Estimation of Glomerular Filtration Rate With Creatinine-Based Versus Cystatin C-Based Equations in Kidney Transplant Recipients

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Introduction. Serum cystatin C is more sensitive for glomerular filtration rate (GFR) measurement, but it is not available for clinical use in all laboratories. Regarding the importance of accurate estimation of GFR in kidney transplant recipients, we compared cystatin C-based equations with creatinine-based formulas to estimate GFR as precisely and simply as possible in kidney transplant recipients.

Materials and Methods. Seventy living donor kidney transplant recipients with stable kidney function were enrolled in our study. The patients' GFRs were estimated by 3 creatinine-based equations (the modification of diet in renal disease [MDRD], abbreviated MDRD, and Cockcroft-Gault) and 5 cystatin C-based equations (Filler, Le Bricon, Rule, Hoek, and Larsson), and the results were analyzed.

Results. The mean age of the recipients was 38.7 ± 13.4 years. The mean GFRs were 67.1 ± 25.9 mL/min/1.73 m^2, by the Cockcroft-Gault; 61.0 ± 17.7 mL/min/1.73 m^2, by the abbreviated MDRD; and 60.0 ±18.6 mL/min/1.73 m^2, by the MDRD formulas. Cystatin C-based GFR estimations were 43.6 ± 16.2 mL/min/1.73 m^2, 44.0 ± 13.2 mL/min/1.73 m^2, 33.8 ± 14.1 mL/min/1.73 m^2, 35.6 ± 13.7 mL/min/1.73 m^2, and 36.9 ± 13.6 mL/min/1.73 m^2 by the Filler, Le Bricon, Larsson, Rule, and Hoek equations, respectively. The estimates by creatinine-based and cystatin C-based equations were significantly different and the MDRD estimate was the closest to the cystatin C-based GFRs.

Conclusions. Our findings revealed the MDRD equation could be provide a closer estimate of GFR to the cystatin C-based equations than other creatinine-based GFR calculations in kidney transplant recipients.

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INTRODUCTION

Accurate measurements of glomerular filtration rate (GFR) and early kidney dysfunction recognition are critical in the follow-up of kidney transplant recipients.[1] Therefore, a variety of markers for evaluation of glomerular dysfunction have been proposed. In 2002, the National Kidney Foundation published the *Kidney Disease Outcomes Quality Initiative* guidelines for the diagnosis and classification of chronic kidney disease on the

basis of creatinine-based formulas.[2] Recent studies concluded that the cystatin C-based equations were more accurate in GFR estimation than the modification of diet in renal disease (MDRD) equations.[3-5] Cystatin C, which is produced endogenously at a constant rate, is freely filtered in the glomeruli and is completely reabsorbed and catabolized by the proximal renal tubule.[3] To date, numerous cystatin C-based equations have been designed in different populations to introduce a direct GFR estimation.[4,5] However, there are some challenges on the accuracy of these equations in kidney transplant recipients yet.[4,6] We planned a study on renal transplant recipients in order to compare the performance of the three- creatinine based equations (MDRD, abbreviated MDRD, and Cockcroft-Gault [CG] equations) with 5 cystatin C-based equations for GFR measurements.

MATERIALS AND METHODS

Patients

In this cross-sectional study, we selected 70 living kidney transplant recipients with stable serum creatinine levels in 2 consecutive visits and more than 6 months history of transplantation. They were 46 men and 24 women. Immunosuppressive drugs were cyclosporine, mycophenolate mefotil, and prednisolone. Our exclusion criteria were hyperthyroidism or hypothyroidism, a body mass index greater than 30 kg/m^2, pregnancy, liver cirrhosis, or administration of any medication interfering with creatinine tubular secretion.

Methods

Data including age, sex, weight, body mass index, last serum creatinine level measured on follow-up visits were collected. Then blood samples were collected for serum creatinine, cystatin C, and albumin measurements. The method for creatinine measurement was the Jaffe method with a Roche/Hitachi 747 analyzer (Boehringer, Mannheim, Germany). Serum cystatin C and serum albumin levels were analyzed with the Dade-Behrings method using the Behring Nephelometer II (Marberg, Germany).

The patients' GFRs were calculated using the CG, MDRD, abbreviated MDRD, and 5 cystatin C-based equations including the Filler, Le Bricon, Rule, Hoek, and Larsson equations (Table 1).[7-12] All models were standardized for body surface area (1.73 m^2) as shown in Table 1.

Statistical Analyses

The SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA) was used. The normality of the distributions of variables were checked by the Kolmogrov–Smirnov test. The Spearman correlation coefficient test was applied to determine the relationships and the linear regression models for the relationship between different methods of GFR assessment. *P* values less than .05 were considered significant.

RESULTS

The participants were 46 men and 24 women. The mean age of the kidney recipients was 38.7 ± 13.4 years. Their other characteristics are summarized in Table 2. The mean estimated GFRs by 3 creatinine-based formulas (CG, MDRD, and abbreviated MDRD) and 5 Cystatin C-based equations (Filler, Le Bricon, Larsson, Rule, and Hoek) are demonstrated in Table 3. There were significant correlations

Table 1. Five Cystatin C-Based and 3 Creatinine-Based Estimates of Glomerular Filtration Rate

Equation	Formula, mL/min/1.73 m^2
Cystatin C-based	
Filler	Log (GFR) = 1.962 + [1.123 × log (1/cystatin C)]
Le Bricon	GFR = [78 × (1/cystatin C)] + 4
Hoek	GFR = -4.32 + (80.35 × 1/cystatin C)
Larsson	GFR = 77.24 × cystatin C$^{-1.2623}$
Rule	GFR = 76.6 ×cystatin C$^{-1.16}$
Creatinine-based	
MDRD	GFR = 170 × creatinine$^{-0.999}$ × age$^{-0.176}$ × blood urea nitrogen$^{-0.170}$ × albumin$^{0.318}$ × (0.762 for women) × (1.180 for African-Americans)
Abbreviated MDRD	GFR = 186 × creatinine$^{-1.154}$ × age$^{-0.203}$ × (0.742 for women) × (1.212 for African-Americans)
Cockcroft-Gault	[(140 – age) × body weight]/(creatinine × 72) (for women, × 0.85)

Table 2. Characteristics of Kidney Transplant Recipients*

Characteristic	Value
Sex	
Male	46 (65.7)
Female	24 (34.3)
Age, y	38.7±17.4 (16 to 64)
Height, cm	168.0 ± 9.2 (140 to 195)
Body weight, kg	70.0 ± 12.0 (45 to 92)
Body mass index, Kg/m^2	25.0 ± 3.3 (17.6 to 29.9)
Blood urea nitrogen, mg/dL	25.4 ±10.4 (6 to 64)
Serum creatinine, mg/dL	1.4 ± 0.3 (0.7 to 2.2)
Serum albumin, g/dL	4.3 ± 0.3 (2.9 to 5.1)
Serum cystatin C, mg/L	2.1± 0.7 (0.9 to 5.2)

*Values in parentheses are percents for sex distributions and range for the other parameters.

Table 3. Mean Glomerular Filtration Rates Estimated by Creatinine-Based and Cystatin C-Based Equations*

Equation	Value
Cystatin C-based	
Filler	43.5 ± 16.1 (14.1 to 95.0)
Le Bricon	43.8 ± 13.1 (18.7 to 84.5)
Hoek	36.8 ± 13.5 (10.8 to 78.7)
Larsson	33.8 ± 14.1 (9.4 to 80.4)
Rule	35.6 ± 13.6 (11.1 to 79.5)
Creatinine-based	
MDRD	59.9 ± 18.6 (30.7 to 124.8)
Abbreviated MDRD	61.0 ± 17.7 (32.5 to 123.3)
Cockcroft-Gault	67.0 ± 25.8 (36.5 to 196.1)

*Values are mean ± standard deviation (range) and all units are mL/min/1.73 m^2.

between cystatin C-based equations (r = 0.99 to 1, $P < .01$) and between creatinine-based formulas (r = 0.83 to 0.86, $P < .01$). There were significant differences between creatinine-based estimates and cystatin C-based equations for GFR ($P = .01$). Table 4 demonstrates correlations determined between creatinine-based formulas and cystatin C-based equations. The MDRD formula showed more association than the CG and abbreviated MDRD with the Filler, Le Bricon, Rule, Larsson, and Hoek formulas. The MDRD formula results were closer than other equations to cystatin C-based estimates of GFR (Figures 1 to 3).

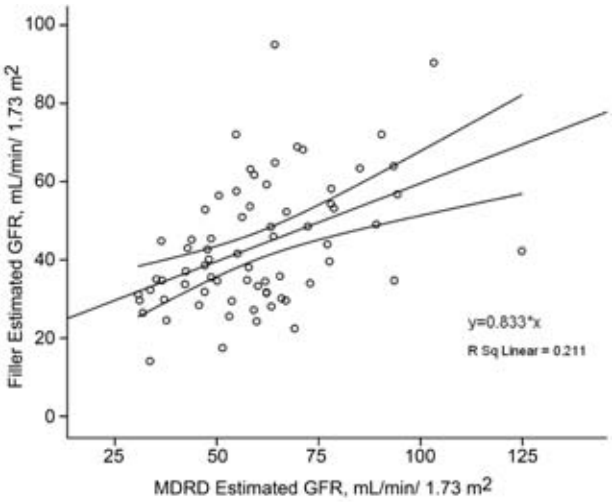

Figure 1. Association of the estimated glomerular filtration rate by the modification of diet in renal disease (MDRD) formula with that by cystatin C-based Filler formula in kidney transplant recipients.

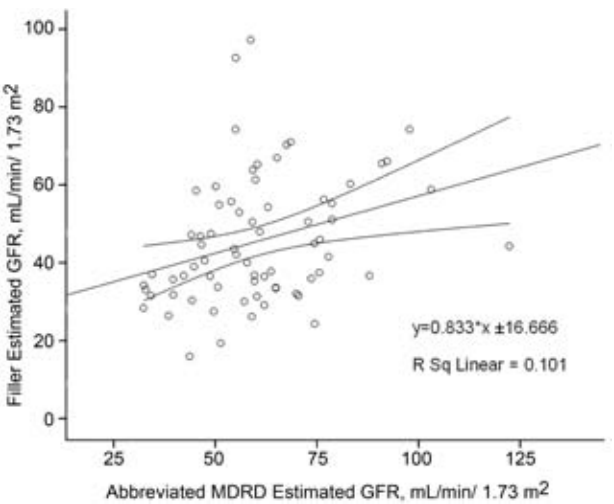

Figure 2. Association of the estimated glomerular filtration rate by the abbreviated modification of diet in renal disease (abbreviated MDRD) formula with that by cystatin C-based Filler formula in kidney transplant recipients.

DISCUSSION

Management of kidney transplant recipients requires a simple, reliable, and accurate method for the estimation of GFR. Many reports clearly

Table 4. Regression of Cystatin C-Based Equations and Creatinine-Based Glomerular Filtration Rate Estimates

	Cystatin C-Based Equations									
	Rule		Larsson		Hoek		Le Bricon		Filler	
Creatinine-Based Equations	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
MDRD	0.459	< .001	0.457	< .001	0.460	< .001	0.460	< .001	0.459	< .001
Abbreviated MDRD	0.316	.008	0.312	.009	0.322	.007	0.322	.007	0.317	.007
Cockcroft-Gault	0.246	.04	0.243	.04	0.251	.04	0.251	.04	0.247	.04

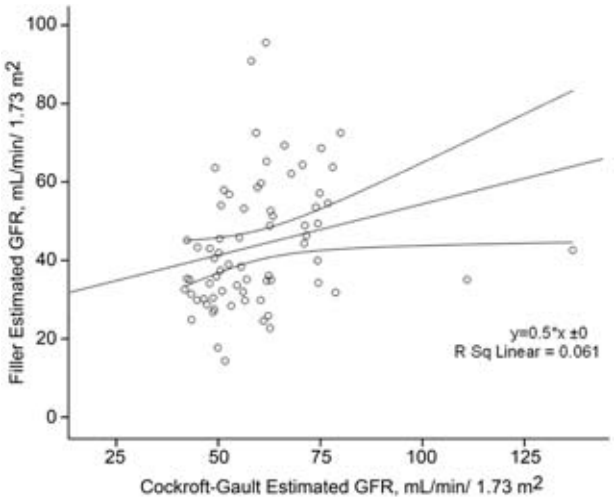

Figure 3. Association of the estimated glomerular filtration rate by the Cockroft-Gault formula with that by cystatin C-based Filler formula in kidney transplant recipients.

demonstrated that among all available markers, serum cystatin C had the best correlation with GFR and reinforced the usefulness of cystatin C as a test for kidney impairment diagnosis.[13,14] A meta-analysis of combined data from 46 studies on different age groups of healthy volunteers and patients with different degrees of kidney impairment, caused by a diverse group of conditions, demonstrated serum cystatin C was clearly superior to serum creatinine as a marker used for GFR measurement.[15] Accordingly, researchers have recommended serum cystatin C be applied as an accurate and rapid endogenous marker of GFR in research and clinical practice.[15,16] Mussap and colleagues showed that cystatin C might be considered as an alternative and more accurate serum marker than serum creatinine or the CG estimate of GFR in discriminating type 2 diabetic patients with reduced GFR from those with normal GFR.[17] More recently, Beringer and coworkers found that cystatin C clearance improved sensitivity, specificity, and precision for estimating GFR in adult patients with cystic fibrosis, when compared with creatinine based equations. The authors recommended cystatin C equations be considered in these patients, particularly in those who are at a higher risk of chronic kidney disease and those who undergo multiple intravenous drug therapies.[18]

In 125 kidney allograft recipients with stable graft function, Christensson and colleagues evaluated the GFR level by reciprocal of serum creatinine, cystatin C, and iohexol clearance. They showed that serum cystatin C levels correlated significantly closer to accurate measurements of GFR and were significantly more sensitive to detect early GFR impairment than enzymatic serum creatinine measurements.[19] Among different methods for cystatin C-based GFR stimulations, the equations proposed by Filler and Lepage[8] and Le Bricon and colleagues[9] provided a more accurate estimate of GFR than creatinine or other cystatin C-based equations in kidney transplant recipients.[20] According to the previous reports on the accuracy of cystatin C levels for measurements of GFR, we planned a study to compare the performance of the 3 creatinine-based equations with 5 cystatin C-based equations in kidney transplant recipients. In our study, significant differences were shown between creatinine-based estimates and cystatin C-based equations. Creatinine levels vary due to muscle mass and the tubular secretion of creatinine which makes the test prone to some limitations. Cystatin C is produced endogenously at a constant rate, freely filtered in the glomeruli, and completely reabsorbed and catabolized by the renal tubule cells, but it is not to be affected by severe illness, age, gender, height, and obesity; therefore, it is found to be a reliable indicator of kidney function. These could be the cause of the difference between the equations which was confirmed by other studies, too.[7,17]

Our study demonstrated that the MDRD estimate was closer to cystatin C-based equations which was in agreement with a study of Mariat and associates who showed that in kidney transplant recipients, both MDRD study equations could perform better than the CG equation; however, these equations did not seem to accurately predict kidney allograft function to meet the Kidney Disease Outcomes Quality Initiative standards as defined in nontransplanted patients.[5] In another study which included 187 former kidney donors, Louvar and colleagues also suggested the MDRD equation as the preferred model in their population.[21]

In order to better understand and validate the accuracy of creatinine and cystatin C equations for GFR measurement in kidney transplant recipients, more studies are suggested to compare these equations with renal clearance using exogenous substances (inulin, creatinine-ethylenediamine

tetraacetic acid, and iothalamate) that are considered the "gold standards" for determining GFR. Since these gold standard methods are used in research or highly specialized clinical settings and they are time-consuming, expensive, and associated with significant side effects such as anaphylactic reactions,[22] we did not use them in our series of kidney transplant recipients.

CONCLUSIONS

Our findings revealed the MDRD equation could be provide a closer estimate of GFR to the cystatin C-based equations than other creatinine-based GFR calculations in kidney transplant recipients. Concerning the accessibility and convenience of the measurement of creatinine, we recommend the MDRD formula be used in these patients.

CONFLICT OF INTEREST

None declared.

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