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Residual renal function calculated from serum Cystatin C measurements and knowledge of the weekly standard Kt/V urea

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SHORT REPORTS

Residual Renal Function Calculated from Serum Cystatin C Measurements and Knowledge of the Weekly Standard Kt/V Urea

Residual renal clearance was found to be a predictor of survival in dialysis patients (1,2). Monitoring and preserving residual renal function (RRF) in dialysis patients is therefore important (3,4). Cystatin C (CysC) is a protein of low molecular weight. Studies by Delaney *et al.* and Hoek *et al.* showed strong correlations between serum levels of CysC and RRF in dialysis patients (5,6). The Hoek study developed an estimated equation:

$$\text{Estimated RRF (mL/min/1.73 m}^2) = -0.70 + [22 / \text{CysC (mg/L)}].$$

A recent study by Al Malki *et al.* (7) showed a significant inverse relationship between serum levels of CysC and values of "weekly standardized" Kt/V (Std Kt/V) in functionally anephric patients:

$$\text{Std Kt/V} = -0.703 \times \text{CysC} + 7.254.$$

In the present study, we aimed to assess the role of serum levels of CysC and dialytic clearance in measuring RRF. We hypothesized that the difference between measured CysC and an estimate from the Al Malki equation would correlate with RRF as measured by the average of urinary creatinine and urea clearance. We also postulated that the hypothesized correlation might be stronger than Hoek's RRF, which uses 1 / CysC alone.

METHODS

In this cross-sectional, single-center pilot study, blood and urine samples were prospectively collected from patients (n = 15) with end-stage renal disease receiving peritoneal dialysis (n = 7) and conventional thrice-weekly high-flux hemodialysis therapy (3 – 4 hours thrice weekly; n = 8). All patients provided written informed consent. Patients were excluded if their dialysis prescription had been changed within the preceding 3 months. The study was approved by the Health Sciences Research Ethics Board at the University of Western Ontario (HSREB #16598E).

We measured serum levels of CysC, urea, and creatinine in the study patients. For the hemodialysis patients, pre-dialysis blood samples were used to measure serum CysC before the mid-week hemodialysis session, although our recent study demonstrated that pre-dialysis serum CysC does not vary between hemodialysis sessions (8). Serum levels of CysC were determined by immunonephelometry using an N Latex Cystatin C kit (Siemens Healthcare Diagnostics, Deerfield, IL, USA) on a BN ProSpec analyzer (Dade Behring, Marburg, Germany) at the reference laboratory at the Children's Hospital of Eastern Ontario in Ottawa, Canada, with an established coefficient of variation.

We also obtained 24- to 45-hour urinary collections from the patients. The RRF was determined as the average of urinary creatinine and urea clearances, further adjusted for body surface area using the DuBois formula (9). From the peritoneal dialysis patients, we also obtained a 24-hour peritoneal effluent collection for measurement of total urea loss. Using those samples, daily urea clearances were calculated, and values of Std Kt/V were derived (7 × daily K in liters) using the Watson equation for V (4,10). To derive the Std Kt/V for the hemodialysis patients, the efficacy of a single hemodialysis treatment was taken as the single-pool Kt/V, calculated using urea kinetic modeling (3,11,12).

For all 15 patients, RRF was estimated using the Hoek equation (5). By rearranging the Al Malki equation, Std Kt/V could be used to predict the pre-dialysis levels of CysC ("expected pre-dialysis CysC"). The expected levels of CysC did not consider RRF (7). The difference between the expected pre-dialysis CysC and the measured CysC was defined as ΔCysC. The equation for ΔCysC-estimated RRF was derived using the ΔCysC value.

Statistical analysis was performed using the GraphPad Prism software for Windows (version 4.03: GraphPad Software, San Diego, CA, USA). Means and standard deviations are reported for normally distributed data; otherwise, medians, with 25th and 75th percentiles (interquartile range) are given. A linear regression equation was derived from the values of ΔCysC. The Pearson correlation coefficient was used to assess the strength of the relation between measured RRF and values of ΔCysC, and between the measured RRF and the estimated RRF

using both the Hoek equation and the ΔCysC equation. The Bland–Altman test was used to calculate bias and the standard deviation of the bias between the estimated RRF and the measured RRF. A value of $p < 0.05$ was considered significant.

RESULTS

For the 15 patients with completed measurements, mean age was 63 ± 15 years. The three most common causes of end-stage renal disease were hypertensive nephropathy (33%), diabetic nephropathy (27%), and glomerulonephritis (14%). The mean measured pre-dialysis CysC was 4.57 ± 1.02 mg/L. The mean Std Kt/V was 2.61 ± 0.67 and 1.65 ± 0.59 with and without consideration of RRF respectively. The mean measured RRF was 1.73 ± 0.67 mL/min/1.73 m^2.

We observed a statistically significant correlation between measured RRF and ΔCysC ($r = 0.90$, $p < 0.0001$). The association between measured RRF and ΔCysC could be expressed as

$$\text{measured RRF (mL/min/1.73 m}^2) = \Delta\text{CysC} \times 0.3601 + 0.5034.$$

The ΔCysC-estimated RRF was plotted against measured RRF, with a significant linear correlation being obtained ($r^2 = 0.81$, $p \leq 0.001$, Figure 1). The bias was 0.001 ± 0.290 mL/min/1.73 m^2. The correlation coefficient between the Hoek RRF and the measured RRF was $r^2 = 0.69$ ($p < 0.0001$, Figure 1), with a bias of 2.70 ± 0.847 mL/min/1.73 m^2.

DISCUSSION

Hoek *et al.* derived an equation to obtain RRF using serum 1 / CysC in both hemodialysis and peritoneal dialysis patients. However, those authors ignored the dialytic clearance of CysC (5). In the present study, we showed a strong correlation between measured RRF and ΔCysC ($r = 0.90$, $p < 0.0001$), which considers only the dialytic clearance. The linear relationship between the two parameters is expressed as

$$\text{measured RRF (mL/min/1.73 m}^2) = \Delta\text{CysC} \times 0.3601 + 0.5034.$$

The bias was 0.001 ± 0.290 mL/min/1.73 m^2 ($p = 0.40$). Figure 1 shows that the regression lines for the ΔCysC-estimated RRF is closer to the line of identity than is Hoek's estimated RRF.

Why does the Hoek approach overestimate measured RRF? The overestimation probably reflects a difference in the Std Kt/V between our study population and the

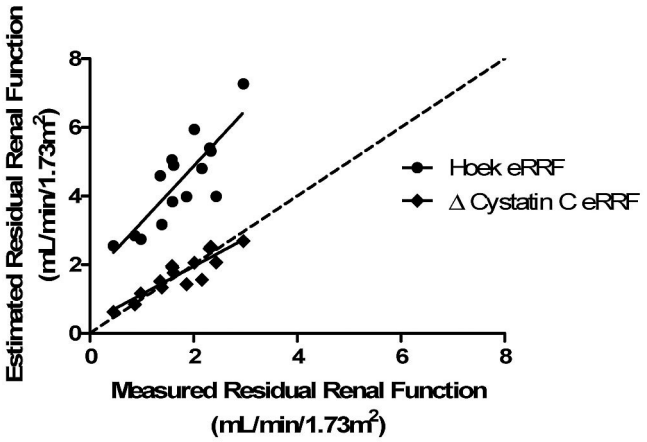

Figure 1 — Correlation analysis of the Hoek estimated residual renal function (eRRF) and the measured residual renal function (RRF), and of the change (Δ) in cystatin C eRRF and the measured RRF ($r^2 = 0.69$ and 0.81 respectively, $p \leq 0.0001$).

Hoek study population. In the Hoek study, the mean pre-dialysis CysC was significantly higher (5.8 – 6.1 mg/L) that that observed in our study (4.6 ± 1.20 mg/L), despite the measured RRF in our study being lower than that in Hoek's study (1.73 ± 0.67 mL/min/1.73 m^2 and 2.7 to 3.3 ± 1.3 to 1.5 mL/min/1.73 m^2 respectively). Those findings indicate that the mean Std Kt/V, without consideration of renal clearance, was lower in the Hoek study than in our study. It is therefore not surprising that the Hoek RRF systemically overestimated RRF in our study population. Incorporating Std Kt/V can eliminate this systematic error.

When the glomerular filtration rate is below 30 mL/min/1.73 m^2, the accuracy of the nuclear medicine isotopic measurement method for that rate is limited (13). We therefore used the average of the urinary creatinine and urea clearances as our reference RRF. We did not find a correlation between Std Kt/V and CysC, and we did not expect to because of the small sample size and the narrow range of Std Kt/V values obtained from patients on identical dialysis modalities. Although Sjostrom *et al.* (14) suggested that renal clearance of CysC takes the form of hyperbolic function (1 / X), we were unable to incorporate Std Kt/V in deriving RRF without using the Al Malki equation.

The major limitation of our study is its small size. Moreover, both the Al Malki equation, which was used to derive ΔCysC, and the estimated RRF equation in the present study require further validation. Another limitation is the small and narrow range of RRF values among the study patients. However, the present study was designed as a pilot to test our hypothesis. Our work uncovered the importance of incorporating Std Kt/V into the estimated RRF equation, because failure to do so can

result in systemic bias when Std Kt/V values are different. We plan to conduct a larger study with wide ranges of Std Kt/V values to validate the ΔCysC equation.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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