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Original Article

Comparison of glomerular filtration rates calculated by different serum cystatin C-based equations in patients with chronic kidney disease

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Abstract

Background: We aimed to evaluate the performance of serum cystatin C-based equations in calculating the glomerular filtration rate (GFR) in patients with varying stages of chronic kidney disease (CKD).

Methods: Serum cystatin C and creatinine levels were measured in 615 CKD patients. The CKD stage was determined by the creatinine-based estimated GFR (eGFR) equation using the four-variable abbreviated Modification of Diet in Renal Disease equation suggested by the Kidney Disease Outcome Quality Initiative with the addition of a coefficient applicable to Korean populations (K-aMDRD). In each CKD stage, the ratio of serum cystatin C to creatinine was calculated and six different cystatin C-based equations were used to estimate GFR. Cystatin C-based eGFR and aMDRD eGFR values were compared using the paired *t* test, Pearson correlation test, and the Bland–Altman plot.

Results: The mean age of patients was 53.21 $\pm$ 14.45 years; of the 615 patients, 346 were male. The serum cystatin C-to-creatinine ratio was inversely correlated with the CKD stage. Compared with the K-aMDRD values, the results of the Hoek, Filler, and Le Bricon's cystatin C-based eGFR equations were lower in CKD Stages 1–3 and higher in Stages 4 and 5. However, the results of the Orebro-cystatin (Gentian) equation [GFR = 100/ScytC (mL/minute/1.73 m^2) – 14] were similar to those of the K-aMDRD equation in CKD Stages 4 and 5 (15.44 $\pm$ 9.45 vs. 15.17 $\pm$ 9.05 mL/minute/1.73 m^2, respectively; $P = 0.722$; bias = 0.27 $\pm$ 8.87).

Conclusion: The eGFRs obtained from the six cystatin C-based equations differed widely. Therefore, further studies are required to determine the most accurate equation to estimate GFR in Koreans with CKD.

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Introduction

Estimation of the glomerular filtration rate (GFR) is the most important step in the diagnosis of chronic kidney disease (CKD), and significant research has been directed toward developing the most accurate, convenient, and reproducible equation. Traditionally, the Modification of Diet in Renal

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Disease (MDRD) [1], Cockcroft–Gault [2], and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [3] equations have been considered the most acceptable creatinine-based equations for estimating GFR. The Kidney Disease Outcome Quality Initiative (K/DOQI) recommends using an abbreviated form of the MDRD equation (aMDRD) for clinical purposes [4]. A recent publication by Lee et al [5] adapted the aMDRD equation for a Korean population by adding a coefficient (K-aMDRD), which improved the estimated GFR (eGFR) performance and more closely approximated inulin clearance. However, there are a number of disadvantages in using serum creatinine itself as a filtration marker [6,7]. Therefore, identifying a new endogenous filtration marker is necessary for the accurate and convenient estimation of GFR.

Serum cystatin C is a cationic nonglycosylated low-molecular-weight cysteine proteinase inhibitor produced at a constant rate by all nucleated cells and freely filtered at the glomerulus [8]. Approximately 99% of filtered cystatin C is reabsorbed in the proximal tubule, where it undergoes near-complete catabolization [9,10]. Because of these features, serum cystatin C was proposed as a superior marker of GFR, and its superiority over serum creatinine in the early detection of acute kidney injury is already well established [11,12]. However, its role as a filtration marker is still conflicting [13–15], and there is no validated cystatin C-based eGFR equation in predicting the glomerular rate in CKD patients [16–20].

Thus, in this study, we aimed to determine the performance of cystatin C in estimating GFR and the accuracy of six different cystatin C-based eGFR equations and compared the results with that of the K-aMDRD equation according to the CKD stage.

Methods

Patients

Serum creatinine and cystatin C levels were measured in 615 CKD patients who visited the Pusan National University Hospital between January 2011 and December 2011. The recruited patients were aged $\geq$ 18 years. Patients with thyroid dysfunction, inflammation, severe liver disease, or a history of steroid therapy were excluded [21–23]. Patients with extremely high eGFR calculated using the MDRD equation (eGFR > 130 mL/minute/1.73 m^2) [5] and patients with end-stage renal disease on maintenance dialysis were also excluded. The local Ethics Committee approved this study to analyze anonymous, routinely collected clinical data and waived the requirement of informed consent.

Laboratory methods

Serum creatinine and serum cystatin C levels were measured in the same serum sample. Serum creatinine values were measured by the alkaline picrate Jaffe kinetic method, and cystatin C values were determined by turbidimetry-based immunoassays using reagents from Healthcare Innovation (HBI Co, Anyang, Korea). The ratio of serum cystatin C to creatinine (mg/L to mg/dL) was calculated without adjustment of the unit for ease of application.

GFR measurement and estimation

Measured GFR

The measured GFR (mGFR) was obtained by Tc-99m-diethylenetriamine pentaacetate (Tc-99m-DTPA) renal scintigraphy. After a bolus injection of 10-mCi Tc-99m-DTPA, GFR was obtained using the Gates method [24] during a renal scan with VERTEX (EPIC) gamma camera equipped with ADAC's DUAL DETECTOR (ADAC, Milpitas, CA, USA).

eGFR by serum creatinine

Serum creatinine-based eGFR was calculated by the CKD-EPI [3] and K-aMDRD equations [$GFR = 107.904 \times Scr^{-1.009} \times age^{-0.02}$ ($\times 0.667$ if woman)] [5]. The CKD stage was classified according to the recommendation of the Kidney Disease Improving Global Outcomes and National Kidney Foundation-K/DOQI guideline using the K-aMDRD equation [25].

eGFR by serum cystatin C

Serum cystatin C-based eGFR was calculated using six different equations published previously.

- Larsson A et al [16]: $GFR = 99.43 \times ScytC^{-1.5837}$ (mL/minute/1.73 m^2)
- Hoek FJ et al [17]: $GFR = 80.35/ScytC^{-4.32}$ (mL/minute/1.73 m^2)
- Le Bricon T et al [18]: GFR = 78/ScytC + 4 (mL/minute/1.73 m^2)
- Filler G and Lepage N [19]: $GFR = 91.62 \times ScytC^{-1.123}$ (mL/minute/1.73 m^2)
- Orebro-cystatin (DAKO) [19]: GFR = 119/ScytC – 33 (mL/minute/1.73 m^2)
- Orebro-cystatin (Gentian) [19]: GFR = 100/ScytC – 14 (mL/minute/1.73 m^2)

Statistical analysis

Data were analyzed using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA). The Student *t* test was used for analysis of continuous variables and results are presented as mean $\pm$ standard deviation (SD). The Chi-square test was used for analysis of categorical variables. Differences in eGFR in each of the CKD stage were compared using a paired *t* test. The mean difference (bias) between the paired observation is given with SD (precision) and *P* values. The Bland–Altman plot was used to test the agreement between eGFRs from the K-aMDRD formula and the cystatin C-based equations, as well as between the K-aMDRD and mGFR [26]. Values of $P < 0.05$ were considered statistically significant.

Results

Baseline characteristics

A total of 615 patients were enrolled in this study. The mean age of the recruited patients was 53.21 $\pm$ 14.45 years with 56.3% of patients being male. Patients with diabetes mellitus comprised 23.9% of the study population and hypertensive patients comprised 35.1%. The mean serum creatinine level was 2.52 $\pm$ 3.14 mg/dL and the mean serum cystatin C level was 1.79 $\pm$ 1.18 mg/L. The mean and upper 99th percentile serum cystatin C, respectively, according to the stages of CKD were as follows: CKD 1, 0.87 $\pm$ 0.20 mg/L and 1.45 mg/L; CKD 2, 1.20 $\pm$ 0.43 mg/L and 2.20 mg/L; CKD 3, 1.94 $\pm$ 0.49 mg/L and 3.08 mg/L; CKD 4, 3.13 $\pm$ 0.61 mg/L and 4.29 mg/L; CKD 5

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