Ethnic coefficients for glomerular filtration rate estimation by the Modification of Diet in Renal Disease study equations in the Korean population

Lee, Chung Sik; Cha, Ran-hui; Lim, Youn-Hee; Kim, Ho; Song, Ka Heon; Gu, Namyi; Yu, Kyung Sang; Lim, Chun Soo; Han, Jin Suk; Kim, Suhnggwon; Kim, Yon Su

Published in:
Journal of Korean Medical Science

DOI:
10.3346/jkms.2010.25.11.1616

Publication date:
2010

Document version
Publisher's PDF, also known as Version of record

ORIGINAL ARTICLE
Nephrology

JKMS

DOI: 10.3346/jkms.2010.25.11.1616 • J Korean Med Sci 2010; 25: 1616-1625

Ethnic Coefficients for Glomerular Filtration Rate Estimation by the Modification of Diet in Renal Disease Study Equations in the Korean Population

Chung Sik Lee[1,*], Ran-hui Cha[1,*], Youn-Hee Lim[2], Ho Kim[2], Ka Heon Song[3], Namyi Gu[3], Kyung Sang Yu[3], Chun Soo Lim[1], Jin Suk Han[1], Suhnggwon Kim[1,4], and Yon Su Kim[1,4]

Department of Internal Medicine[1], Seoul National University College of Medicine; Department of Epidemiology and Biostatistics[2], School of Public Health, Seoul National University; Department of Clinical Pharmacology[3], Seoul National University College of Medicine; Kidney Research Institute[4], Seoul National University Medical Research Center, Seoul, Korea

*Chung Sik Lee and Ran-hui Cha contributed equally to this work.

Received: 5 March 2010
Accepted: 6 September 2010

Address for Correspondence:
Yon Su Kim, M.D.
Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehang-no, Jongno-gu, Seoul 110-744, Korea
Tel: +82.2-2072-2264, Fax: +82.2-745-2264
E-mail: yonsukim@snu.ac.kr

Race and ethnicity are influential in estimating glomerular filtration rate (GFR). We aimed to find the Korean coefficients for the Modification of Diet in Renal Disease (MDRD) study equations and to obtain novel proper estimation equations. Reference GFR was measured by systemic inulin clearance. Serum creatinine (SCr) values were measured by the alkaline picrate Jaffé kinetic method, then, recalibrated to CX3 analyzer and to isotope dilution mass spectrometry (IDMS). The Korean coefficients for the 4 and 6 variable MDRD and IDMS MDRD study equations based on the SCr recalibrated to CX3 and to IDMS were 0.73989/0.74254 and 0.99096/0.9554, respectively. Coefficients for the 4 and 6 variable MDRD equations based on the SCr measured by Jaffé method were 1.09825 and 1.04334, respectively. The modified equations showed better performances than the original equations. The novel 4 variable equations for Korean based on the SCr measured and recalibrated to IDMS were $107.904 \times SCr^{-1.009} \times age^{-0.02}$ (×0.667, if woman) and $87.832 \times SCr^{-0.882} \times age^{0.01}$ (×0.653, if woman), respectively. Modified estimations of the MDRD and IDMS MDRD study equations with ethnic coefficients and the novel equations improve the performance of GFR estimation for the overall renal function.

Key Words: Coefficient; Glomerular Filtration Rate; Inulin Clearance; Modification of Diet in Renal Disease Study

INTRODUCTION

Chronic kidney disease (CKD) is a world-wide public health problem with adverse outcomes. Strategies to improve outcomes will require a global effort to detect patients with mild renal dysfunction (1).

Glomerular filtration rate (GFR) is traditionally considered the best overall index of renal function in health and disease (2). Estimation of GFR has been considered to be important with the increasing emphasis on the earlier detection and management of CKD. An accurate, convenient, and reproducible GFR estimation will help clinicians to understand the relatively correct prevalence of CKD and follow a proper action plan for patients with CKD (3). However, routine estimated GFR (eGFR) reporting with serum creatinine (SCr) values is not yet universal, and underestimation of reference GFR in higher renal function is a limitation of current estimating equations, especially for the screening of CKD or the determination of CKD prevalence in the general population (4). The National Kidney Disease Education Program (NKDEP) currently recommends that GFR estimated above 60 mL/min/1.73 m^2 be reported simply as >60 mL/min/1.73 m^2 rather than as a discrete numeric value (5, 6). In addition, there is no significant change of SCr levels at near-normal GFR values (7).

Kidney Disease: Improving Global Outcomes (KDIGO) declared that estimating equations for GFR should be developed in large cohort including a variety of racial and ethnic groups for international comparisons (1). Additionaly, the Kidney Disease Outcome Quality Initiative (K/DOQI) of the National Kidney Foundation recommends that GFR should be estimated from SCr values and by using the abbreviated Modification of Diet in Renal Disease (aMDRD) study equation in order to predict kidney function and make a diagnosis of CKD (8). The MDRD study equation is significantly affected by race and ethnicity. A study of African-American has demonstrated that the ethnicity may influence GFR estimation by SCr based equations (2, 9). And Chinese and Japanese coefficients for the MDRD study equations were also reported (3, 8).

pISSN 1011-8934
eISSN 1598-6357

Although race is a very important element for estimating GFR, the Asian population was not included in the MDRD study. Further, equations from Chinese and Japanese studies are not immediately applicable to the Korean population because there are demographic differences among ethnicities and some methodological limitations in developing each coefficient. Therefore, we aimed to derive the ethnic coefficients of the MDRD study equations for Korean and to obtain novel proper estimating equations.

MATERIALS AND METHODS

Subjects

We recruited CKD patients (n=120) in outpatient department and healthy volunteers (n=31) from Seoul National University Hospital for the clinical study, 'Measurement of glomerular filtration rate and calculation of GFR estimates for Korean' granted by the Korean Society of Nephrology from April 2008 to February 2009. All of volunteers showed normal urinalysis and their systemic inulin clearances were greater than 60 mL/min/1.73 m^2 (66.4-151.3 mL/min/1.73 m^2). Inclusion criteria were as follows: 1) participants who agreed with the study and voluntarily signed on informed consent, 2) aged 18 yr or older. Exclusion criteria of this study were as follows: 1) rapid decline of renal function within 3 months, 2) edema or ascites, 3) proteinuria greater than 10 g/day or serum albumin less than 2.5 g/dL, 4) active infection, 5) coronary artery intervention i.e., coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) within 1 yr (except stabilization after unstable angina or heart failure), 6) liver enzyme abnormality (serum AST/ALT greater than 2×upper normal range), 7) history of severe allergy like angioedema, 8) pregnant or lactating women, 9) gross hematuria, 10) oliguria less than 500 mL/day), 11) renal replacement therapy. This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 0701-006-193).

Measurements

Inulin clearance (Inutest) (10)

Reference GFR was measured by systemic inulin clearance (Cl_{in}) (Inutest® 25%, Fresenius Kabi Austria GmbH, Austria), in which sinistrin, an inulin analogue, is used as a substitute for inulin because it is more water soluble and easy to handle. The procedure started after an overnight fasting except for pure water one hour prior to injection. Two intravenous lines, one for injection and the other for sampling, were established. Hydration to produce a good urine volume was achieved by oral loading with pure water (10 mL/kg) for 2.5 hr. Participants had abstained from high integrity carbohydrate such as coffee, black tea, sugar, or juice. A blank blood sample was drawn, and inulin was then injected. We used a single shot method: A total of 20 mL of Inutest® (5 g Sinistrin: equivalent to bounded fructose) was mixed with 30 mL of normal saline, and the mixture was injected at a constant rate over one minute. Participants drank 50 mL of pure water every 30 min. Six consecutive blood samplings (5, 10, 15, 30, 75, and 150 min after the injection) were collected from the antecubital vein of opposite from inulin injection. Each blood sample was centrifuged at 2,500 rpm for 10 min. After serum extraction, it was preserved at –80°C until analysis.

Inulin concentration (μg/mL) was determined by HPLC method (11). The HPLC system, with a delivery system, autoinjector, and ultraviolet detector was a Gilson Model (Gilson Inc., 305/306 HPLC Pumps, 234 autoinjector, 118 UV detector, Villiers Le Bel, France).

Reference GFR was determined by the systemic Cl_{in}, which was calculated by dividing the infusion dose with the area under the curve obtained by curve fitting. The plasma decay curves were fitted to a modified two-compartment pharmacokinetic model with zero order administration of the dose over one minute. Inulin clearance was normalized to a standard body surface area of 1.73 m^2 BSA using the Dubois-Dubois formula (12).

Measurement of SCr concentration

SCr values were measured by the alkaline picrate Jaffé kinetic method using a Hitachi 7600 analyzer (Toshiba, 200FR, Japan). To ensure that our SCr values were calibrated equally to those in the MDRD study, we randomly selected 40 fresh frozen serum samples from our specimens (ranging from 0.6 to 5.7 mg/dL) and analyzed them in the Cleveland Clinic Reference Laboratory. The SCr values measured by our laboratory can be calibrated to those obtained using a CX3 analyzer (Beckman Coulter Inc., Fullerton, CA, USA), via a linear regression equation: CX3 SCr (mg/dL)=1.148×Hitachi SCr (mg/dL)–0.420 (r=0.9955, P<0.001). Then, the measured SCr level was recalibrated to the isotope dilution mass spectrometry (IDMS) (College of American Pathologists [CAP]). The equation of correction is as follows: recalibrated SCr=1.0734×measured $SCr^{-0.2418}$ (mg/dL) (r=0.9989, P<0.001).

Measurement of estimated GFR (eGFR) (2, 7)

GFR estimation was calculated by the following four equations.

- Abbreviated (a) MDRD equation=$186\times SCr^{-1.154}\times age^{-0.203}$ (×0.742, if woman) (equation 1)
- Six variable MDRD equation=$170\times SCr^{-0.999}\times age^{-0.176}\times BUN^{-0.170}\times albumin^{0.318}$ (×0.762, if woman) (equation 2)
- Four variable IDMS MDRD equation=$175\times SCr^{-1.154}\times age^{-0.203}$ (×0.742, if woman) (equation 3)
- Six variable IDMS MDRD equation=$161.5\times SCr^{-0.999}\times age^{-0.176}\times BUN^{-0.170}\times albumin^{0.318}$ (×0.762, if woman) (equation 4)

In these equations, GFRs are expressed in mL/min/1.73 m^2, SCr and blood urea nitrogen (BUN) are expressed in mg/dL, albumin is expressed in g/dL, and age is expressed in years. The

BUN and albumin levels were measured by the urease/GLDH and bromocresol green (BCG) methods, respectively.

Korean coefficients of the MDRD and IDMS MDRD study equations and novel equations for estimating GFR

A total of 151 participants were included, and four participants whose GFRs exceeded 130 mL/min/1.73 m^2 were excluded. The remaining 147 patients were used for further analysis. We intended to simplify the models by forcing the intercepts to be zero. We also reconstructed two additional regression models using the measured SCr levels, because recalibration of SCr values to the Cleveland Clinic Reference Laboratory values for applying MDRD study equations is cumbersome in clinical practice in Korea. Log transformation was applied before the linear regression, and linearity and equal variance tests were satisfactory. Due to the concern that retransformation back to the usual scale might induce bias, the eGFR equations were adjusted using the smearing method.

Statistical analysis

We used the R software (version 2.8.0; The Comprehensive R Archive Network: http://cran.r-roject.org) and SAS 9.1 (SAS Institute Inc., Cary, NC, USA). A Student's t-test was used for continuous variables and presented as mean±SD. The chi-square test was used for categorical variables. For comparison of methods used for GFR estimation, the method of Bland and Altman was applied (13). Precision was expressed as the width between the 95% limits of agreement. Accuracy was measured as the percentage of estimated GFR that did not deviate >15, 30, and 50% from the reference GFR (systemic Cl_{in}). Bias was measured as the sum of area between the axis X and the slopes in Bland and Altman figure. Values of $P<0.05$ were considered statistically significant.

RESULTS

Baseline characteristics of participants

A total of 147 participants, excluding those whose systemic Cl_{in} exceeded 130 mL/min/1.73 m^2, were included in the analysis (CKD [n=118, 80.3%], healthy volunteer [n=29, 19.7%]). Mean age was 48.0 yr and 49% of the participants were female. Underlying causes of CKD were as follows: diabetes (12.9%), hypertension (12.9%), glomerulonephritis (32.7%), polycystic kidney disease (2.7%), and other or unknown causes (19.7%). The mean value of measured SCr was 1.9 mg/dL. Systemic Cl_{in} was distributed from 4.5 to 121.1 mL/min/1.73 m^2 (mean: 55.6 mL/min/1.73 m^2). Mean systolic and diastolic blood pressure were 122.8 and 74.5 mmHg, respectively. Mean body mass index and body surface area were 23.85 kg/m^2 and 1.68 m^2, respectively (Table 1).

Modification of MDRD study equations and overall performance

In the first linear regression, the intercepts of the modified MDRD and IDMS MDRD study equations were different from zero (22.37 for aMDRD with SCr values recalibrated to CX3; 17.15 for 4 variable IDMS MDRD). Although the intercepts of the modified equations were not assumed to be same with zero, we forced the intercepts to be zero to simplify application of the modified equations in real clinical practice. Then, the modified MDRD and IDMS MDRD study equations with ethnic coefficients were derived (equations 5-8) (Table 2).

The overall diagnostic performances of the modified MDRD and IDMS MDRD equations with ethnic coefficients (equations 5-8) were compared with those of the original MDRD and IDMS MDRD study equations (equations 1-4). Linear regressions were made using eGFR compared to reference GFR (systemic Cl_{in}).

The slopes of equations 1 and 2 using SCr values recalibrated to the CX3 analyzer were significantly closer to the identical line after modification (equations 5 and 6) ($P<0.05$). However, the changes of the slopes of equations 3 and 4 using SCr values recalibrated to IDMS were not statistically significant after modification (equations 7 and 8). The adjusted r^2 values (equations 1-4) were not changed after modification.

Table 1. Baseline characteristics of the participants (n=147; excluding participants whose reference GFR exceeded 130 mL/min/1.73 m^2)

Characteristic	Mean±SD or No. (%)	Range
Age (yr old)	48.0±14.99	19-80
Sex (Male:Female)	75 (51.0%):72 (49.0%)	
BMI (kg/m^2)	23.85±3.297	14.48-33.93
BSA (m^2)	1.68±0.178	1.26-2.11
Underlying disease		
DM	19 (12.9%)	
Hypertension	19 (12.9%)	
GN	48 (32.7%)	
PKD	4 (2.7%)	
Others	28 (19.0%)	
Healthy volunteer	29 (19.7%)	
Systolic BP (mm/Hg)	122.8±18.80	86-186
Diastolic BP (mm/Hg)	74.5±11.94	47-114
Measured SCr (mg/dL)	1.9±1.15	0.7-5.7
Corrected SCr to IDMS (mg/dL)	1.9±1.25	0.5-5.9
Corrected SCr to CX3 (mg/dL)	1.8±1.32	0.4-6.1
Hemoglobin (g/dL)	12.7±2.03	8.0-17.9
Blood urea nitrogen (mg/dL)	27.1±17.67	8-96
Albumin (g/dL)	4.3±0.36	2.9-5.1
Systemic inulin clearance (mL/min/1.73 m^2 BSA)	55.60±27.793	4.5-121.1
≥90	19 (12.9%)	
60-89	43 (29.3%)	
30-59	53 (36.1%)	
15-29	28 (19.0%)	
<15	4 (2.7%)	

BMI, Body mass index; BP, Blood pressure; BSA, Body surface area; CAP, College of American Pathologists; CX3, Beckman Synchron CX3 chemistry analyzer; DM, Diabetes mellitus; GN, Glomerulonephritis; IDMS, Isotope Dilution Mass Spectrometry; PKD, Polycystic kidney disease; SCr, Serum creatinine.

DOI: 10.3346/jkms.2010.25.11.1616

The mean difference and absolute difference of equations 1 and 2 significantly fell after modification (equations 5 and 6) (mean difference: from 4.4 and 5.2 to −7.9 and −7.1, $P<0.05$; mean absolute difference: from 15.0 and 14.8 to 12.0 and 12.1, $P<0.05$, respectively). The mean difference of equations 3 and 4 also decreased after modification (equations 7 and 8) (from −4.4 and −2.3 to −4.6 and −4.5, $P<0.05$), but the mean absolute differences remained unchanged.

The biases of the modified MDRD study equations (equations 5 and 6) were much less than those of the original MDRD study equations (equations 1 and 2). The biases of the IDMS MDRD study equations were not changed after the modification, with exception of the 6 variable IDMS MDRD study equation. Fifteen to thirty percent accuracy of most modified MDRD and IDMS MDRD study equations were higher than those of the original equations, although statistical significances were not valid (Table 3, Fig. 1).

Novel GFR estimating equations and overall performance

Calibrat ed CX3 SCr values were needed for the simple modification of the MDRD study equations (equations 1, 2, 5, and 6), but such calibration is not convenient for clinical application in Korea. Therefore, we tried to reconstruct another regression models with ethnic coefficients using the SCr values measured by the Jaffé kinetic method using a Hitachi 7600 analyzer (equations 9 and 10). These equations were also obtained after adjustment using the smearing method (Table 4).

Then, we derived novel equations to permit more accurate estimation of GFR by using multiple linear regression models.

Equations with SCr values measured by a Hitachi 7600 analyzer included:

- Four variable equation=$107.904\times SCr^{-1.009}\times age^{-0.02}$ (×0.667, if woman) (equation 11)
- Six variable equation=$56.694\times SCr^{-0.899}\times age^{0.01}\times BUN^{-0.081}\times albumin^{0.5}$ (×0.674, if woman) (equation 12)

Equations with SCr values recalibrated to IDMS included:

- Four variable IDMS equation=$87.832\times SCr^{-0.882}\times age^{0.01}$ (×0.653,

Table 2. Ethnic coefficients of the MDRD study equations for Korean population (n=147; excluding participants whose reference GFR exceeded 130 mL/min/1.73 m^2)

Equation	Exponent-transformed intercept	Coefficient of continuous parameters				Exponent-transformed coefficient of dichotomous variables
		SCr	Age	BUN	Alb	
SCr recalibrated to CX3 analyzer, Beckman (Cleveland Clinic Reference Laboratory)						
5	186	−1.154	−0.203	-	-	0.742, if woman 0.73989, if Korean
6	170	−0.999	−0.176	−0.170	0.318	0.762, if woman 0.74254, if Korean
SCr recalibrated to IDMS (College of American Pathologists)						
7	175	−1.154	−0.203	-	-	0.742, if woman 0.99096, if Korean
8	161.5	−0.999	−0.176	−0.170	0.318	0.762, if woman 0.9554, if Korean

Alb, Albumin; BUN, Blood urea nitrogen; IDMS, Isotope Dilution Mass Spectrometry; MDRD, Modification of Diet in Renal Disease; SCr, Serum creatinine.

Table 3. Overall performance of the original and modified MDRD study equations (equations 1-8) compared to systemic inulin clearance (reference GFR) (n=147; excluding participants whose reference GFR exceeded 130 mL/min/1.73 m^2)

	Intercept 95% C.I.	Slope 95% C.I.	Adjusted R^2	Median difference 25%, 75%	Median abs. difference 25%, 75%	Bias	Precision	Accuracy		
								15%	30%	50%
MDRD and IDMS MDRD study equations										
aMDRD[1]	-7.86 (-17.24,1.53)	1.32 (1.17,1.47)	0.67	4.4 (-8,21.8)	15.0 (6.4,29.4)	3,476.7	20.7	21.1	50.3	74.8
6v MDRD[2]	-6.97 (-16.18,2.24)	1.31 (1.16,1.46)	0.67	5.2 (-7.6,24.9)	14.8 (6,32.1)	3,417.7	20.5	20.4	51.0	74.1
4v IDMS MDRD[3]	2.58 (-3.879.04)	0.88 (0.78,0.99)	0.65	-4.4 (-15.4,5.3)	10.2 (4.8,20.5)	517.7	17.9	32.7	61.9	82.3
6v IDMS MDRD[4]	2.07 (-3.84,8.95)	0.93 (0.828,1.03)	0.66	-2.3 (-14.7,7.4)	9.9 (5.2,19.8)	795.0	18	34	64.6	82.3
MDRD and IDMS MDRD study equations multiplied by the Korean ethnic coefficients										
aMDRD[5]	-5.81 (-12.75,1.13)	0.98* (0.87,1.09)	0.67	-7.9* (-19.5,2.2)	12.0* (5.8,22.7)	1,129.2	18.3	29.9	52.4	82.3
6v MDRD[6]	-5.18 (-12.02,1.67)	0.97* (0.867,1.08)	0.67	-7.1* (-18.1,2)	12.1* (6.0,22.1)	1,075.1	18.1	32.7*	51.7	82.3
4v IDMS MDRD[7]	2.56 (-3.84,8.95)	0.88 (0.77,0.98)	0.65	-4.6† (-15.7,4.8)	10.4 (4.6,20.5)	553.8	17.8	33.3	60.5	82.3
6v IDMS MDRD[8]	1.97 (-4.37,8.32)	0.89 (0.78,0.99)	0.66	-4.5† (-16,4.8)	9.8 (4.6,20.7)	573.6	17.6	33.3	61.2	84.4

Difference, absolute difference and precision: mL/min/1.73 m^2, Bias: arbitrary unit.
*$P<0.05$, compared with equation 1 and 2; †$P<0.05$, compared with equation 3 and 4.
[1-8]numbers in parenthesis mean the number of equation.
IDMS, Isotope Dilution Mass Spectrometry; MDRD, Modification of Diet in Renal Disease; SCr,Serum creatinine.

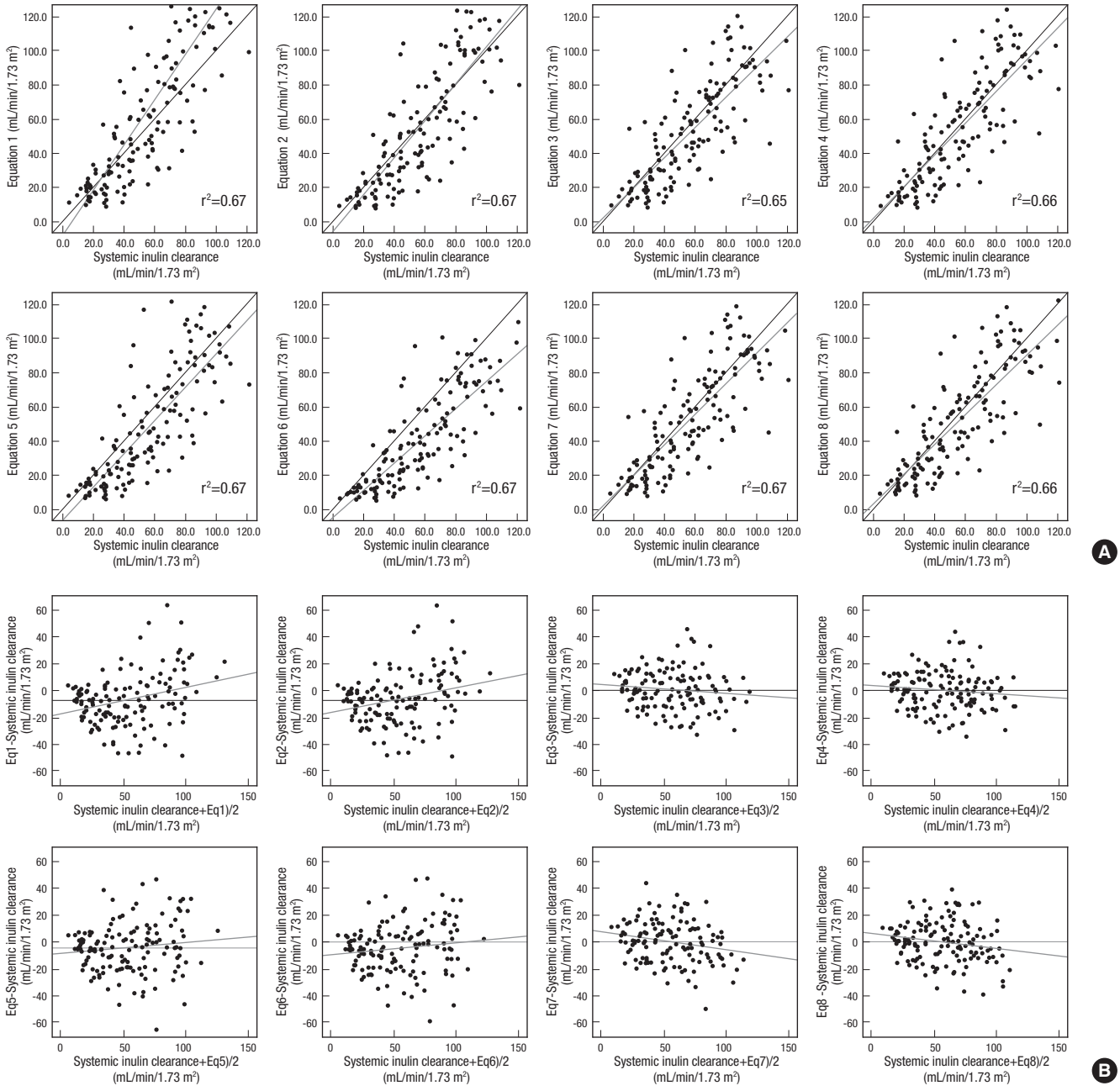

Fig. 1. Correlation of estimated glomerular filatration rate (eGFR) (equations 1-8) with systemic inulin clearance (reference GFR) (**A**) and Bland and Altman plots between eGFR (equations 1-8) and systemic inulin clearance (**B**) (n=147; excluding participants whose reference GFR exceeded 130 mL/min/1.73 m^2). (**A**) Black line: Identical line, gray line: Fit line between systemic inulin clearance and eGFR. Modification of the Modification of Diet in Renal Disease (MDRD) study equations using serum creatinine (SCr) values recalibrated to CX3 analyzer (Cleveland Clinic Reference Laboratory) underestimated GFR for all stages of renal function. (**B**) Solid red line represents the regression line of difference between methods against average of methods. The mean difference is indicated by center line, limits of agreement are indicated by the upper (mean+2SD) and lower (mean−2SD) lines. Eq1-Eq4: Equations 1-4: The MDRD and Isotope Dilution Mass Spectrometry (IDMS) MDRD study equations using SCr values recalibrated to CX3 analyzer and to IDMS. Eq5-Eq8: Equations 1-4 multiplied by the Korean ethnic coefficients.

if woman) (equation 13)

- Six variable IDMS equation=$71.381\times SCr^{-0.65}\times age^{0.07}\times BUN^{-0.249}\times albumin^{0.445}$ (×0.762, if woman) (equation 14)

The slopes of equations 9 and 10 were significantly closer than the slopes of equations 1 and 2 to the identical line (P<0.05). The slopes of equations 11 and 12 were also closer than those of equations 1 and 2, although statistical significance was not valid. The slopes of equations 13 and 14 were more distant from the identical line than those of equations 3 and 4 (P<0.05). The values of the adjusted r^2 for equations 9-14 were much better than those for equations 1-4.

The mean difference and absolute difference of equations 9 and 10 decreased in comparison to equations 1 and 2 (mean difference: from 4.4 and 5.2 to –2.1 and –3.0, P<0.05; mean ab-

DOI: 10.3346/jkms.2010.25.11.1616

Table 4. Ethnic coefficients of the MDRD study equations for Korean population using measured serum creatinine values by a Hitachi 7600 (n=147; excluding participants whose reference GFR exceeded 130 mL/min/1.73 m^2)

Equation	Exponent-transformed intercept	Coefficient of continuous parameters				Exponent-transformed coefficient of dichotomous variables
		SCr	Age	BUN	Alb	
Measured SCr (Hitachi 7600, Toshiba-200FR autoanalyzer)						
9	186	-1.154	-0.203	-	-	0.742, if woman 1.09825, if Korean
10	170	-0.999	-0.176	-0.170	0.318	0.762, if woman 1.04334, if Korean

Alb, Albumin; BUN, Blood urea nitrogen; IDMS, Isotope Dilution Mass Spectrometry; MDRD, Modification of Diet in Renal Disease; SCr, Serum creatinine.

Table 5. Overall performance of the novel equations (equations 9-14) compared to systemic inulin clearance (reference GFR): (n=147; excluding participants whose reference GFR exceeded 130 mL/min/1.73 m^2)

	Intercept 95% C.I.	Slope 95% C.I.	Adjusted R^2	Median difference 25%, 75%	Median abs. difference 25%, 75%	Bias	Precision	Accuracy		
								15%	30%	50%
Modified MDRD study equations using measured SCr values by a Hitachi 7600 and multiplied by the Korean ethnic coefficients (9, 10)										
aMDRD[9]	5.84 (0.57,11.11)	0.86* (0.77,0.94)	0.73	-2.1* (-10,7.4)	9.0* (4.5,15.1)	311.4	15.1	42.2*	67.3*	87.8
6v MDRD[10]	4.77 (-0.68,10.23)	0.87* (0.78,0.96)	0.72	-3.0* (-10.7,6.9)	8.2* (4.3,16.6)	309.7	15.5	39.5*	69.4*	86.4
Novel equations for Korean population using SCr values measured by a Hitachi 7600 (11, 12) and recalibrated to IDMS (13, 14)										
aMDRD[11]	12.48 (7.93,17.03)	0.79* (0.71,0.86)	0.75	0.4* (-8.2,10.4)	9.1* (3.7,15.15)	604.0	13.6	45.6*	68.7*	86.4
6v MDRD[12]	11.99 (7.41,16.56)	0.80* (0.72,0.87)	0.76	1.2* (-8.7,9.8)	9.2* (3.8,15.3)	534.9	13.6	48.3*	67.3*	87.8
4v IDMS MDRD[13]	14.54 (9.78,19.29)	0.75† (0.67,0.83)	0.72	0.6† (-11.2,10.2)	10.7† (4.1,15.8)	769.4	14.5	43.5	70.1	86.4
6v IDMS MDRD[14]	13.86 (9.03,18.69)	0.76† (0.69,0.84)	0.72	1.6† (-8.9,10.1)	9.6† (4,16.2)	656.3	14.6	45.6	66.7	87.8

Difference, absolute difference and precision: mL/min/1.73 m^2, Bias: arbitrary unit.
*P<0.05, compared with equations 1 and 2; †P<0.05, compared with equations 3 and 4.
[9-14]numbers in parenthesis mean the number of equation.
IDMS, Isotope Dilution Mass Spectrometry; MDRD, Modification of Diet in Renal Disease; SCr,Serum creatinine.

solute difference: from 15.0 and 14.8 to 9.0 and 8.2, P<0.05, respectively). The mean difference and absolute difference of equations 11-14 decreased compared to equations 1-4.

The biases of equations 9-12 were much less than those of the original MDRD study equations (equations 1 and 2). The biases of the equations using SCr values recalibrated to IDMS increased after modification with ethnic coefficients. Fifteen to thirty percent accuracy of equations 9-12 were higher than those of the original MDRD study equations (equations 1 and 2) (P< 0.05). Fifteen to thirty percent accuracy of equations 13 and 14 were improved against equations 3 and 4, although statistical significance was not valid (Table 5, Fig. 2).

The performance of the equations was analyzed after dividing participants based on systemic Cl_{in} less than or greater than 60 mL/min/1.73 m^2. In the group of participants with systemic Cl_{in} less than 60 mL/min/1.73 m^2 (n=85), the bias, precision, and accuracy of the original MDRD equations were not changed after the modification. In the group of participants with systemic Cl_{in} of 60 mL/min/1.73 m^2 or more (n=62), the bias was significantly decreased after the modification, even though precision and accuracy were not significantly improved (data not shown).

DISCUSSION

About fifty thousand patients were receiving renal replacement therapy by the end of 2008 in Korea (hemodialysis, 33,427; peritoneal dialysis, 7,840; kidney transplantation, 10,722) (14). The number of patients and the budget to support those patients is increasing by a geometric progression. However, the increased prevalence of end stage renal disease patients accounts for just small portion of the huge number of CKD patients. To allow clinicians to recognize early CKD patients and figure out the prevalence of CKD in Korean population, we derived ethnic coefficients modifying the original MDRD and IDMS MDRD study equations from participants with all stages of renal function. Ethnic coefficients for the 4 and 6 variable MDRD/IDMS MDRD study equations based on SCr values recalibrated to CX3 analyzer and to IDMS were 0.73989/0.74254 and 0.99096/0.9554, respectively, and SCr measured by the Jaffé method using a Hitachi 7600 were 1.09825/1.04334 (Tables 2, 4).

In the present study, the modified MDRD study equations with ethnic coefficients based on SCr values recalibrated to CX3 analyzer (equations 5 and 6) and SCr measured by the Jaffé

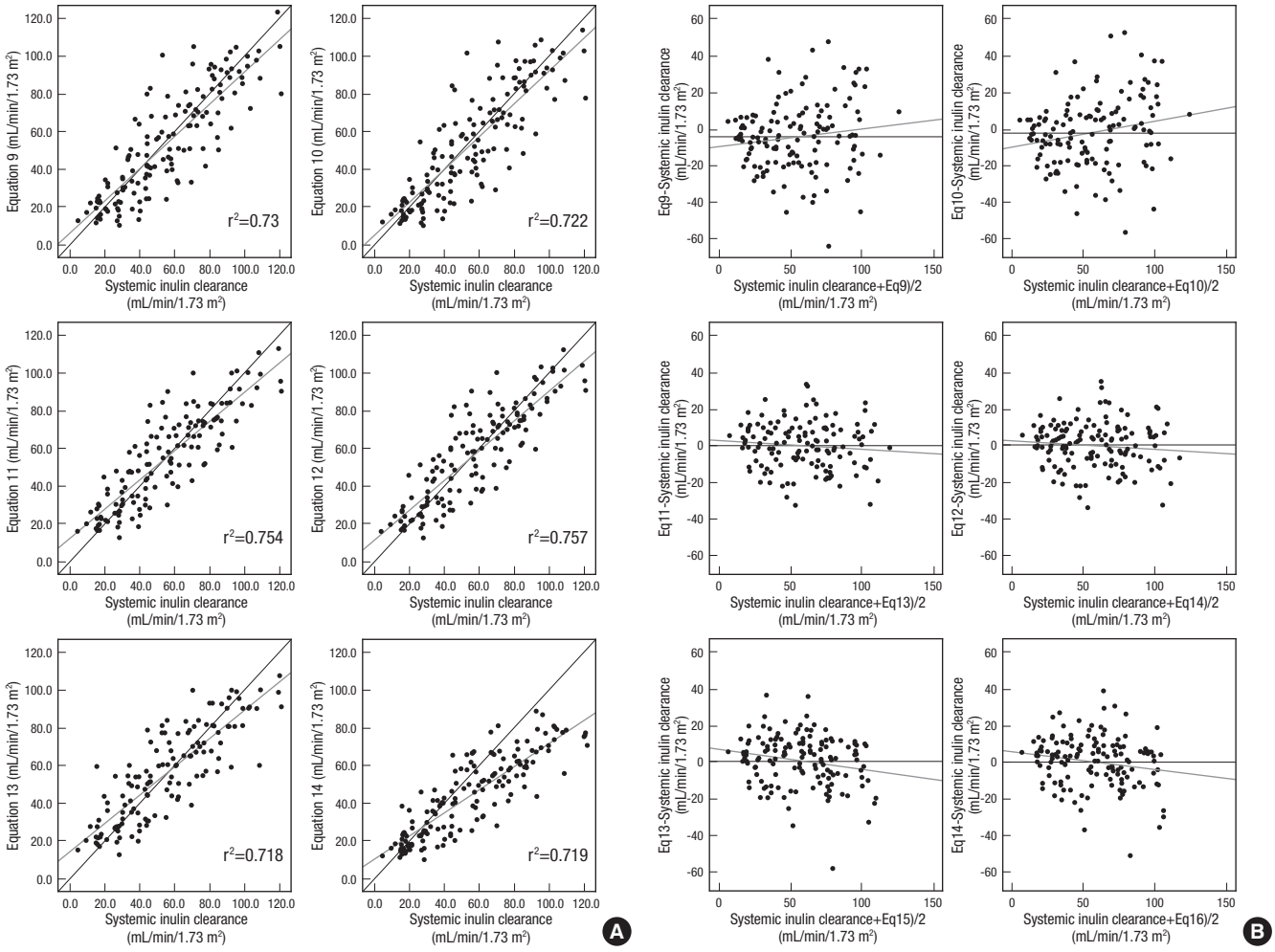

Fig. 2. Correlation of estimated glomerular filatration rate (eGFR) (equations 9-14) with systemic inulin clearance (reference GFR) (**A**) and Bland and Altman plots between eGFR (equations 9-14) and systemic inulin clearance (**B**) (n=147; excluding participants whose reference GFR exceeded 130 mL/min/1.73 m^2). (**A**) Black line: Identical line, gray line: Fit line between systemic inulin clearance and eGFR. Overestimation in advanced renal dysfunction or underestimation in near normal renal function was still observed. (**B**) Solid red line represents the regression line of difference between methods against average of methods. The mean difference is indicated by center line, limits of agreement are indicated by the upper (mean+2SD) and lower (mean−2SD) lines. Eq9-Eq10: The Modification of Diet in Renal Disease (MDRD) study equations using locally measured serum creatinine (SCr) values by a Hitachi 7600 and multiplied by the Korean ethnic coefficients. Eq11-Eq14: Novel 4 and 6 variable equations using SCr values recalibrated to CX3 analyzer (equations 11 and 12) and to Isotope Dilution Mass Spectrometry (IDMS) (equations 13 and 14).

method using a Hitachi 7600 (equations 9 and 10) showed better performance than did the original MDRD study equations (equations 1 and 2), although these improvements were not always statistically significant. These results guarantee that we could easily apply these ethnic coefficients and equations for usual clinical practice in Korea. The modified MDRD study equations with ethnic coefficients based on SCr recalibrated to CX3 analyzer showed more underestimation. This finding may originate from our statistical intention to force the intercept to be zero to permit simple practical application. In fact, the intercepts of the modified MDRD equation were different from zero (22.37 for the aMDRD and 21.74 for the 6 variable MDRD). Statistical design forcing the intercept to be zero also explains the discrepancies between the Korean coefficient of 0.74 and the Japanese coefficient of 0.881 (8). Because the procedure of recalibration to the CX3 analyzer is cumbersome and impractical as well, we suggest that modification of the original abbreviated and 6 variable MDRD equations with 1.09825 and 1.04334 (based on the locally measured SCr values by the Jaffé method) would be more clinically useful.

Although modification of the MDRD study equations with the measured SCr values (equations 9 and 10) showed sufficiently good slopes, biases, and accuracies, the ethnic coefficients of the IDMS MDRD study equations were close to '1' and the modified IDMS MDRD study equations showed comparable performance to equations 9 and 10. IDMS, high order reference method, have been developed for the assignment of reference materials and proficiency testing using a commutable specimen made each institution derives the correlation coefficient for individual measurement methods versus reference measurement

DOI: 10.3346/jkms.2010.25.11.1616

procedures (6, 15). Additionally, calibration improved the performance of the MDRD study equation, although larger errors still remained for GFR estimates greater than 60 mL/min/1.73 m^2 after calibration (16). Based on our results and those of others, we suggest that the IDMS MDRD equation will also offer a plausible option hereafter.

In contrast to the meaningful change in the GFR, there is no significant change in SCr levels for near normal GFR levels. The NKDEP currently recommends that a GFR estimated above 60 mL/min/1.73 m^2 be reported simply as >60 mL/min/1.73 m^2 rather than as a discrete numeric value (5, 6). Variation in the calibration of the SCr values, biologic and measurement variability of GFR at higher levels, and the use of an equations developed in a population with CKD provide possible explanations for the variable results of estimation in a population without the disease (5). In this study, percentages of estimated GFR above 60 mL/min/1.73 m^2 increased after the modification of equations 1 and 2 in CKD stage 2. Further, equations modified with ethnic coefficients generally showed better discrimination of estimated GFR less than 60 mL/min/1.73 m^2 in CKD stage 3 (data not shown). This means that clinicians could identify patients who should be managed more carefully and prevent the useless consumption of medical resources. Of course, modification of the MDRD study equations based on SCr values recalibrated to CX3 analyzer (Cleveland Clinic Reference Laboratory) (equations 5 and 6) may result in over-treatment of patients due to GFR estimation. Because the original MDRD study equations overestimated the real GFR for participants with normal to moderate renal dysfunction (slopes for 4 and 6 variable MDRD equations: 1.32 and 1.31, respectively), however, underestimation with the modified MDRD study equations might help clinicians to screen CKD patients more easily. In summary, we suggest that modification of the MDRD study equations with ethnic coefficients (equations 5-10) is very useful and should be adopted into routine clinical practice.

Ma et al. (3) reported that using a Chinese coefficient of 1.233 for the original abbreviated MDRD equation improved the GFR estimation for the Chinese population. However, the coefficient of 1.233 is much higher than the Korean coefficient of 0.74 and the Japanese coefficient of 0.881 (based on the SCr values recalibrated to CX3 analyzer) (8). Several criticisms to the result of the Chinese population study exist, including false measurement unit for creatinine, use of ^{99m}Tc-DTPA (which differs substantially from renal clearance), and GFR measurement after breakfast. ^{125}I-iothalamate and radio-labeled DTPA renal clearance seem to overestimate the GFR by about 5 mL/min/1.73 m^2 compared to inulin clearance, and Agarwal et al. reported that plasma clearance over 4 hr overestimated the GFR by 22% to 50% (17, 18). All of these matters may explain the discrepancies among the coefficients for East Asians.

GFR is measured using a variety of methods and filtration markers. Urinary Cl_{in}, using a constant infusion, has long been recognized as the gold standard method (19). However, multiple complications (e.g., glucose interference and the difficulty in adequate collection of urine) have led to the development of alternative methods (19). Total systemic Cl_{in} overestimated urinary Cl_{in}, however, it had a much better reproducibility than did the urinary Cl_{in}. And the difference in results generated by the single injection method and continuous infusion method in children was small and was considered acceptable in clinical practice (20, 21). Determination of systemic Cl_{in} with a single injection method is therefore a method of general validity for measuring the GFR without urine collection (21, 22). Theoretically, it is even possible that the single injection method may provide a more accurate representation of urinary Cl_{in} than the continuous infusion method (23).

In this study, urinary Cl_{in} was greater than systemic Cl_{in} ($Y=1.199\times X+1.087$, $r=0.797$). Multiple stepwise errors during timed urine collection and sample dilution occurring due to excessive inulin concentrations in the urine might explain this finding. We suggest that the acquisition of systemic Cl_{in} would offer a better approach to measure the GFR, and previous several evidences lead us to believe that the Korean ethnic coefficients are more plausible than Japanese coefficients.

When the calibration of SCr methods is traceable to the SCr reference system, GFR should be estimated using the MDRD study equation that has been re-expressed for standardized SCr values (23). Imai et al. reported that the Japanese coefficients for the 4 variable IDMS MDRD study equation was 0.763/0.808 (24, 25). These values are markedly different from the Korean coefficient of 0.99. Imai et al. used continuous renal Cl_{in} to measure GFR, whereas we used total systemic Cl_{in} after single shot injection of inulin. Differences in the reference GFR, creatinine calibration, inclusion and exclusion criteria, and statistical method used may explain the differences in the coefficients for the two ethnicities. More studies to identify and verify the IDMS MDRD study equation coefficients for Korean and other populations in Asia are required. Other variables with the potential to predict GFR (e.g., serum cystatin C) may be included to improve the performance of the GFR estimating equations, especially in the early stages of CKD (26). Recent investigations suggest that cystatin C may be a better filtration marker than SCr, especially at higher levels of GFR. Novel estimations of GFR using cystatin C for Korean, based on the participants of this study, will be reported soon.

This study is superior to previous studies because both CKD patients and healthy volunteers were recruited for this study. Thus, ethnic coefficients and novel equations reported here are easily applicable for screening and monitoring CKD (27). However, it is the limitation of this study that the study population was restricted to patients with native kidney disease and without serious comorbid conditions that would exclude them from

participating in clinical trials. And the fact that we did not validate estimation equations described above is the limitation of this study.

In conclusion, Modified estimations of the MDRD and IDMS MDRD study equations with ethnic coefficients and the novel equations improve the performance of GFR estimation for the overall renal function. Another study to validate these estimation equations and to compare systemic Cl_{in} (using sinistrin) with urinary inulin clearance will be needed. Furthermore, we assert that future studies (based on SCr values recalibrated to IDMS) to identify and verify the novel equations for East Asian population using the same GFR measurement protocol and eligible criteria should be performed.

ACKNOWLEDGMENTS

We are grateful to the Cleveland Clinic Reference Laboratory for calibration of serum creatinine.

REFERENCES

1. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. *Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005; 67: 2089-100.*
2. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. *A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130: 461-70.*
3. Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, Xu JS, Huang SM, Wang LN, Huang W, Wang M, Xu GB, Wang HY. *Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 2006; 17: 2937-44.*
4. Accetta NA, Gladstone EH, DiSogra C, Wright EC, Briggs M, Narva AS. *Prevalence of estimated GFR reporting among US clinical laboratories. Am J Kidney Dis 2008; 52: 778-87.*
5. Stevens LA, Coresh J, Greene T, Levey AS. *Assessing kidney function – Measured and estimated glomerular filtration rate. N Engl J Med 2006; 354: 2473-83.*
6. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, Hostetter T, Levey AS, Panteghini M, Welch M, Eckfeldt JH; National Kidney Disease Education Program Laboratory Working Group. *Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem 2006; 52: 5-18.*
7. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration. *Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006; 145: 247-54.*
8. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, Ura N, Kiyohara Y, Hirakata H, Watanabe T, Moriyama T, Ando Y, Inaguma D, Narita I, Iso H, Wakai K, Yasuda Y, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S. *Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. Clin Exp Nephrol 2007; 11: 41-50.*
9. Lewis J, Agodoa L, Cheek D, Greene T, Middleton J, O'Connor D, Ojo A, Phillips R, Sika M, Wright J Jr; African-American Study of Hypertension and Kindey Disease. *Comparison of cross-sectional renal function measurements in African-Americans with hypertensive nephrosclerosis and of primary formulas to estimate glomerular filtration rate. Am J Kidney Dis 2001; 38: 744-53.*
10. Prescott LF, Freestone S, McAuslane JA. *Reassessment of the single intravenous injection method with inulin for measurement of the glomerular filtration rate in human. Clin Sci (Lond) 1991; 80: 167-76.*
11. Pastore A, Bernardini S, Dello Strologo L, Rizzoni G, Cortese C, Federici G. *Simultaneous determination of inulin and p-aminohippuric acid in plasma and urine by reversed-phase high-performance liquid chromatography. J Chromatogr B Biomed Sci Appl 2001; 751: 187-91.*
12. DuBois D, DuBois EF. *A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916; 17: 863–71.*
13. Bland JM, Altman DG. *Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1: 307-10.*
14. ESRD Registry Committee; Korean Society of Nephrology. *Current renal replacement therapy in Korea: Insan Memorial Dialysis Registry 2008. Korean J Nephrol 2009; 28 (Suppl 3): S403-510.*
15. Miller WG, Myers GL, Ashwood ER, Killeen AA, Wang E, Thienpont LM, Siekmann L. *Creatinine measurement: state of the art in accuracy and interlaboratory harmonization. Arch Pathol Lab Med 2005; 129: 297-304.*
16. Stevens LA, Manzi J, Levey AS, Chen J, Deysher AE, Greene T, Poggio ED, Schmid CH, Steffes MW, Zhang YL, Vana Lente F, Coresh J. *Impact of creatinine calibration on performance of GFR estimating equations in a pooled individual patient database. Am J Kidney Dis 2007; 50: 21-35.*
17. Perrone RD, Steinman TI, Beck GJ, Skibinski CI, Royal HD, Lawlor M, Hunsicker LG. *Utility of radioisotopic filtration markers in chronic renal insufficiency: simultaneous comparison of ^{125}I-iothalamate, ^{169}Yb-DTPA, ^{99m}Tc-DTPA, and inulin. The Modification of Diet in Renal Disease Study. Am J Kidney Dis 1990; 16: 224-35.*
18. Agarwal R, Bills JE, Yigazu PM, Abraham T, Gizaw AB, Light RP, Bekele DM, Tegegne GG. *Assessment of iothalamate plasma clearance: Duration of study affects quality of GFR. Clin J Am Soc Nephrol 2009; 4: 77-85.*
19. Florijn KW, Barendregt JN, Lentjes EG, van Dam W, Prodjosudjadi W, van Saase JL, van Es LA, Chang PC. *Glomerular filtration rate measurement by "single-shot" injection of inulin. Kidney Int 1994; 46: 252-9.*
20. van Rossum LK, Mathot RA, Cransberg K, Vulto AG. *Optimal sampling strategies to assess inulin clearance in children by the inulin single-injection method. Clin Chem 2003; 49: 1170-9.*
21. van Rossum LK, Cransberg K, de Rijke YB, Zietse R, Lindemans J, Vulto AG. *Determination of inulin clearance by single injection or infusion in children. Pediatr Nephrol 2005; 20: 777-81.*
22. Orlando R, Floreani M, Padrini R, Palatini P. *Determination of inulin clearance by bolus intravenous injection in healthy subjects and ascitic patients: equivalence of systemic and renal clearances as glomerular filtration markers. Br J Clin Pharmacol 1998; 46: 605-9.*
23. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration. *Expressing the modification of diet in renal disease study equation for estimating glo-*

 DOI: 10.3346/jkms.2010.25.11.1616

merular filtration rate with standardized serum creatinine values. Clin Chem 2007; 53: 766-72.

24. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S. *Modification of the modification of diet in renal disease (MDRD) study equation for Japan. Am J Kidney Dis 2007; 50: 927-37.*
25. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. *Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009; 53: 982-92.*
26. Han KH, Han SY, Kang YS, Cha DR. *Serum cystatin C concentration compared with serum creatinine concentration as a marker of glomerular filtration rate. Korean J Nephrol 2006; 25: 737-44.*
27. Rule AD, Teo BW. *GFR estimation in Japan and China: what accounts for the difference? Am J Kidney Dis 2009; 53: 932-5.*