based on creatinine, age, sex, and a two-level variable for race, which is more accurate than the MDRD Study equation, particularly at higher levels of GFR and in populations without CKD,[5,10,11] and provides better risk prediction.[12,13] We hypothesized that the performance of the CKD-EPI equation could be further improved in Asians and in Native Americans and Hispanics by utilizing coefficients specific for these groups. In this study, we report on the development of an GFR-estimating equation that includes a four-level race variable in a diverse population from the United States and Europe, and its evaluation compared with the CKD-EPI (two-level race) equation in separate populations from the United States and Europe as well as in populations from other countries.

RESULTS

The clinical characteristics differed significantly among racial and ethnic groups. In the development data set (Table 1a), mean measured GFR ranged from 55 to 73 ml/min per 1.73 m^2 among racial/ethnic groups, and was lower in Blacks and Asians and higher in Native Americans and Hispanics compared with Whites and others. Blacks were older, more likely to be female, and had a larger body size compared with the other groups. In the CKD-EPI external validation data set, measured GFR ranged from 53 to 105 ml/min per 1.73 m^2 and was lower in Asians and higher in Native Americans and Hispanics compared with Whites and others (Table 1b). In the non-US and Europe validation data set, measured GFR ranged from 53 and 60 ml/min per 1.73 m^2, and body mass index (BMI) was lower than in the CKD-EPI development and validation data sets (Table 1b). Supplementary Appendix A and B describe the distribution of race and ethnic groups for each study.

Table 2 shows the coefficients for each race and ethnic groups refit in the CKD-EPI combined development and internal validation data set. The coefficients for Black and Asian are significantly larger than the reference group (White and other), resulting in higher eGFR for the same level of creatinine. The coefficient for Native American and Hispanic was smaller and not statistically significant, but was retained in the model. For both the two- and four-level race equations, eGFR is 15% higher for Blacks than for Whites or others. In the four-level race equation, eGFR is 5% higher in Asians but only 1% higher in Native Americans and Hispanics compared with Whites or others. Table 3 shows the two- and four-level race equations developed using the coefficients from the combined development and internal validation data sets, expressed for different combinations of race, sex, and serum creatinine.

Tables 4 and 5 show the performance of both models in the two external validation data sets. In the CKD-EPI

Table 1a | Clinical characteristics of the participants in development data sets

		Race/ethnicity				
Variable	Overall	White and other	Black	Asian	Native American and Hispanic	*P*-values
N	8254	5216	2585	100	353	
Age, mean (s.d.) in years	47 (15)	44 (15)	53 (12)	49 (15)	43 (12)	<0.001
Age categories, N *(%)*						<0.001
<40 years	3076 (37)	2464 (47)	422 (16)	36 (36)	154 (44)	
40–65 years	4154 (50)	2149 (41)	1766 (68)	50 (50)	189 (54)	
>65 years	1024 (12)	603 (11)	397 (16)	14 (11)	10 (3)	
Sex, N *(%)*						<0.001
Female	3606 (44)	2353 (45)	1019 (39)	41 (41)	193 (55)	
Male	4648 (56)	2863 (55)	1566 (61)	59 (59)	160 (45)	
Diabetes, N *(%)*						<0.001
Yes	2406 (29)	1885 (36)	280 (11)	33 (33)	208 (59)	
No	5848 (71)	3331 (64)	2305 (89)	67 (67)	145 (41)	
Transplant, N *(%)*						<0.001
Yes	360 (4)	330 (6)	24 (1)	5 (5)	1 (0.3)	
No	7894 (96)	4886 (94)	2561 (99)	95 (95)	352 (100)	
GFR mean (s.d.), ml/min per 1.73 m^2	68 (40)	73 (43)	55 (27)	57 (31)	90 (45)	<0.001
Serum creatinine, mean (s.d.), mg/dl	1.66 (1.16)	1.58 (1.19)	1.87 (1.09)	1.73 (0.91)	1.23 (1.02)	<0.001
Body surface area, mean (s.d.), m^2	1.91 (0.24)	1.90 (0.23)	2.00 (0.25)	1.77 (0.21)	1.91 (0.25)	<0.001
BMI, mean (s.d.), kg/m^2	28 (6)	27 (5)	31 (7)	26 (5)	31 (9)	<0.001
BMI categories, N *(%)*						<0.001
<20 kg/m^2	287 (3)	218 (4)	60 (2)	4 (4)	5 (1)	
20–25 kg/m^2	2447 (30)	1896 (36)	446 (17)	40 (40)	65 (18)	
26–30 kg/m^2	2922 (35)	1930 (37)	857 (33)	37 (37)	98 (28)	
>30 kg/m^2	2598 (31)	1172 (23)	1222 (47)	19 (19)	185 (52)	

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate.
To convert GFR from ml/min per 1.73 m^2 to ml/s per 1.73 m^2, multiply by 0.0167.

Table 1b | Clinical characteristics of the participants in validation data sets

	CKD-EPI (US and Europe)				Non-US and Europe			
Variable	White and other	Black	Asian	Native American and Hispanic	Asian	Asian	Black	*P*-values
N	3378	384	67	185	248	675	99	
Age, mean (s.d.) in years	49 (15)	50 (15)	51 (15)	45 (12)	50 (18)	50 (15)	47 (17)	0.001
Age categories, N *(%)*								<0.001
<40 years	978 (29)	112 (29)	19 (28)	68 (37)	95 (38)	207 (31)	42 (43)	
40–65 years	1898 (56)	224 (58)	35 (52)	107 (58)	92 (37)	333 (49)	42 (43)	
>65 years	502 (15)	48 (13)	13 (19)	10 (5)	61 (25)	135 (20)	15 (15)	
Sex, N *(%)*								0.001
Female	1513 (45)	184 (48)	32 (48)	130 (70)	112 (45)	328 (49)	49 (49)	
Male	1865 (55)	200 (52)	35 (52)	55 (30)	136 (55)	347 (51)	50 (50)	
Diabetes, N *(%)*								<0.001
Yes	975 (29)	95 (25)	14 (21)	119 (64)	35(14)	21(3)	6 (6)	
No	2403 (71)	289 (75)	53 (79)	66 (67)	213 (86)	654 (97)	93 (94)	
Transplant, N *(%)*								<0.001
Yes	1072 (32)	52 (14)	7 (10)	3 (2)	0	0	0	
No	2306 (68)	332 (86)	60 (90)	182 (98)	0	0	0	
GFR, mean (s.d.), ml/min per 1.73 m^2	69 (36)	62 (34)	53 (31)	105 (47)	53 (31)	55 (35)	61 (32)	<0.001
Serum creatinine, mean (s.d.), mg/dl	1.48 (0.94)	1.80 (0.29)	1.99 (1.41)	0.90 (0.73)	1.24 (0.56)	2.25 (2.18)	1.77 (1.71)	<0.001
Body surface area, mean (s.d.), m^2	1.90 (0.23)	1.95 (0.23)	1.70 (0.20)	1.98 (0.29)	1.62 (0.18)	1.71 (0.18)	1.77 (0.17)	<0.001
BMI, mean (s.d.), kg/m^2	27 (5)	30 (7)	24 (4)	34 (8)	23 (4)	24 (4)	26 (5)	<0.001
BMI categories, N *(%)*								<0.001
<20 kg/m^2	225 (7)	17 (4)	5 (7)	2 (1)	55 (22)	107 (16)	15 (15)	
20–25 kg/m^2	1223 (36)	84 (22)	34 (51)	22 (12)	137 (55)	354 (52)	44 (44)	
25–30 kg/m^2	1178 (35)	115 (30)	24 (36)	49 (26)	45(18)	181 (27)	20 (20)	
>30 kg/m^2	752 (22)	168 (44)	4 (6)	112 (61)	11 (4)	33 (5)	20 (20)	

Abbreviations: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate.
To convert GFR from ml/min per 1.73 m^2 to ml/s per m^2, multiply by 0.0167.

Table 2 | Race/ethnicity coefficients (95% confidence intervals)[a]

Equation	White and other	Black	Asian	Native American and Hispanic
Two-level race	1.0 (reference group)	1.157 (1.144, 1.170)	1.0	1.0
Four-level race	1.0 (reference group)	1.160 (1.146, 1.173)	1.052 (1.004, 1.102)	1.010 (0.984, 1.037)

Coefficients are adjusted for creatinine, sex, and age.
[a]Corresponds to percent increase in estimated glomerular filtration rate (eGFR) for the same level of serum creatinine.

validation data set, performance of the equation with the two- and four-level race terms was similar in both the Black and White and other groups (Table 4). In Asians, there was a significant improvement in bias and root mean square error with the four-level compared with the two-level equation (0.8 (−2.2, 2.6) ml/min per 1.73 m^2 vs 2.1 (0.3, 4.4) ml/min per 1.73 m^2 ($P<0.005$) and 0.293 (0.178, 0.424) vs 0.302 (0.188, 0.436), $P=0.003$)), but there was a small higher interquartile range with the four-level equations (12.3 (9.0, 16.1) vs 10.5 (8.0, 14.6) ml/min per 1.73 m^2 ($P=0.001$)) and no significant difference in percentage of estimates within 30% of the measured GFR (P_{30}). There were no significant differences in performance between the two equations for Native Americans and Hispanics. In the Chinese data set (Table 5, column 1), as in the Asians in the CKD-EPI validation data set, there was an improvement in performance with the four-level race equation compared with the two-level race equation in bias (1.3 (0.6, 2.2) vs 2.7 (1.9, 3.7) ml/min per 1.73 m^2 ($P<0.0001$)), interquartile range (15.5 (14.4, 17.4) vs 16.7 (15.0, 18.5) ml/min per 1.73 m^2, $P<0.0001$), root mean square error (0.318 (0.295, 0.343) vs 0.325 (0.302, 0.348) ml/min per 1.73 m^2, $P=0.002$)), as well as in P_{30} (72.1 (68.7, 75.7) vs 73.2 (69.9, 76.6), $P=0.01$). In the Japanese data set (Table 5, column 2), performance for the two-level race equation was substantially worse than for the Asians in the CKD-EPI validation data set and not improved with the use of the four-level race equation. In the South African data set (Table 5, column 3), performance of both the two- and four-level race equations was substantially worse than for the Blacks in the CKD-EPI validation data set. Performance was better for the South African data set when the Black coefficient was not used (bias of −12.4 (−18.3, −7.6) with the use of the Black term vs −4.9 (−7.0, −0.5) ml/min per 1.73 m^2 without the use of the Black term).

Figure 1 summarizes the comparison of bias between the two- and four-level race equation by level of eGFR within

Table 3 | CKD-EPI equation for estimating GFR on the natural scale expressed for race, sex, and range of serum creatinine

Race	Sex	Serum creatinine	eGFR (ml/min per 1.73 m^2)
Two-level race equation			
Black	Female	≤ 0.7 mg/dl	$166 \times (0.993)^{Age} \times (Scr/0.7)^{-0.329}$
Black	Female	>0.7 mg/dl	$166 \times (0.993)^{Age} \times (Scr/0.7)^{-1.209}$
Black	Male	≤ 0.9 mg/dl	$163 \times (0.993)^{Age} \times (Scr/0.9)^{-0.411}$
Black	Male	>0.9 mg/dl	$163 \times (0.993)^{Age} \times (Scr/0.9)^{-1.209}$
White and other	Female	≤ 0.7 mg/dl	$144 \times (0.993)^{Age} \times (Scr/0.7)^{-0.329}$
White and other	Female	>0.7 mg/dl	$144 \times (0.993)^{Age} \times (Scr/0.7)^{-1.209}$
White and other	Male	≤ 0.9 mg/dl	$141 \times (0.993)^{Age} \times (Scr/0.9)^{-0.411}$
White and other	Male	>0.9 mg/dl	$141 \times (0.993)^{Age} \times (Scr/0.9)^{-1.209}$
Four-level race equation			
Black	Female	≤ 0.7	$167 \times (0.993)^{Age} \times (Scr/0.7)^{-0.328}$
Black	Female	>0.7	$167 \times (0.993)^{Age} \times (Scr/0.7)^{-1.210}$
Black	Male	≤ 0.9	$164 \times (0.993)^{Age} \times (Scr/0.9)^{-0.412}$
Black	Male	>0.9	$164 \times (0.993)^{Age} \times (Scr/0.9)^{-1.210}$
Asian	Female	≤ 0.7	$151 \times (0.993)^{Age} \times (Scr/0.7)^{-0.328}$
Asian	Female	>0.7	$151 \times (0.993)^{Age} \times (Scr/0.7)^{-1.210}$
Asian	Male	≤ 0.9	$149 \times (0.993)^{Age} \times (Scr/0.9)^{-0.412}$
Asian	Male	>0.9	$149 \times (0.993)^{Age} \times (Scr/0.9)^{-1.210}$
Hispanic and Native American	Female	≤ 0.7	$145 \times (0.993)^{Age} \times (Scr/0.7)^{-0.328}$
Hispanic and Native American	Female	>0.7	$145 \times (0.993)^{Age} \times (Scr/0.7)^{-1.210}$
Hispanic and Native American	Male	≤ 0.9	$143 \times (0.993)^{Age} \times (Scr/0.9)^{-0.412}$
Hispanic and Native American	Male	>0.9	$143 \times (0.993)^{Age} \times (Scr/0.9)^{-1.210}$
White and other	Female	≤ 0.7	$144 \times (0.993)^{Age} \times (Scr/0.7)^{-0.328}$
White and other	Female	>0.7	$144 \times (0.993)^{Age} \times (Scr/0.7)^{-1.210}$
White and other	Male	≤ 0.9	$141 \times (0.993)^{Age} \times (Scr/0.9)^{-0.412}$
White and other	Male	>0.9	$141 \times (0.993)^{Age} \times (Scr/0.9)^{-1.210}$

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate.
To convert GFR from ml/min per 1.73 m^2 to ml/s per 1.73 m^2, multiply by 0.0167. To convert serum creatinine from mg/dl to μmol/l, multiply by 88.4. CKD-EPI equation coefficients derived from pooled development and internal validation data sets.
CKD-EPI two-level race equation expressed as a single equation: $GFR=141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black] where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.
The four-level equation expressed as a single equation: $GFR=141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.210} \times 0.993^{Age} \times 0.993$ [if female] $\times$ 1.16 [if Black] $\times$ 1.05 [if Asian] $\times$ 1.01 [if Hispanic and Native American] where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.328 for females and −0.412 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ.
In the table, the multiplication factors for race and sex are incorporated into the intercept, resulting in different intercepts for age and sex combinations.

Table 4 | Performance in CKD-EPI external validation data set (US and Europe) by race/ethnicity

Measures	Equation	Total	White and other	Black	Asian	Native American and Hispanic
N		4014	3378	384	67	185
Bias, ml/min per 1.73 m^2	Two-level	2.5 (2.1, 2.9)	2.8 (2.4, 3.2)	−0.8 (−2.0, 0.6)	2.1 (0.3, 4.4)	2.3 (−2.1, 5.1)
	Four-level	2.5 (2.1, 2.9)	2.9 (2.5, 3.4)	−0.9 (−2.0, 0.6)	0.8 (−2.2, 2.6)	1.6 (−3.0, 4.2)
IQR, ml/min per 1.73 m^2	Two-level	17.0 (16.1, 17.6)	16.8 (16.0, 17.6)	15.1 (12.6, 17.6)	10.5 (8.0, 14.6)	25.6 (20.8, 32.0)
	Four-level	17.0 (16.2, 17.6)	16.8 (16.0, 17.6)	15.1 (12.6, 17.6)	12.3 (9.0, 16.1)	26.1 (20.8, 32.2)
P_{30}, %	Two-level	84 (83, 85)	84 (83, 86)	82 (78, 85)	85 (76, 93)	80 (74, 85)
	Four-level	84 (83, 85)	84 (83, 85)	82 (80, 85)	85 (76, 93)	81 (76, 87)
RMSE	Two-level	0.250 (0.242, 0.259)	0.250 (0.240, 0.258)	0.242 (0.221, 0.265)	0.302 (0.188, 0.436)	0.265 (0.223, 0.310)
	Four-level	0.250 (0.242, 0.259)	0.250 (0.240, 0.259)	0.243 (0.221, 0.266)	0.293 (0.178, 0.424)	0.264 (0.222, 0.310)

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; IQR, interquartile range, 25–75th percentile; P_{30}, percentage of GFR estimates within 30% of measured GFR; RMSE, root mean square error.
Bias is calculated as measured GFR−estimated GFR.
Numbers in brackets are 95% confidence intervals.
To convert GFR from ml/min per 1.73 m^2 to ml/s per 1.73 m^2, multiply by 0.0167.

each racial/ethnic category. In the CKD-EPI validation data set, using either the two- and four-level race equation, bias was less than ~5 ml/min per 1.73 m^2 except for Blacks with eGFR >90 ml/min per 1.73 m^2, as we have previously reported. In the Asians in the CKD-EPI data set and in the Chinese data sets, the bias exceeded 5 ml/min per 1.73 m^2 for some eGFR groups, but improved with the use of the four-level race equation. For both equations, the bias varied substantially throughout the eGFR range in the Japanese and South African data sets.

DISCUSSION

Differences across race and ethnic groups in relationships between serum creatinine and measured GFR primarily

Table 5 | Performance in non-US and Europe external validation data set by country and race/ethnicity

Measures	Equation	China (Asian)	Japan (Asian)	South Africa (Black)
N		675	248	99
Bias, ml/min per 1.73 m^2	Two-level	2.7 (1.9, 3.7)	−17.8 (−20.1, −14.7)	−12.4 (−18.3, −7.6)
	Four-level	1.3 (0.6, 2.2)	−21.4 (−23.3, −18.2)	−12.5 (−18.3, −7.6)
IQR, ml/min per 1.73 m^2	Two-level	16.7 (15.0, 18.5)	21.0 (18.5, 23.9)	28.0 (20.8, 33.3)
	Four-level	15.5 (14.4, 17.4)	23.5 (20.4, 26.0)	28.0 (20.8, 33.4)
P_{30}, %	Two-level	73.2 (69.9, 76.6)	29.4 (23.8, 35.1)	55.6 (46.5, 64.6)
	Four-level	72.1 (68.7, 75.7)	36.3 (30.6, 42.3)	55.6 (46.5, 64.6)
RMSE	Two-level	0.325 (0.302, 0.348)	0.469 (0.424, 0.515)	0.326 (0.292, 0.361)
	Four-level	0.318 (0.295, 0.343)	0.507 (0.463, 0.553)	0.327 (0.292, 0.362)

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; IQR, interquartile range, 25–75th percentile; P_{30}, percentage of GFR estimates within 30% of measured GFR; RMSE, root mean square error.
Bias is calculated as measured GFR−estimated GFR.
Numbers in brackets are 95% confidence intervals.
To convert GFR from ml/min per 1.73 m^2 to ml/s per 1.73 m^2, multiply by 0.0167.

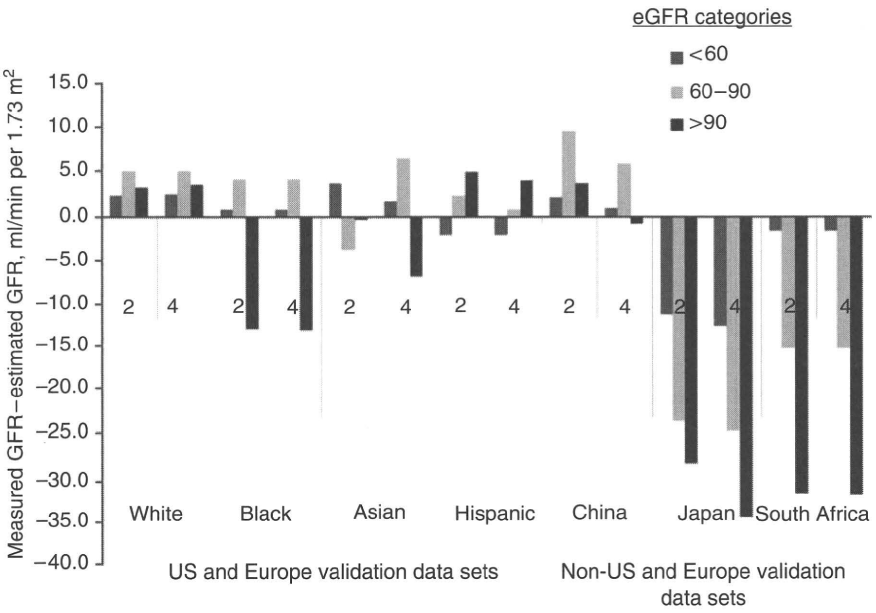

Figure 1 | Performance by level of estimated glomerular filtration rate (eGFR): Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) validation data set.

reflect variation in creatinine generation because of muscle mass or diet. The definition of the race coefficient as Black vs White and other in the MDRD Study does not account for differences in creatinine generation among other racial and ethnic groups. In the process of developing the CKD-EPI equation, we sought to develop an equation that better captures the variation in creatinine generation among racial and ethnic groups other than Blacks and Whites. The results of this process are described in this study. The four-level race equation that was developed is more accurate than the CKD-EPI (two-level race) equation in some, but not all, populations, and both equations demonstrated heterogeneous results within racial and ethnic groups across geographic regions. Given these results, we concluded that the four-level race equation was not sufficiently accurate to be implemented in clinical practice, and had selected the CKD-EPI equation with its two-level race variable.[10] Nevertheless, these results are informative for use of the two-level race CKD-EPI equation in these groups, and also suggest future research directions to derive generalizable racial and ethnic coefficients for GFR-estimating equations based on serum creatinine.

The coefficient for Blacks in the two- and four-level race term yielded a 15% higher eGFR for Blacks than for Whites at a given serum creatinine level, which is consistent with physiological data showing greater skeletal muscle mass in Blacks than otherwise equivalently matched White subjects.[14,15] Similarly, African Black athletes also have greater lean body mass compared with Whites.[16] Using either equation, the eGFR for Blacks in the CKD-EPI validation data set accurately estimated measured GFR. In contrast, these equations led to an overestimation of measured GFR by 12 ml/min per 1.73 m^2 in the South African data. This indicates a different relationship between serum creatinine and GFR for Black South Africans vs US and European Blacks, as shown previously for the MDRD Study equation

using these data[17] as well as in a separate population in Ghana.[18] This difference may be because of lower muscle mass in African Blacks compared with African Americans, potentially secondary to poorer diet or overall health, related to HIV infection or other chronic diseases. Indeed, the mean BMI in the Ghanaian and South African populations was lower than in the Blacks in the CKD-EPI validation data set. In a previous publication, we showed that the CKD-EPI equation overestimates measured GFR in people with low BMI.[5] Our data from South Africa, as well as the data from Ghana, demonstrated that GFR estimates are more accurate if the Black term is omitted. These data raise important questions about the appropriateness of use of the Black coefficient in the CKD-EPI and MDRD Study equations for GFR estimation in Blacks outside the United States and Europe.

The Asian coefficient in the four-level race equation translates into a 5% higher GFR at a given serum creatinine value compared with Whites and others. This is unexpected, given that some previous physiological and epidemiological data suggest that Asians have less muscle mass and lower dietary intake than Whites. For example, in an analysis of people in Pakistan, participants had lower mean creatinine excretion rates than those estimated for age- and gender-matched white individuals.[19] In other studies, Asians have been shown to have a higher percent body fat for the same level of BMI than Whites, suggesting lower levels of muscle mass.[20] The direction of the Asian coefficient is consistent with the modification of the MDRD Study equation for Chinese reported by Ma *et al.*,[8] whose data are included here as part of the non-US and Europe validation data set. Although the 5% higher eGFR was substantially lower than the 23% reported by Ma *et al.*,[8] they are both in contrast to the Japanese coefficient for the modification of the MDRD Study and CKD-EPI equations of 0.808 (ref. 9) and 0.8132 (ref. 21), respectively, which translate to a 19% lower GFR at a given serum creatinine.

The Asian coefficient in the four-level race equation led to more accurate GFR estimates in Asians in the CKD-EPI validation data set as well as in the Chinese data set, but neither the two-level or four-level equation resulted in accurate estimates in the Japanese. Both the Chinese and Japanese cohorts had a greater proportion of people with BMI $<20\,kg/m^2$ than the CKD-EPI development and validation data sets, but were similar to each other, suggesting that the overestimation of measured GFR in the Japanese cohort is not related solely to differences in levels of BMI. Factors other than muscle mass and diet may explain the difference between the Chinese and Japanese coefficients, such as differences in GFR measurement methods and the accuracy of creatinine calibration.[22] The countries of origin for the Asians in the CKD-EPI data sets are not known, and therefore we are not able to ascertain whether the Asian coefficient >1.0 in the four-level race CKD-EPI equation reflects Chinese origin. If future analyses establish that creatinine generation varies among Asian groups, then coefficients for subgroups of Asians in the CKD-EPI and other creatinine-based equations will need to reflect this variation.

The Native American and Hispanic coefficient resulted in a nonstatistically significant 1% higher eGFR for each serum creatinine value compared with Whites and others, and did not improve GFR estimation, suggesting that modification of the CKD-EPI equation may not be necessary for GFR estimation in Native Americans and Hispanics. To our knowledge, this is the only demonstration of the performance of the CKD-EPI equation in these groups. We are not aware of data on muscle mass in Native American and Hispanic populations. Data from NHANES (National Health and Nutrition Examination Survey) show a 5.3% lower mean level of serum creatinine for young healthy Mexican American men compared with Whites,[4] which has been interpreted as lower creatinine generation, but it may also reflect higher GFR. Furthermore, there is likely to be heterogeneity among Hispanic populations based on country of origin. There are only a small number of Native Americans and Hispanics in the CKD-EPI development data set and we do not have information on their country of origin.

The strengths of this study include the large diverse study population, with and without kidney diseases; calibration of the creatinine assays in each study to standardized values; rigorous and sophisticated statistical techniques for equation development; and evaluation of the equations in a separate data set of multiple studies that maximized external generalizability.

Our database had several limitations. First, it included only a small number of non-Blacks and non-Whites in both the CKD-EPI development and validation data sets. Nonetheless, the confidence intervals for the Asian and Native American and Hispanic coefficients were narrow, suggesting little variability among these groups in non-GFR determinants of serum creatinine. Second, the studies used a variety of methods to measure GFR that may have affected model evaluation. Finally, because we did not have information on country of origin for Asians and Hispanics in the CKD-EPI data sets, we grouped all Asians together and also grouped Hispanics and Native Americans, limiting a more nuanced analysis. Finally, the studies differed in their racial distributions, and hence the race effects cannot be entirely disentangled from study differences. Nevertheless, comparison of equations in a separate validation data set overcomes some of the limitations of differences among studies in patient characteristics and methods for measurement of GFR and serum creatinine, and provides support for the generalization of these results.

This study has several implications for clinical practice and research. First, the MDRD Study equation is currently widely used by clinicians, researchers, and public health officials, and is automatically reported by clinical laboratories whenever serum creatinine is ordered in the United States and Canada as well as in several countries in Europe.[23] In these countries, we suggest that the CKD-EPI (two-level race) equation could be used across a wide range of race and ethnicity, with the understanding that there is likely to be variation in accuracy of GFR estimates among and within

racial and ethnic groups based on factors associated with variation in creatinine generation, just as there is variation in accuracy within age and sex groups. Additional studies with a greater number and better characterization of participants from racial and ethnic minorities are necessary to develop more accurate estimates. Second, in geographic regions outside the United States and Europe, differences in creatinine generation within race and ethnic groups may limit the application of any creatinine-based estimating equation, unless the equation was specifically developed in that region. This limitation could possibly apply to immigrants of the same race and ethnicity from one region to another. Before recommending the CKD-EPI equation (or any creatinine-based estimating equation) in clinical practice, studies are required to determine whether modifications to the CKD-EPI (two-level race) equation are necessary.[8,21] Third, emphasis should be placed on investigation of filtration markers that may be less affected than creatinine by race and ethnicity, such as cystatin C and other novel markers.

In summary, racial differences in performance of creatinine-based estimating equation likely reflect geographic and ethnic differences rather than race *per se*. The four-level race equation was more accurate in some populations but not all. The CKD-EPI (two-level race) equation can be used in the United States and Europe across a wide range of race and ethnicity with appropriate attention to factors that affect creatinine generation.

MATERIALS AND METHODS

Sources of data and measurements

CKD-EPI is a research group funded by the NIDDK (National Institute of Diabetes, Digestive and Kidney Disease) to address challenges in the study and care of CKD, including development and validation of improved GFR-estimating equations by pooling data from research studies and clinical populations (hereafter referred to as 'studies').[10] The design and studies have been previously described and are briefly reviewed here.[10] We developed and internally validated the CKD-EPI equation in a database of 10 studies with a total of 8254 participants, divided randomly into separate data sets for development ($n=5504$) and internal validation ($n=2750$). The equations were then externally validated in a separate data set of 16 other studies with a total of 3896 participants. In the current report, we use the same data set as previously described for development and internal validation.[10] We also use the same external validation data set as previously described,[10] with the addition of data from Native Americans that were not available in the original report because of absence of creatinine calibration at the time of the original report, but now available to us (herein referred to as 'CKD-EPI validation data set') ($N=4014$). We also evaluated the equations in three separate studies from outside of United States and Europe; two are from Asia[8,21] (referred to as 'China' and 'Japan') and one is from South Africa[17] (referred to as 'South Africa'), each of which has been previously described (herein referred together as 'non-US and Europe validation data sets').

GFR was measured using urinary clearance of iothalamate in the development data set and iothalamate and other filtration markers in the external validation data sets (Supplementary Appendix A and Appendix B). Serum creatinine values were calibrated to standardized creatinine measurements using the Roche enzymatic method (Roche-Hitachi P-Module instrument with Roche Creatininase Plus assay; Hoffmann–La Roche, Basel, Switzerland) at the Cleveland Clinic Research Laboratory (Cleveland, OH).[24,25]

Development and validation

Methods for development and validation have been previously described in detail.[10] In brief, we used least squares linear regression to relate measured GFR to serum creatinine and clinical characteristics available in the development data set. Predictor variables included serum creatinine, age, sex, and race in all equations. GFR was adjusted for body surface area.[26] GFR and serum creatinine were transformed to natural logarithms to reflect their inverse relationship and satisfy the assumption of a normal error distribution to stabilize variance across the range of GFR. We tested multiple forms of creatinine and age, and the final model includes a piecewise linear spline of log serum creatinine with a knot at 0.7 mg/dl in men and 0.9 mg/dl in women, and linear age.

Information on race and ethnicity was provided in the original study data. Race was defined as a two-level variable (Black vs White and other) and as a four-level variable (Black, Asian, Native American and Hispanic vs White and other). The specific origin of Asians was not specified in the original studies. The rationale for grouping Native Americans and Hispanics together is that the majority of non-Black Hispanics in the United States are from Mexico, and they are considered to be of mixed European-Native American descent.[27,28] The rationale for grouping others with White is that many of the other groups are defined as of Caucasian descent (for example, Arabs, non-Black, and non-Native American Hispanics). In some studies, information on ethnicity is not available, and it is possible that some Blacks or Whites were also Hispanics. We developed models in parallel using two- and four-level variables for race. Race groups were defined using a categorical variable with all levels necessarily included in the models using indicator variables. We selected models to bring forth from development into internal and then external validation based on analyses of the two-level race variable, with models using the four-level race variable brought along in parallel. For clarity of presentation, we will refer to the two equations as two- and four-level race equations.

Models created in the development database were first validated in the internal validation database. The development and internal validation data sets were then combined and equations were refit to yield more precise final coefficients to be used in subsequent analyses. Models were then evaluated in the CKD-EPI validation data set and a final two-level race model was selected using a prespecified series of steps, as has been previously described.[10] The four-level race variable model presented here is the parallel model to the final two-level race model, which is known as the CKD-EPI equation.[10] Results are also presented in the non-US and Europe validation data set by study.

Model performance

Performance of the equations was evaluated using similar metrics in both the development and two validation databases. Bias was expressed as the difference (mGFR–eGFR) and percent difference ($100 * [\text{mGFR}-\text{eGFR}]/\text{mGFR}$) between measured GFR (mGFR) and eGFR, with positive values indicating lower eGFR than mGFR (underestimation). Precision was expressed as interquartile range for the differences. Accuracy was expressed as P_{30} that takes into

account higher errors at higher values. We defined the probability of a large error as $1-P_{30}$.

Performance was evaluated within subgroups defined by the following clinical characteristics: age (<40, 40–65, and >65 years), sex, race (Black, Asian, Native American and Hispanic, and White and other), diabetes (yes, no), previous organ transplant (yes, no), and BMI (<20, 20–25, 26–30, and $>30\,kg/m^2$). Level of eGFR was categorized as <60, 60–90, and >90 ml/min per $1.73\,m^2$.

Confidence intervals were calculated by bootstrap methods (2000 bootstraps) for difference, percent difference, and for P_{30}. Significance testing between metrics for each equation was computed using the Wilcoxon rank test on the bootstrapped estimates. Analyses were computed using R (Version 2, Free Software Foundation, Boston, MA) and SAS software (version, 9.1, Cary, NC). Smooth estimates of the mean in the figures were created using the lowess function in R.

The institutional review boards of all participating institutions approved the study.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This study was supported by grants UO1 DK 053869, UO1 DK 067651, and UO1 DK 35073.

SUPPLEMENTARY MATERIAL

Appendix A. Development and internal validation race/ethnic group, *N* (%).

Appendix B. External validation.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

REFERENCES

1. Levey AS, Atkins R, Coresh J *et al.* Chronic kidney disease as a global public health problem: approaches and initiatives — a position statement from Kidney Disease Improving Global Outcomes. *Kidney Int* 2007; **72**: 247–259.
2. U.S. Renal Data System. *USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2008.
3. U.S. Renal Data System. *USRDS 2007 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2007.
4. Jones CY, Jones CA, Wilson IB *et al.* Cystatin C and creatinine in an HIV cohort: the nutrition for healthy living study. *Am J Kidney Dis* 2008; **51**: 914–924.
5. Stevens LA, Schmid CH, Zhang YL *et al.* Development and validation of GFR-estimating equations using diabetes, transplant and weight. *Nephrol Dial Transplant* 2010; **25**: 449–457.
6. Baxmann AC, Ahmed MS, Marques NC *et al.* Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. *Clin J Am Soc Nephrol* 2008; **3**: 348–354.
7. Banfi G, Del Fabbro M, Lippi G. Relation between serum creatinine and body mass index in elite athletes of different sport disciplines. *Br J Sports Med* 2006; **40**: 675–678; discussion 678.
8. Ma YC, Zuo L, Chen JH *et al.* Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006; **17**: 2937–2944.
9. Matsuo S, Imai E, Horio M *et al.* Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**: 982–992.
10. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–612.
11. Stevens LA, Schmid CH, Greene T *et al.* Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 ml/min/1.73 m(2). *Am J Kidney Dis* 2010; **56**: 486–495.
12. White SL, Polkinghorne KR, Atkins RC *et al.* Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations: the AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. *Am J Kidney Dis* 2010; **55**: 660–670.
13. Matsushita K, Selvin E, Bash LD *et al.* Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD Study equation for estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis* 2010; **55**: 648–659.
14. Gallagher D, Visser M, De Meersman RE *et al.* Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. *J Appl Physiol* 1997; **83**: 229–239.
15. He Q, Heo M, Heshka S *et al.* Total body potassium differs by sex and race across the adult age span. *Am J Clin Nutr* 2003; **78**: 72–77.
16. Holden C. Peering under the hood of Africa's runners. *Science* 2004; **305**: 637–639.
17. van Deventer HE, George JA, Paiker JE *et al.* Estimating glomerular filtration rate in black South Africans by use of the modification of diet in renal disease and Cockcroft-Gault equations. *Clin Chem* 2008; **54**: 1197–1202.
18. Eastwood JB, Kerry SM, Plange-Rhule J *et al.* Assessment of GFR by four methods in adults in Ashanti, Ghana: the need for an eGFR equation for lean African populations. *Nephrol Dial Transplant* 2010; **25**: 2178–2187.
19. Jafar TH, Schmid CH, Levey AS. Serum creatinine as marker of kidney function in South Asians: a study of reduced GFR in adults in Pakistan. *J Am Soc Nephrol* 2005; **16**: 1413–1419.
20. Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obes Rev* 2002; **3**: 141–146.
21. Horio M, Imai E, Yasuda Y *et al.* Modification of the CKD Epidemiology Collaboration (CKD-EPI) Equation for Japanese: accuracy and use for population estimates. *Am J Kidney Dis* 2010; **56**: 32–38.
22. Rule AD, Teo BW. GFR estimation in Japan and China: what accounts for the difference? *Am J Kidney Dis* 2009; **53**: 932–935.
23. College of American Pathologists. Current Status of Reporting Estimated Glomerular Filtration Rate (eGFR). Accessed 10 August 2010. Available from http://www.cap.org/apps/docs/committees/chemistry/current_status_of_reporting_eGFR.pdf.
24. Levey AS, Coresh J, Greene T *et al.* Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007; **53**: 766–772.
25. Stevens LA, Manzi J, Levey AS *et al.* Impact of creatinine calibration on performance of GFR estimating equations in a pooled individual patient database. *Am J Kidney Dis* 2007; **50**: 21–35.
26. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987; **317**: 1098.
27. US Census Bureau. Hispanic Population of the United States. Accessed 11 April 2010. Available from http://www.census.gov/population/www/socdemo/hispanic/tables.html.
28. U.S. Census Bureau. The Hispanic Population. Census 2000 Brief. Accessed 23 April 2010. Available from http://www.census.gov/prod/2001pubs/c2kbr01-3.pdf.

Clin Exp Nephrol (2010) 14:427–430
DOI 10.1007/s10157-010-0325-9

ORIGINAL ARTICLE

Comparison of a simple and a standard method for inulin renal clearance

Masaru Horio · Yoshinari Yasuda · Shiro Takahara · Enyu Imai · Tsuyoshi Watanabe · Seiichi Matsuo

Received: 5 April 2010 / Accepted: 4 July 2010 / Published online: 28 July 2010

Abstract
Background The standard method of renal inulin clearance consists of three sets of 30-min clearances. We previously proposed a simple method with a single urine collection for 1 h and two blood samples. In this study, we compared the two methods.
Methods The study involved 112 individuals. Three sets of 30-min urine sample collections were started 45 min after inulin infusion , and serum concentrations were measured at the midpoint (60, 90, 120 min) of each clearance period. The mean of the three (Cin-ST) or average of the first two (Cin-ST2) clearances was used for the standard method. Clearance calculated by the simple method (Cin-S) combined the first two collections and the mean of serum concentrations at the beginning (45 min) and end (105 min) of the clearance period. Clearance was also calculated by estimated area under the plasma concentration curve from 45 to 105 min (Cin-A) as a more reliable value.
Results Cin-S correlated highly with Cin-ST ($r = 0.992$). Bland–Altman plot indicated that Cin-S was lower than Cin-ST at the same rate in all glomerular filtration rate (GFR) ranges. Total Cin-S of all patients was significantly lower (5.9%, 4.8%, and 3.6%) than Cin-ST, Cin-ST2, and Cin-A, respectively. Cin-ST2 was 1.3% higher than Cin-A. The change in serum inulin concentration by time from 45 to 105 min was not linear but concave. This led to the underestimation of clearance by the simple method.
Conclusion The simple method of renal inulin clearance gives slightly lower results than the standard method. The difference was small, indicating the simple method is accurate enough for use in clinical practice.

Keywords Inulin clearance · Simple method · Standard method

M. Horio (✉)
Department of Functional Diagnostic Science,
Osaka University Graduate School of Medicine,
Suita, Osaka 565-0871, Japan
e-mail: horio@sahs.med.osaka-u.ac.jp

Y. Yasuda · E. Imai · S. Matsuo
Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan

S. Takahara
Department of Advanced Technology of Transplantation, Osaka University Graduate School of Medicine, Osaka, Japan

T. Watanabe
Third Department of Medicine,
Fukushima Medical University, Fukushima, Japan

Introduction

Renal inulin clearance with continuous venous injection is the gold standard for measuring glomerular filtration rate (GFR) [1]. The standard method of inulin clearance consists of three sets of 30-min clearance periods [2]. Successive samplings of urine and blood alternately every 15 min are cumbersome for patients and clinical staff. We previously reported that a single urine collection for 60 min could be used with sufficient accuracy [3]. For a practical application of the inulin clearance method, we proposed a simple method with a prolonged single urine collection with two blood samples taken at the beginning and the end of the clearance period instead of a single sample at midpoint during the clearance period [3]. In the study reported here, we compared the two methods and show that the value by the simple method was slightly

lower than the value by the standard method. However, the difference was small, indicating the acceptability of the simple method in the clinical situation.

Methods

Patients

A total of 112 patients from two hospitals (Nagoya University Hospital $N = 12$, Inoue Hospital $N = 100$) were enrolled for the study. They were mainly patients with chronic kidney disease and kidney donors. Patient characteristics are shown in Table 1. Ethical approval for the study was obtained from the ethical committee of each hospital. All patients provided written informed consent.

Inulin renal clearance

Inulin was from Fujiyakuhin Co. Ltd (http://www.fujiyakuhin.co.jp). Inulin concentration was measured by the enzymatic method using an autoanalyzer. The reagents for inulin measurement were from Toyobo Co. Ltd (http://www.Toyobo.co.jp). Both diagnostic reagents were approved by the Ministry of Health, Labor and Welfare of the Japanese government and have been clinically used to measure GFR in Japan. Details of the reagents are shown in the company home page. Three sets of 30-min urine collections were started 45 min after the continuous intravenous infusion of 1% inulin given under fasting and hydrated conditions (Fig. 1). Patients received 500 ml of water orally 30 min before the infusion. To maintain hydration, 60 ml of water was given at 45, 75, and 105 min after the start of inulin infusion. Infusion rate was 300 ml/h for the first 30 min and 100 ml/min for the following 105 min. Blood samples for serum inulin concentration were collected at 45, 60, 90, 105, and 120 min after the start of inulin infusion. Urine samples for inulin concentration were collected between 45 and 75 min, between 75 and 105 min, and between 105 and 135 min after the patient completely emptied the bladder at 45 min. Inulin concentration was assayed by the enzymatic method.

According to the standard method, clearance was calculated by 30-min urine collection and serum concentration at the midpoint (60, 90, 120 min) of each clearance period. Average of the three clearances (Cin-ST) or average of first two clearances (Cin-ST2) was used as the clearance by the standard method. Clearance by the simple method (Cin-S) was calculated by combining the first two urine collections and averaging the serum concentrations at the beginning (45 min) and end (105 min) of the clearance period. We also calculated inulin clearance by combining the first two urine collections and estimating the area under the plasma concentration curve (AUC) from 45 to 105 min (Cin-A). True renal clearance can be calculated by urine excretion/AUC. Because AUC cannot be obtained exactly, a concentration at midpoint or an average of the concentrations at the beginning and end of the clearance period has been used as the mean plasma concentration. Cin-A was derived from four serum concentrations and had higher reliability during the clearance period from 45 to 105 min in this study. Estimated AUC was calculated by the following equation.

$$\mathrm{AUC} = 15(S1 + S2)/2 + 30(S2 + S3)/2 + 15(S3 + S4)/2$$

$S1$, $S2$, $S3$ and $S4$ are serum concentration of inulin at 45, 60, 90, and 105 min.

Statistics

The differences in total Cin-ST, Cin-ST2, Cin-S, and Cin-A from all patients were evaluated by paired t test and regression analysis. We used Bland and Altman recommendation to compare the inulin clearance methods [4]. A value of $p < 0.05$ was considered statistically significant. Statview, version 4.02 (SAS Institute Cary, NC, USA) was used for statistical analysis.

Table 1 Patient characteristics

Characteristic	
Total number of patients	112
Male, n (%)	40 (36%)
Age (year)	56.0 ± 13.4
Height (cm)	161.4 ± 8.7
Weight (kg)	60.6 ± 12.8
Body surface area (m^2)	1.63 ± 0.19
Body mass index	23.1 ± 3.8

Data are expressed as mean ± standard deviation or number (%)

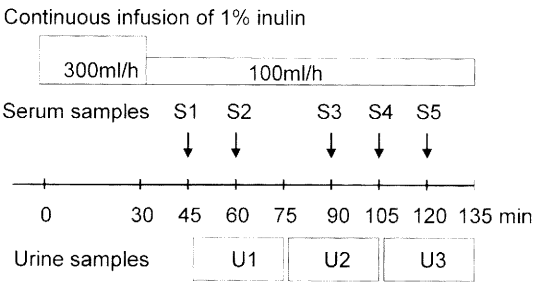

Fig. 1 Procedure of inulin clearance. Three sets of urine samples ($U1$, $U2$ and $U3$) and five blood samples ($S1$–$S5$) were collected

Results

Inulin clearance

Values of renal inulin clearance by the simple method (Cin-S) were highly correlated with values by the standard method (Cin-ST) ($r = 0.992$) (Fig. 2). Linear regression line in the Bland–Altman plot showed the slope was 0.059 [95% confidence interval (CI) 0.034–0.084, $p < 0.0001$] and the intercept was 0.134 (95% CI −1.573 to 1.840, $p = 0.9$), close to zero, indicating that Cin-S was lower than Cin-ST at the same rate in all GFR ranges. Total Cin-ST and Cin-S of all patients were 66.8 ± 25.7 ml/min/1.73 m^2 and 62.8 ± 24.3 ml/min/1.73 m^2, respectively. Cin-S was significantly (5.9%) lower than Cin-ST ($p < 0.0001$). Then, we compared the differences among Cin-S, Cin-ST2, and Cin-A with clearances during a same period from 45 to 105 min. Bland–Altman plot between Cin-S and Cin-A showed the slope was 0.041 (95% CI 0.029–0.053, $p < 0.0001$) and the intercept was −0.304 (95% CI −1.123 to 0.513, $p = 0.5$), indicating that Cin-S was lower than Cin-A (Fig. 3). Bland–Altman plot between Cin-ST2 and Cin-A showed the slope was −0.016 (95% CI −0.020 to −0.011, $p < 0.0001$) and the intercept was 0.171 (95% CI −0.130 to 0.473, $p = 0.3$), indicating that Cin-ST2 was significantly higher than Cin-A. Total Cin-ST2 and Cin-A of all patients were 66.0 ± 25.7 ml/min/1.73 m^2 and 65.2 ± 25.3 ml/min/1.73 m^2, respectively. Cin-ST2 was significantly (1.3%) higher, and Cin-S was significantly (3.6%) lower than Cin-A.

Serum inulin concentration

Serum inulin concentrations at 45, 60, 90, 105, and 120 min are shown in Fig. 4. Generally, serum inulin concentration increased over time in patients with low GFR (<60 ml/min/1.73 m^2) and decreased in patients with normal GFR (≥90 ml/min/1.73 m^2). Serum inulin concentration by time from 45 to 105 min was not linear but slightly concave.

Discussion

We previously reported that single urine collection for 60 min could be used with sufficient accuracy [3]. In the study, we used two blood samples at midpoints of the first 30 min and the second 30 min to obtain the average of serum inulin concentration for the simple method. Clearance was almost identical to that by the standard method [3]. In the study reported here, we used two blood samples at the beginning and end of the 60-min period to obtain the average serum inulin concentration. Differently from the previous report, clearance by Cin-S was slightly lower than clearance by Cin-ST. Serum inulin concentration was not linear during the 60 min but was slightly concave. Schedule of blood sampling leads to the difference of the average values of serum concentrations and the final clearance values calculated from them. Accordingly, Cin-S in this study was slightly lower than Cin-ST.

Although renal inulin clearance was performed by constant infusion, serum inulin concentration did not reach equilibrium during the measurement period. Generally, serum inulin concentration is increased in patients with low GFR and decreased in patients with normal GFR (Fig. 4). These results were consistent with our previous report [3]. Serum inulin concentration was not linear from 45 to 105 min but was slightly concave. The rate of infusion was 300 ml/h for the first 30 min and 100 ml/min for the following 105 min. The change of infusion rate at 30 min may generate the concave shape of serum concentration of inulin during the period. True renal inulin clearance can be calculated by the amount of urinary excretion divided by AUC. If the change of plasma concentration by time is linear during measurement, clearances calculated by serum

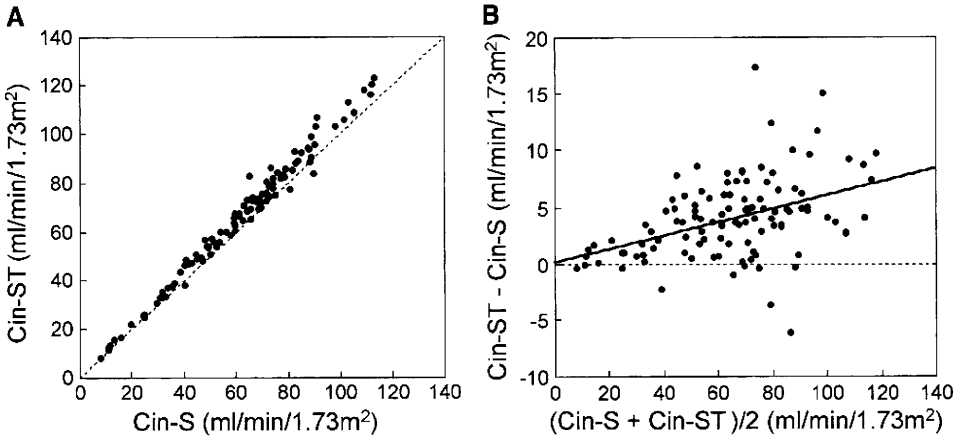

Fig. 2 Relationship between inulin clearance by the simple method (Cin-S) and by the standard method (Cin-ST). **a** Correlation between Cin-S and Cin-ST. Correlation coefficient is 0.992. *Dotted line* indicates a line of identity. **b** Bland–Altman plot of Cin-S and Cin-ST. *Solid line* indicates a regression line

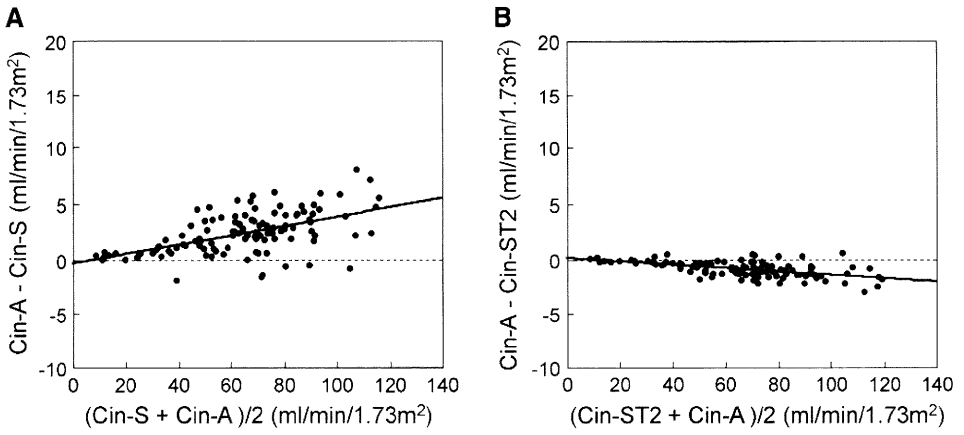

Fig. 3 Relationship among inulin clearance by the simple method (Cin-S), the standard method (Cin-ST2), and by estimated area under the plasma concentration time curve (AUC) (Cin-A). **a** Bland–Altman plot of Cin-S and Cin-A. *Solid line* indicates a regression line. **b** Bland–Altman plot of Cin-ST2 and Cin-A. *Solid line* indicates a regression line

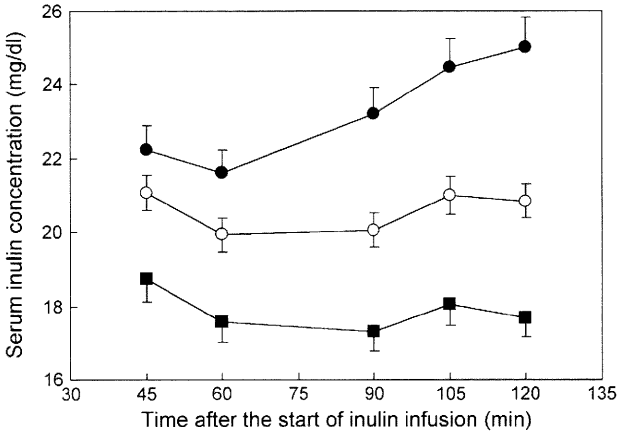

Fig. 4 Serum inulin concentrations of patients with normal glomerular filtration rate (GFR) [average of the three clearances (Cin-ST) $\geq$ 90 ml/min/1.73 m^2, *closed square*), moderate GFR (60 $\leq$ Cin-ST < 90 ml/min/1.73 m^2, *open circle*) and low GFR (Cin-ST < 60 ml/min/1.73 m^2, *closed circle*) were plotted by time

concentration at midpoint or average of the concentrations between the beginning and end of the measurement must be the same as the true clearance calculated by AUC. However, when the change of plasma concentration by time has a concave shape, there should be some differences among them. Clearances calculated by serum concentration at midpoint should be higher than the true clearance calculated by AUC. Clearances calculated by average of the concentrations at the beginning and end of the clearance period should be lower than the true clearance calculated by AUC.

In this study, Cin-S was significantly lower than Cin-ST and Cin-A. Cin-ST2 was significantly higher than Cin-A. We showed that serum inulin concentration by time from 45 to 105 min was slightly concave. This could account for the differences between clearances. The amount of variance by underestimation and overestimation were small. The simple method for renal inulin clearance is sufficiently accurate to use as the standard method in the clinical setting.

Conclusion

We conclude that inulin clearance by the simple method was slightly lower than the value by the standard method. The amount of the underestimation was small, indicating the simple method is sufficiently accurate for measuring GFR in the clinical situation.

Acknowledgments This study was supported by the grant from the Japanese Society of Nephrology. We thank Yuji Yamauchi for data collection.

References

1. Shannon JA, Smith HW. The excretion of inulin, xylose, and urea by normal and phlorizinized man. J Clin Invest. 1935;14:393–401.
2. Orita Y, Gejyo F, Sakatsume M, Shiigai T, Maeda Y, Imai E, Fujii T, Endoh M, Jinde K, Haneda M, Sugimoto T, Hishida A, Takahashi S, Hosoya T, Yamamoto H, Hora K, Okada Y, Hosaka N, Oguchi T, Kanno Y, Nishio Y, Yano S, Aikawa K, Yasui K. Estimation of glomerular filtration rate by inulin clearance: comparison with creatinine clearance. Jpn J Nephrol. 2005; 47:804–12.
3. Horio M, Imai E, Yasuda Y, Hishida A, Matsuo S, on behalf of the collaborators for developing the Japanese equation for estimating GFR. Simple sampling strategy for measuring inulin renal clearance. Clin Exp Nephrol. 2009;13:50–4.
4. Bland JM, Altman DG. Statistical method for assessing agreement between two methods of clinical measurement. Lancet. 1986;1:307–10.

Clin Exp Nephrol (2010) 14:144–151
DOI 10.1007/s10157-009-0249-4

ORIGINAL ARTICLE

Design and methods of a strategic outcome study for chronic kidney disease: Frontier of Renal Outcome Modifications in Japan

Kunihiro Yamagata · Hirofumi Makino · Tadao Akizawa · Kunitoshi Iseki · Sadayoshi Itoh · Kenjiro Kimura · Daisuke Koya · Ichiei Narita · Tetsuya Mitarai · Masanobu Miyazaki · Yoshiharu Tsubakihara · Tsuyoshi Watanabe · Takashi Wada · Osamu Sakai · Advisory Committee for FROM-J

Received: 11 June 2009 / Accepted: 10 November 2009 / Published online: 18 December 2009

Abstract

Background The continuous increase in the number of people requiring dialysis is a major clinical and socioeconomical issue in Japan and other countries. This study was designed to encourage chronic kidney disease (CKD) patients to consult a physician, enhance cooperation between nephrologists and general practices, and prevent the progression of kidney disease.

Methods Subjects comprise CKD patients aged between 40 and 74 years consulting a general physician, and patients in CKD stage 3 with proteinuria and diabetes or hypertension. This trial is a stratified open cluster-randomized study with two intervention groups: group A (weak intervention) and group B (strong intervention). We have recruited 49 local medical associations (clusters) in 15 different prefectures, which were classified into four

K. Yamagata (✉)
Department of Nephrology, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1, Ten-oudai, Tsukuba, Ibaraki 305-8575, Japan
e-mail: k-yamaga@md.tsukuba.ac.jp

H. Makino
Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

T. Akizawa
Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

K. Iseki
Dialysis Unit, University Hospital of The Ryukyus, Okinawa, Japan

S. Itoh
Division of Nephrology, Endocrinology and Vascular Medicine, Tohoku University Graduate School of Medicine, Miyagi, Japan

K. Kimura
Department of Nephrology and Hypertension, St. Marianna University School of Medicine, Kanagawa, Japan

D. Koya
Division of Endocrinology and Metabolism, Kanazawa Medical University, Ishikawa, Japan

I. Narita
Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Science, Niigata, Japan

T. Mitarai
Division of Nephrology and Hypertension, Saitama Medical Center, Saitama Medical School, Saitama, Japan

M. Miyazaki
Department of Internal Medicine, Miyazaki Clinic, Miyazaki, Japan

Y. Tsubakihara
Department of Nephrology, Osaka General Medical Center, Osaka, Japan

T. Watanabe
Department of Internal Medicine III, Fukushima Medical University School of Medicine, Fukushima, Japan

T. Wada
Department of Laboratory Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Faculty of Medicine, Kanazawa University, Ishikawa, Japan

O. Sakai
Japan Kidney Foundation, Tokyo, Japan

regions (strata) based on the level of increase rate of dialysis patients. The patients in group A clusters were instructed initially to undergo treatment in accordance with the current CKD treatment guide, whereas patients in group B clusters were not only instructed in the same fashion but also received support from an information technology (IT)-based system designed to help achieve the goals of CKD treatment, consultation support centers, and consultations by dietitians visiting the local general practice offices. We assessed the rates of continued consultation, collaboration between general practitioners and nephrologists, and progression of CKD (as expressed by CKD stage).

Conclusion Through this study, filling the evidence-practice gap by facilitating effective communication and supporting general physicians and nephrologists, we will establish a CKD care system and decrease the number of advanced-stage CKD patients.

Keywords Chronic kidney disease · Evidence-practice gap · Cluster-randomized study · Educational intervention · Cooperation between nephrologists and general physicians

Introduction

The number of dialysis patients is continually increasing, with consequent rises in medical costs for the treatment of end-stage kidney disease (ESKD) patients becoming a socioeconomical concern worldwide. In fact, there are 2,153.2 dialysis patients per million of population in Japan [1]. Chronic dialysis treatment not only reduces the quality of life (QOL) of patients [2, 3] but also places considerable financial strain on society, with annual medical costs of five to six million yen per dialysis patient, or total expenses of one trillion yen. Moreover, it is estimated that there are more than ten million chronic kidney disease (CKD) patients in Japan [4]. Previous studies suggested that CKD is one of the most important risk factors for cardiovascular disease, among known risk factors of diabetes, hypertension, hyperlipidemia, obesity, smoking, and lifestyle-related disease [5–8]. Therefore, early detection and control of CKD are also important in terms of preventing cardiovascular complications and deaths.

The definition of CKD first appeared in the Kidney Disease Outcome Quality Initiative (KDOQI) Guidelines issued by the National Kidney Foundation (NKF) in 2002 [9], and was revised by Kidney Disease: Improving Global Outcomes (KDIGO) in 2005 [10]. Since then, the definition of CKD and renal function assessment methods are being accepted worldwide. CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for 3 months or more, irrespective of cause. The concept of CKD comprehensively addresses a wide range of kidney patients, including ESKD and transplant patients. It is important to establish appropriate, consistent, and specific treatment and prevention-based care systems according to the progression of kidney disease. The Ministry of Health, Labor, and Welfare organized a study group to design strategic outcome studies and discuss the following research subjects: prevention of diabetes, prevention of suicide and depression (2005), cancer prevention, and AIDS/HIV prevention (2006), which have been started. Following these studies, a strategic study to improve the progression of CKD was planned based on these social and scientific demands to reduce new patients with initiation of renal replacement therapy due to ESKD, termed the Frontier of Renal Outcome Modifications in Japan (FROM-J).

Diabetic nephropathy, nephrosclerosis due to hypertension, and chronic glomerulonephritis are three major primary renal diseases in ESKD, not only in Japan but also in Western countries [1]. In Japan, the proportion of new ESKD patients due to chronic glomerulonephritis has recently been decreasing, while that of diabetic nephropathy is rapidly increasing. If this trend continues, in 5 years, patients undergoing dialysis due to diabetic nephropathy will account for 50.82% of the total whereas those with chronic glomerulonephritis will account for 19.54%. In other words, the primary renal disease in half of dialysis patients will be diabetic nephropathy, and the number of dialysis patients with chronic glomerulonephritis will decrease by 17%. The decreasing trend in chronic glomerulonephritis is due to annual urinalysis screening programs established by the Japanese government [11]. Also, more attention should be paid to preventing deterioration of renal function in patients with diabetic nephropathy and nephrosclerosis.

Although diabetic nephropathy is the primary underlying disease in dialysis patients in many developed countries, it has been showing a decreasing trend in some regions and countries, including Denmark. In Denmark, after a steady increase from 52 in 1990 to 183 in 2002, the number of dialysis patients with diabetic nephropathy decreased by 15%, to 155–156 patients per million people [12]. This indicates that aggressive management of both blood pressure and glucose, administration of renin angiotensin system (RAS) inhibitors, and advice on lifestyle can reduce ESKD with diabetic nephropathy by more than 15%. According to the 2002 diabetes survey conducted by the Ministry of Health, Labor, and Welfare of Japan, only 33.3% of patients in Japan had controlled their HbA1c to less than 6.5%, and these interventions are expected to achieve marked effects. Furthermore, although 50.2% of males and 38.3% of females aged 40 years or

older in Ibaraki Prefecture showed hypertension, only 41.9% and 49.2% of them, respectively, were receiving antihypertensive treatment [13], and blood pressure was not adequately controlled in about 50% of those who were receiving treatment [14]. Appropriate interventions are assumed to bring about noticeable effects in Japan, in which RAS inhibitors have not been used effectively as antihypertensive therapy, although a slight increase has occurred in recent years [15].

Recently, the CKD Clinical Practice Guide for future treatment methods was developed by the Japanese Society of Nephrology [16], describing the treatment target for every CKD stage. Although all items of the treatment method were supported by clinical evidence, there were no prospective studies showing the effect of practices such as the CKD Clinical Practice Guide targets on renal and cardiovascular outcomes in sufficient number of CKD patients.

In this strategic CKD study, a prospective stratified cluster-randomized trial to examine the effectiveness of a care system designed to prevent progression of CKD through collaboration between nephrologists and general physicians was selected. One of the goals of the study is a 15% reduction in the estimated number of new dialysis patients in 5 years by increasing the rates of compliance with the CKD Clinical Practice Guide. The study also aims to encourage CKD patients to see their family physician, consult a nephrologist, and receive nutritional and lifestyle advice, while discussing health care measures to reduce the number of new dialysis patients.

Hypotheses of study

The study hypothesis encompasses the following four core issues:

1. Clinical practice in accordance with the Japanese CKD Clinical Practice Guide will improve the prognosis of CKD patients and reduce the speed of renal function deterioration.
2. Education-based interventions for CKD patients by registered dietitians and other co-medicals will help achieve strict CKD treatment goals in accordance with the Japanese CKD Clinical Practice Guide.
3. Collaboration concerning clinical practices among general physicians, nephrologists, and co-medicals will reduce the gap between clinical practice and evidence-based care measures, and improve the rate of continued consultation and prognosis in CKD patients.
4. These active interventions to improve CKD treatment will achieve the desired effects in terms of medico-economics.

Subjects and methods

Study organization and duration

Since the increase in the rate of dialysis patients varies from region to region in Japan [17], we divided the country into four regions (Fig. 1) as strata, so that they would

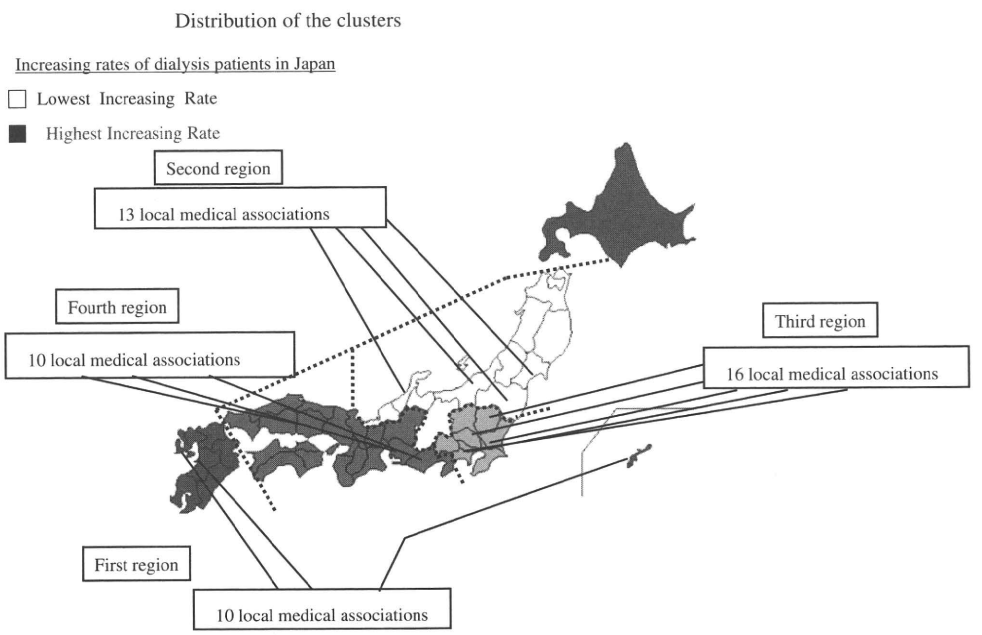

Fig. 1 Distribution of the clusters. We have recruited 49 local medical associations (clusters) in 15 different prefectures, which were classified into four regions (strata) based on the level of increase in the rate of dialysis patients [17]

include at least one managing facility and two or more clusters. The primary intervention study duration is from October 2008 to March 2012.

Rationale for setting the number of patients

This project aims to examine whether or not intervention can reduce the incidence of dialysis patients by 15% over the next 5 years. Regarding the calculation, we estimated the annual decrease in GFR as 0.59 ml/min/year (standard deviation (SD) 0.04 ml/min/year), based on changes in renal function among healthy Japanese people who underwent health checkups [17, 18] and the rate of renal deterioration in patients in CKD stage 3 with diabetes or hypertension [mean serum creatinine = 1.69 mg/dl (SD = 0.57 mg/dl), annual decrease rate = 5.93 ml/min/year (SD 4.321 ml/min/year), $n = 569$] [18, 19]. The required study size was calculated as 2,038 when the unknown intracluster correlation coefficient was assumed to be 0.5. We determined the required number as 2,264 for groups A and B, assuming that 10% would withdraw. We applied the simple number of 2,500 (1,250 for each group) as the target number of patients to perform this study.

Eligible patients

Each registered general physician obtained written informed consent for the study from eligible patients. They were formerly registered after the data center verified their eligibility. Inclusion criterion were: (1) age between 40 and 74 years; (2) in CKD stage 1, 2, 4, or 5; (3) in CKD stage 3 with proteinuria (ratio of urinary protein/urinary creatinine ≥ 0.3, or proteinuria $\geq 1+$) and diabetes or hypertension.

Dialysis patients and those who did not consent were excluded from this study.

Assignment and randomization

This trial is a stratified open cluster-randomized study with two intervention groups: group A (weak intervention) and group B (strong intervention). We have recruited 49 local medical associations (clusters) in 15 different prefectures, which were classified into four regions (strata) based on the level of increase in the rate of dialysis patients (Fig. 1). Each local medical association recruited 10–58 general physicians by whom patients in this study has been treated. Local medical associations are randomized when the enrolment period is completed.

Intervention methods

Patients in group A clusters are instructed initially to undergo treatment in accordance with the current CKD treatment guide only, whereas patients in group B clusters are not only instructed in the same fashion but also receive consultations by dietitians visiting the local general practice offices. In addition, the data center closely monitors the treatment status and provides the group B general practice office with comments on the data.

Goals for the treatment of chronic kidney disease (groups A and B)

Participants in the study, or patients, will receive treatment according to the CKD Clinical Practice Guide [16]. Table 1 shows a summary of targets for CKD treatment applied to all patients. In patients with CKD, lifestyle modifications to avoid obesity and stop smoking are necessary. Strict blood pressure control (less than 130/80 mmHg), strict blood sugar control (HbA1c <6.5%), and low-density lipoprotein (LDL)-cholesterol control (LDL-C <120 mg/dl) are shown as targets for CKD treatment. The standards for referral from general physicians to nephrologists are as follows: (1) ratio of urinary protein/urinary creatinine ≥ 0.5, or proteinuria $\geq 1+$; (2) estimated GFR (eGFR) <50 ml/min/1.73 m^2; (3) both proteinuria and hematuria positive ($\geq 1+$); and (4) when family physicians judge that patients should consult a nephrologist. Estimated GFRs in this study are calculated using the following formula:

$$\mathrm{eGFR(ml/min/1.73\ m^2)} = 194 \times \mathrm{Age}^{-0.287} \times \mathrm{Cre}^{-1.094} (\times 0.739 \text{ in the case of women}).$$

Monitoring of treatment status by the data center (only group B)

The data center closely monitors the treatment status and provides the group B general practice office with comments on the data. In addition, the data center will provide information on the patients scheduled to visit the office, examinations, and treatment that patients should undergo on their next visit, patients who did not visit hospitals as scheduled, those who are going to receive lifestyle/dietary advice, and those who meet the conditions for referral to nephrologists. The center also monitors patients and their schedules: the next consultation date, required examinations, details of treatment and care provided, and advice on lifestyle and nutrition. The centers will contact patients by mail, telephone, or email a week before the consultation day and encourage those who have not consulted a physician for over 2 months to receive care, trying to prevent their withdrawal from treatment. To facilitate referrals to nephrologists, the centers send a list of patients who meet the criteria for referral to the physicians and clinical research coordinators (CRCs).

Table 1 CKD practice guide target in this study

CKD stages	Lifestyle	Diet	Blood pressure	Blood sugar	Lipid metabolism	Hemoglobin
Stage 1	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	
Stage 2	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	
Stage 3	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives DPI: 0.6-0.8 g/kg/day	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	Hb 10–12 g/dl
Stage 4	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives DPI: 0.6–0.8 g/kg/day Potassium restriction	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	Hb 10–12 g/dl
Stage 5	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives DPI: 0.6–0.8 g/kg/day Potassium restriction	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	Hb 10–12 g/dl
Others			<125/75 mmHg If proteinuria >1 g/day			

BMI body mass index, *DPI* dietary protein intake

Nutrition and lifestyle improvement (only group B)

Registered dietitians provide support according to the instructions and advice from family physicians. They help patients achieve their CKD treatment goals, explaining to patients about examination results, achievements in CKD care, and their implications. Registered dietitians receive training so that they will be able to provide integrated and consistent advice.

Data collection

At each consultation, physicians will measure patients' blood pressure, and check their blood pressure conditions at home. Examinations or surveys will be performed every 6 months regarding body weight, abdominal circumference, smoking status, fasting serum creatinine, blood urea nitrogen (BUN), potassium, hemoglobin (Hb), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG), uric acid, total protein, albumin, fasting blood glucose, HbA1c (only in the case of diabetes), urinary creatinine levels, amount of urinary proteins, eGFR, number of patients referred by nephrologists, number of new dialysis patients, and incidence of cardiovascular events.

Parameters for assessment

Primary parameters for assessment are: (1) the rate of continuous clinic visits of CKD patients, (2) the proportion of patients under cotreatment between general physicians and nephrologists, and (3) annual changes in CKD stage.

Secondary parameters are: (1) the proportion of adherence to the complete CKD treatment guide, (2) the rate of achievement of blood pressure goals, (3) the number of subjects with 50% reduction in urinary protein, (4) the number of subjects with a doubling of serum creatinine or 50% reduction in eGFR, (5) yearly changes in the number of patients starting renal replacement therapy, and (6) the incidence of cardiovascular events.

Statistical analysis

Statistical analyses will be performed using an intent-to-treat approach. Differences in primary endpoints between intervention groups are described by their 95% confidence intervals. The declining velocity of eGFR is tested by analysis of variance, using the efficacy of interventions as fixed effects and cluster effects as random effects. We employ a generalized linear model with age, gender, complications, and previous GFR as covariates where appropriate. The significance level on both sides in hypothesis testing is set at 0.05.

For secondary endpoints, we will use analysis of variance with a generalized linear model.

Ethical considerations

This study is being conducted in accordance with the Ethical Guidelines for Clinical Studies (revised on December 28, 2004, of the Ministry of Health, Labor, and Welfare) and the Ethical Guidelines for Epidemiological Studies (revised on August 16, 2007, of the Ministries of Education, Culture, Sports, Science, and Technology/Health, Labor, and Welfare). All medical professionals involved in this study must comply with these ethical standards. This study is a Central Institutional Review Board (Central IRB) program, and the Committee on Ethics in Strategic Research of the Kidney Foundation, Japan, will examine and approve implementation plans and their revision.

Discussion

The purpose of this study is to enhance cooperation between nephrologists and general physicians, improve lifestyle and dietary advice provided by registered dietitians at general physicians' offices, and offer measures to control blood pressure and other critical parameters in practice, thereby filling the evidence-practice gap, which will slow the progression of kidney disease.

Recently, the concept of chronic kidney disease has been announced not only in Japan, but also throughout the world [9, 10]. There are more than ten million CKD patients in Japan [4], and so CKD is regarded as a public health problem.

CKD guidelines for general physicians or patients have been published in European countries [9, 20–22]. The USA is also preparing similar measures for CKD [23, 24]. In Japan, annual urinalysis for early detection of renal disease started in the 1970s [11, 25], and a serum creatinine test was included in health examinations as early as 1989 to detect kidney failure among adults aged 40 years or older [26]. However, the number of dialysis patients is increasing by approximately 4% each year. It is necessary to implement more appropriate measures to reduce the rate of new dialysis patients in Japan as soon as possible.

In 2007, the Japanese Society of Nephrology established the CKD Clinical Practice Guide to help family physicians provide care for CKD patients. The guide suggests that lifestyle and dietary advice on obesity prevention [27], smoking cessation [28], and a sodium-restricted diet, and treatment for metabolic disorders [29, 30], hypertension [31], and hyperlipidemia [32] are effective to prevent progression of CKD. However, most people are not making sufficient efforts to manage their own health condition [13]. It is necessary to show the effect on the progression of CKD of treatment as part of the Clinical Practice Guide. Our challenge is to obtain sufficient evidence regarding the efficacy of filling the evidence-practice gap in preventing deterioration of renal function among Japanese patients.

We set the following conditions for patient eligibility in this study: CKD patients aged between 40 and 74 years; patients in CKD stage 1, 2, 4 or 5; and patients in CKD stage 3 with a high level of urinary protein and diabetes or hypertension. Proteinuria is known as the strongest predictor of decreasing renal function [13, 33], and the aggressive management of blood pressure and glucose [29, 31] and administration of RAS inhibitors [34–36] prevent the deterioration of renal function. The reason for the condition regarding urinary proteins in stage 3 patients is that we need to register patients showing significant deterioration in renal function [37].

Regarding lifestyle and dietary advice, we have prepared a list of instructions and advice for individual patients on a priority basis, so that registered dietitians can design a guidance schedule based on the priority list and provide consistent advice. In this study, we focus on preventing progression of CKD in the early stage by giving priority to Japanese CKD practice guide goals. We are preparing a long-term guidance method covering a wide range of health management items while seeking ways to reduce the evidence-practice gap as much as possible.

We predict significant positive effects in intervention group B (increased collaboration in clinical practice) in terms of increases in the rate of continued consultation and collaboration between nephrologists and other physicians, and reduced CKD stage progression as a result of instructions and advice from registered dietitians, compared with intervention group A. This study was designed to examine the effectiveness of a support system for collaborative CKD diagnosis and treatment by conducting a cluster-randomized controlled trial. We expect that this study will help improve clinical practices for CKD patients and provide high-quality clinical findings of global standard. Although the number of CKD patients in Japan is estimated to be more than ten million, there are only 3,000 nephrologists. If effective collaboration is established among nephrologists in CKD care, it will have a significant positive impact on renal care systems. In the area of renal care, few large-scale intervention studies have been performed on kidney care systems, except those aimed to assess the efficacy of drug interventions. Little progress has been made in the development of infrastructure for clinical studies and research environments in Japan. This study is expected not only to help develop the infrastructure required for clinical renal studies but also to generate valuable findings.

Progress of the study

Prior to the study, we selected 15 management facilities and 49 local medical associations, registered 491 family physicians (between April and June 2008), and registered 2,494 study participants on a provisional basis (between April and October 15, 2008), 2,413 of whom were randomly divided into intervention groups A (1,211) and B (1,202) in units of medical associations (or clusters) in September 2008. We started the intervention study on October 20, 2008.

Acknowledgments We express our thanks to the doctors and dietitians who participated in this study. We also express our thanks for the continuous support from members of the Japanese Society of Nephrology, the Japan Dietetic Association, and the Japanese Medical Association. We further thank Dr. Toshiyuki Imasawa, Dr. Chie Saitoh, Dr. Hirayasu Kai, Dr. Hideto Takahashi, Dr. Masafumi Okada, and Ms. Mariko Doi for valuable discussion and preparation of this manuscript. This study was supported by a grant for a strategic outcome study project from the Ministry of Health, Labor, and Welfare of Japan.

References

1. Nakai S, Masakane I, Akiba T, Iseki K, Watanabe Y, Itami N, et al. Overview of regular dialysis treatment in Japan (as of 31 December 2005). Ther Apher Dial. 2007;11:411–41.
2. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003;108:2154–69.
3. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32:S112–9.
4. Imai E, Horio M, Watanabe T, Iseki K, Yamagata K, Hara S, et al. Prevalence of chronic kidney disease (CKD) in Japanese general population. Clin Exp Nephrol, 2009.
5. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001;134:629–36.
6. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.
7. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation. 2000;102:203–10.
8. Brugts JJ, Knetsch AM, Mattace-Raso FU, Hofman A, Witteman JC. Renal function and risk of myocardial infarction in an elderly population: the Rotterdam Study. Arch Intern Med. 2005;165: 2659–65.
9. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39:S1–266.
10. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67:2089–100.
11. Yamagata K, Takahashi H, Suzuki S, Mase K, Hagiwara M, Shimizu Y, et al. Age distribution and yearly changes in the incidence of end-stage renal disease in Japan. Am J Kidney Dis. 2004;43:433–43.
12. Sorensen VR, Hansen PM, Heaf J, Feldt-Rasmussen B. Stabilized incidence of diabetic patients referred for renal replacement therapy in Denmark. Kidney Int. 2006;70:187–91.
13. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int. 2007;71: 159–66.
14. Heagerty A. Optimizing hypertension management in clinical practice. J Hum Hypertens. 2006;20:841–9.
15. Usami T, Nakao N, Fukuda M, Takeuchi O, Kamiya Y, Yoshida A, et al. Maps of end-stage renal disease and amounts of angiotensin-converting enzyme inhibitors prescribed in Japan. Kidney Int. 2003;64:1445–9.
16. CKD Clinical Practice Guidelines: Japanese Society of Nephrology (written and edited), First edition, Tokyo Igakusha, 2007.
17. Usami T, Koyama K, Takeuchi O, Morozumi K, Kimura G. Regional variations in the incidence of end-stage renal failure in Japan. JAMA. 2000;284:2622–4.
18. Imai E, Horio M, Yamagata K, Iseki K, Hara S, Ura N, et al. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. Hypertens Res. 2008;31:433–41.
19. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345:851–60.
20. Churchill DN, Blake PG, Jindal KK, Toffelmire EB, Goldstein MB. Clinical practice guidelines for initiation of dialysis. Canadian Society of Nephrology. J Am Soc Nephrol. 1999;10(Suppl 13): S289–91.
21. Burden R, Tomson C. Identification, management and referral of adults with chronic kidney disease: concise guidelines. Clin Med. 2005;5:635–42.
22. Nicholls K. Prevention of progression of kidney disease: diabetic nephropathy—CARI guidelines. Aust Fam Physician. 2007;36: 137–8.
23. IV. NKF-K/DOQI Clinical practice guidelines for anemia of chronic kidney disease: update 2000. Am J Kidney Dis. 2001; 37:S182–238.
24. Neumann ME. Results in KEEP's first report show progress in early identification of CKD patients. Nephrol News Issues. 2003;17:84–7.
25. Yamagata K, Takahashi H, Tomida C, Yamagata Y, Koyama A. Prognosis of asymptomatic hematuria and/or proteinuria in men. Nephron. 2002;91:34–42.
26. Ishida K, Ishida H, Narita M, Sairenchi T, Saito Y, Fukutomi H, et al. Factors affecting renal function in 119 985 adults over three years. QJM. 2001;94:541–50.
27. Ninomiya T, Kiyohara Y, Kubo M, Yonemoto K, Tanizaki Y, Doi Y, et al. Metabolic syndrome and CKD in a general Japanese population: the Hisayama Study. Am J Kidney Dis. 2006;48: 383–91.
28. Orth SR, Hallan SI. Smoking: a risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients—absence of evidence or evidence of absence?. Clin J Am Soc Nephrol. 2008;3:226–36.
29. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993; 329: 977–86.

30. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28:103–17.
31. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis. 2000;36:646–61.
32. Schaeffner ES, Kurth T, Curhan GC, Glynn RJ, Rexrode KM, Baigent C, et al. Cholesterol and the risk of renal dysfunction in apparently healthy men. J Am Soc Nephrol. 2003;14:2084–91.
33. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int. 2003;63:1468–74.
34. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The angiotensin-converting-enzyme inhibition in Progressive Renal Insufficiency Study Group. N Engl J Med. 1996;334:939–45.
35. Lewis JB, Berl T, Bain RP, Rohde RD, Lewis EJ. Effect of intensive blood pressure control on the course of type 1 diabetic nephropathy. Collaborative Study Group. Am J Kidney Dis. 1999;34:809–17.
36. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861–9.
37. Halbesma N, Kuiken DS, Brantsma AH, Bakker SJ, Wetzels JF, De Zeeuw D, et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. J Am Soc Nephrol. 2006;17:2582–90.

NEPHROLOGY

Nephrology **15** (2010) 27–30

Review Article

Renal outcomes in chronic kidney disease

KUNITOSHI ISEKI

Dialysis Unit, University Hospital of the Ryukyus, Nishihara, Okinawa, Japan

KEY WORDS:
diabetes mellitus, end-stage renal disease, proteinuria, screening.

Correspondence:
Dr. Kunitoshi Iseki, Dialysis Unit, University Hospital of The Ryukyus, 207 Uehara, Nishihara, Okinawa 903-0215, Japan. Email: chihokun@med.u-ryukyu.ac.jp

Accepted for publication 20 January 2010.

doi:10.1111/j.1440-1797.2010.01308.x

ABSTRACT:

The prevalence of treated patients with end-stage renal disease (ESRD) has been increasing steadily in Japan. High ESRD prevalence could be explained by multiple factors such as better survival on dialysis therapy, luxury acceptance due to insurance system to cover dialysis therapy, and 'truly' high incidence and prevalence of chronic kidney disease (CKD). The growing elderly population may also contribute to this trend. The Japanese Society of Nephrology estimated the prevalence of CKD stage 3 as 10.4%, 7.6% within the range of 50–59 mL/min per 1.73 m^2 in a screened population. Strong predictors of treated ESRD shown by using community-based screening programs and an ESRD registry in Okinawa are dip-stick-positive proteinuria and hypertension. Low glomerular filtration rate per se, which is often observed in the elderly population, is not a significant predictor of developing ESRD unless associated with proteinuria. CKD is common in Japan and is expected to increase, particularly in the elderly population. Benefits of proteinuria screening and automatic reporting of estimated glomerular filtration rate on the incidence of ESRD remain to be determined.

According to the annual report of the Japanese Society for Dialysis Therapy (JSDT), the prevalence of treated end-stage renal disease (ESRD) patients has been increasing for the past 20 years (Fig. 1).[1] In the population aged 75 years and over, the prevalence is more than 0.5%. The incidence of ESRD is also increasing, particularly in those aged 75 years and over (Fig. 2). The main causes of ESRD incidence are diabetes mellitus (DM), chronic glomerulonephritis and nephrosclerosis. The incidence of DM is now more than 300 per million populations in those aged 65 years and over (Fig. 3). The mean age at start of dialysis therapy is over 65 years. There is a north (low) to south (high) gradient in the incidence and prevalence of ESRD without obvious explanation.

The CKD prevalence seemed to be increasing in Japan. According to a community-based study in Hisayama, the age-adjusted prevalence of CKD stage 3 and 4 was 4.1% in 1974, 4.8% in 1988 and 8.7% in 2002 in men, and 7.3% in 1974, 11.2% in 1988 and 10.7% in 2002 in women.[2] This secular trend may be related to both genetic and environmental factors. Low birthweight, which is associated with lower nephron number, might develop DM and hypertension and therefore increase risk of ESRD.[3] However, such data is not available in Japan. Lifestyle-related factors that are often associated with obesity and metabolic syndrome may have a role in the development and progression of CKD.[4,5]

PREDICTORS OF ESRD AMONG SCREENED SUBJECTS (Table 1)

Japan has a long history of universal screening systems including urine test for proteinuria and haematuria.[6,7] It is not mandatory, however, so the fraction of people participating has been low at approximately 20–30%. We have been investigating the predictors of ESRD using two independent registries (Okinawa Dialysis Study (OKIDS) for dialysis patients and Okinawa General Health Maintenance Association (OGHMA)) for community-based screenees.[8,9] Screenees who eventually developed ESRD were confirmed by using the two registries and medical records.

Among the commonly measured variables, significant predictors of developing ESRD were dip-stick positive proteinuria and haematuria, and hypertension.[10] We have been reporting the importance of proteinuria and hypertension. Other predictors in Table 1 are also statistically significant, but the clinical significance is less than that of