREA} was 2.6 and 2.4 ml/min, and median $CL_{UREA,\ CREAT}$ was 3.1 and 3.2 ml/min/1.73 m^2, respectively.

RKF and serum concentrations of endogenous filtration markers

In the development cohort with serial measurements of serum markers over 24 hours ($n = 44$ patients with 61 visits), the rate of increase in markers was as follows: urea 10.8 mg/dl/day (95% confidence interval [CI]: 8.1 to 13.5; $P < 0.001$), creatinine 1.3 mg/dl/day (95% CI: 0.9–1.7; $P < 0.001$), BTP 0.09 mg/l/day (95% CI: -0.40 to 0.58; $P = 0.71$), B2M 1.27 mg/l/day (95% CI: 0.01–2.53; $P = 0.05$), and cystatin C 0.30 mg/l/day (95% CI: 0.09–0.52; $P = 0.005$). In both cohorts, filtration markers were negatively correlated with CL_{UREA} (or $CL_{UREA,\ CREAT}$) and positively correlated with each other (Figure 1, Figure S1, and Table S1). BTP, B2M, and cystatin C were highly correlated with each other with the highest correlation between BTP and B2M (RKF Study, 0.807; NECOSAD, 0.759).

In the RKF Study, the concentrations of BTP, B2M, and cystatin C were similar in patients with ($n = 5$) or without a history of liver failure or hepatitis. In a subset of NECOSAD patients with previously measured C-reactive protein ($n = 543$), there was no association between C-reactive protein and endogenous filtration markers (Table S2).

Equation development in RKF Study

Using a prespecified variable selection procedure for equation development (see Materials and Methods), we found coefficients for sex to be significant in the models with BTP and B2M estimating CL_{UREA} or $CL_{UREA,\ CREAT}$ (Table S3). In models that included all 3 low molecular weight proteins, BTP, B2M, and cystatin C, the coefficients for BTP and B2M became smaller and coefficients for cystatin C were no longer significant. Forced addition of age, sex, and race to all models, or excluding patients treated with peritoneal dialysis, minimally changed the values of the markers' coefficients and did not improve estimation (Table S4). Based on these data, we selected the parsimonious equations (without forced variables) presented in Table 2 for testing in the external validation cohort.

Equation performance in NECOSAD

Estimating CL_{UREA}. CL_{UREA} estimation using RKF Study equations had low bias for all equations (Table 3). In general, all equations underestimated CL_{UREA} and $CL_{UREA,\ CREAT}$ (Figure 2). Bias was higher (underestimation of measured CL_{UREA}) using BTP, B2M, and cystatin C equations compared with the urea + creatinine equation. However, precision and accuracy were better using BTP, B2M, and BTP + B2M equations compared with the urea + creatinine equation. The combined BTP + B2M equation had the highest precision (lowest interquartile range [IQR]). Bias was lower and accuracy was higher in patients treated with hemodialysis compared with those treated with peritoneal dialysis (Table S5). The diagnostic accuracy for detecting measured $CL_{UREA} \geq 2$ ml/min by equation-estimated $CL_{UREA} \geq 2$ ml/min was significantly higher for BTP, B2M, and cystatin C equations compared with the urea + creatinine equation ($P < 0.001$) (Figure 3, Table S6).

Estimating $CL_{UREA,\ CREAT}$. Compared with previously published equations in nondialysis patients, the RKF Study equations estimating $CL_{UREA,\ CREAT}$ had significantly lower bias ($P < 0.001$), higher accuracy ($P < 0.001$) but similar precision (Table S7). The Hoek cystatin C equation, developed in NECOSAD, overestimated $CL_{UREA,\ CREAT}$ (as compared to underestimation by the RKF Study equation) but had similar precision and accuracy compared with the RKF Study cystatin C equation.

Repeat measurements. There were 162 repeat measurements over a median of 9.1 months (IQR: 8.9, 9.3). The median (IQR) change in CL_{UREA} was −0.7 ml/min (−1.4, −0.01) and in $CL_{UREA,\ CREAT}$ was −1.1 ml/min/1.73 m^2 (−1.9, −0.05). The decline in RKF over time was associated with increase in serum concentrations of filtration markers (Table S8, Figure S2). There was moderate correlation between the initial and repeat clearance measurements and estimations, although the estimating equations underestimated the change in measured clearances over time (Table S9).

DISCUSSION

In this report, we present dialysis-specific equations to estimate CL_{UREA} and $CL_{UREA,\ CREAT}$ using serum filtration markers. These equations do not require timed-urine collection. We developed these equations in a cohort of dialysis patients in Baltimore, Maryland (RKF Study), with carefully monitored urine clearance measurements and then validated them in an external cohort of dialysis patients in the Netherlands (NECOSAD). The low molecular weight protein (BTP, B2M, and cystatin C) equations had better performance than those including metabolites (urea, creatinine). BTP, B2M, and cystatin C equations also had high diagnostic accuracy for identifying patients with $CL_{UREA} \geq 2$ ml/min, the