The sample size was originally estimated to investigate the relationship of DPO dosage with Hb rise in the dose–response study.

Results

Patients

Two hundred ten patients were screened, and 171 received at least one treatment in the dose–response study. One hundred forty-three patients completed it, and 116 continued on to the follow-up study. Eighty-four patients accomplished this (Fig. 2). Drop-out rates were similar among the treatment groups in both studies. In the dose–response study, the major reason of withdrawal was initiation of renal replacement therapy [12 out of 28 patients (42.8%)]. In the follow-up study, 11 (34.4%) patients dropped out because of the occurrence of an adverse event and 14 (43.7%) because of initiation of renal replacement therapy.

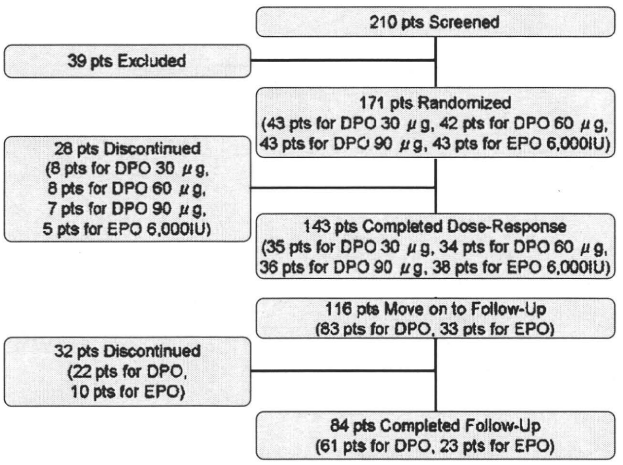

Fig. 2 Patient disposition. Participant flow chart. A total of 171 patients were enrolled in this study; 143 completed the dose–response study, and 84 completed the follow-up study. The major reason for withdrawal was initiation of renal replacement therapy and occurrence of an adverse event. *EPO* Epoetin alfa, *DPO* darbepoetin alfa

No major imbalances were observed in the demographics of the 171 patients who received at least one dose in the dose–response study, although the numbers of females in the EPO group and the group of patients with a heavier weight of DPO 60 μg were slightly higher than in the others (Table 1). There was no difference in cardiovascular history and use of anti-hypertensives as well as the ratio of patients with diabetes.

Anemia correction and maintenance

Figure 3 shows mean Hb throughout the studies. In the dose–response study, mean (±SD) Hb of the integrated value across the groups was 8.76 ± 1.00 g/dl at baseline and rose gradually to 10.58 ± 1.32 g/dl at week 8 and 11.25 ± 1.33 g/dl at week 16. There was no difference in baseline values among the treatment groups, and the mean Hb of patients with DPO increased in a dose-dependent manner after initiation. Significant differences were observed in the Hb rate of rise between 90 and 30 μg ($P < 0.001$), and between 90 and 60 μg ($P = 0.001$). The

Table 1 Patient demographics and baseline characteristics

Dose group	DPO 30 μg	DPO 60 μg	DPO 90 μg	EPO 6,000 IU
Number of subjects	43	42	43	43
Sex, *n* (%)				
Female	21 (48.8)	20 (47.6)	24 (55.8)	31 (72.1)
Male	22 (51.2)	22 (52.4)	19 (44.2)	12 (27.9)
Age (years)[a]	63.0 (27–79)	64.8 (38–79)	60.6 (25–76)	60.3 (23–77)
Weight (kg)[a]	55.64 (40.8–77.2)	59.30 (40.0–78.0)	54.39 (40.5–75.5)	54.04 (41.5–75.7)
Cause of renal failure, *n* (%)				
Chronic glomerulonephritis	20 (46.5)	23 (54.8)	22 (51.2)	16 (41.9)
Diabetic nephropathy	7 (16.3)	9 (21.4)	11 (25.6)	10 (23.3)
Pyelonephritis	1 (2.3)	1 (2.4)	0 (0.0)	2 (6.4)
Congenital cystic kidney disease	1 (2.3)	2 (4.8)	0 (0.0)	4 (9.3)
Nephrosclerosis	9 (20.9)	5 (11.9)	4 (9.3)	3 (7.0)
Other	5 (11.6)	2 (4.8)	6 (14.0)	6 (14.0)
Hb (g/dl)[a]	8.87 (6.3–9.9)	8.99 (6.6–9.9)	8.93 (6.6–9.9)	8.93 (6.5–9.9)
Cr (mg/dl)[a]	4.04 (2.1–9.6)	4.18 (2.1–8.2)	3.88 (2.0–6.5)	4.04 (2.0–8.3)

[a] Mean (range)

EPO Epoetin alfa, *DPO* darbepoetin alfa, *Hb* hemoglobin, *Cr* serum creatinine

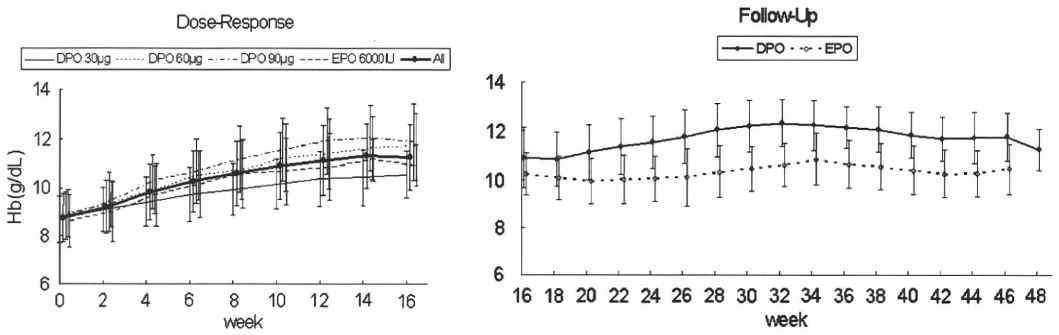

Fig. 3 Hb (mean ± SD) over time by treatment group. Mean Hb transition throughout the studies. *Left* Mean Hb throughout the dose–response study; *right* mean Hb throughout the follow-up study. *EPO* Epoetin alfa, *DPO* darbepoetin alfa, *Hb* hemoglobin

Hb rise of patients with EPO was comparable to 60 μg of DPO. In the follow-up study, the mean Hb of DPO and EPO was 10.88 ± 1.23 and 10.21 ± 0.87 g/dl, respectively. The mean Hb of DPO increased slowly, reached 12.31 ± 0.97 g/dl at week 34 and stayed around 12 g/dl, while EPO was kept around 10 g/dl, as the product label in Japan recommended. Hb values after final dosing were 11.75 ± 0.99 g/dl at week 48 and 11.23 ± 0.87 g/dl at week 50 for DPO, and 10.42 ± 1.04 g/dl at week 48 for EPO. No significant change was observed in the mean weekly dose for both treatment groups in the follow-up study (data not shown).

LVMI

After an independent review, the data of 49 patients for whom all three echocardiographs at baseline, week 16 and week 34 had been judged assessable and comparable were subjected to the analysis. There was no significant difference in mean (±SD) Hb between the treatment groups at baseline (9.18 ± 0.62 g/dl for DPO and 9.09 ± 0.85 g/dl for EPO) and week 16 (11.61 ± 1.15 g/dl for DPO and 11.01 ± 0.75 g/dl for EPO), but the difference became significant at week 34 (12.34 ± 0.93 g/dl for DPO and 10.43 ± 0.90 g/dl for EPO), as expected (Fig. 4a). Inverse changes were observed in the mean (±SD) LVMI. The LVMI of both groups decreased similarly until week 16 (118.1 ± 23.5–110.9 ± 24.3 g/m^2 for DPO and 119.0 ± 31.7–112.5 ± 27.1 g/m^2 for EPO). However, a decrease of LVMI in patients with EPO was retarded, while that of DPO continued to week 34 (100.7 ± 16.6 g/m^2 for DPO and 110.9 ± 25.2 g/m^2 for EPO) (Fig. 4b). There was a significant difference of LVMI score only in the DPO group between baseline and week 34, and between week 16 and week 34. Since DPO has almost the same pharmacological effects as EPO [17], we considered it appropriate to divide patients regardless of their treatment groups into categories based on their Hb level at week 34, adjusted by baseline, and examine the relationships between Hb and

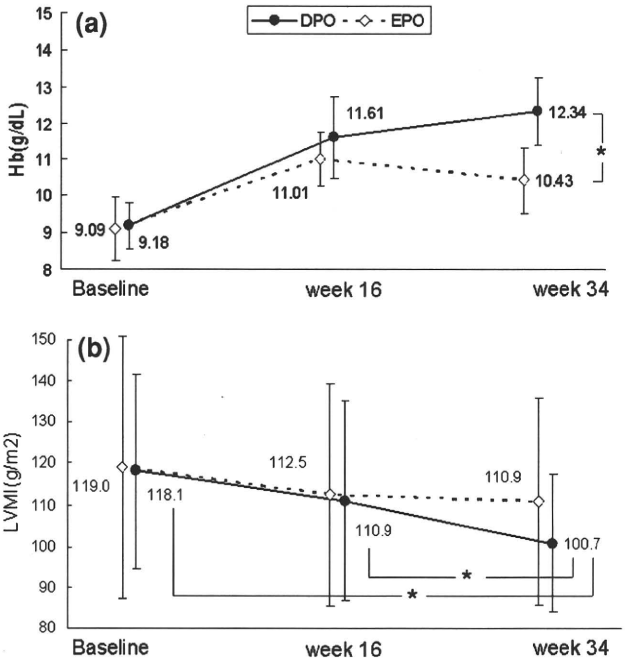

Fig. 4 **a** Hb and **b** LVMI (mean ± SD) over time by treatment group. The transition of Hb and LVMI (mean ± SD) from baseline to week 34 (week 16 in the follow-up study). *Hb* Hemoglobin, *LVMI* left ventricular mass index. *$P < 0.05$

change of LVMI [categories: Hb <10 g/dl ($n = 5$), 10 g/dl ≤ Hb <11 g/dl ($n = 5$), 11 g/dl ≤ Hb <12 g/dl ($n = 14$), 12 g/dl ≤ Hb ($n = 25$)]. A significant decrease was observed in 11 g/dl ≤ Hb <12 g/dl ($P = 0.004$) and 12 g/dl ≤ Hb ($P < 0.001$) compared to that of baseline (Fig. 5). Although the numbers of the lower Hb subsets were limited, significant correlation was demonstrated by linear regression analysis ($P = 0.004$) (data not shown). No significant change was detected in electrocardiograms and the chest-thoracic ratio measured from chest X-rays. The incidences of patients who initiated renal replacement therapy were similar in both groups in the follow-up study. Furthermore, the number of patients who used anti-hypertensives such as ARB or ACEi was 31 (88.6%) for the DPO

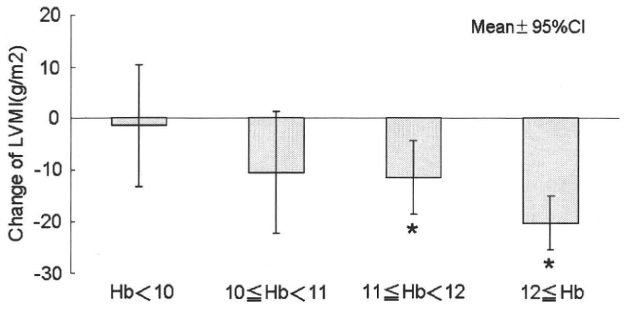

Fig. 5 Relationships between Hb and LVMI from baseline (week 34). The variation of LVMI adjusted by baseline at week 34 (week 16 in the follow-up study), stratified into four groups by Hb values at week 34. *$P < 0.05$

group and 13 (92.9%) for the EPO group. At the start of the study, the numbers of these patients were 30 (85.7%) and 12 (85.7%), respectively, and the ratio was nearly the same throughout the study.

Quality of life assessment

All 171 patients who received at least one treatment filled out the questionnaire. One hundred sixty-three and 143 patients repeated it at week 8 and 16, respectively. Means of most domains of the SF-36 and FACIT fatigue score in week 8 and 16 rose higher than baseline. The difference was significant ($P < 0.05$) in four (RP, role-physical; GH, general health; VT, vitality; FF, FACIT fatigue) and 2 (GH and FF) items at week 8 and 16, respectively (Fig. 6). Baseline to week 8 was prominent, especially for vitality among the SF-36 domains. The correlation between change of vitality and Hb at week 8 was examined by stratifying Hb into three categories: Hb <10 g/dl ($n = 47$), 10 g/dl ≤ Hb <11 g/dl ($n = 47$) and 11 g/dl ≤ Hb ($n = 69$). The result adjusted by sex, age, weight and baseline value demonstrated a significant increase in subsets 10 g/dl ≤ Hb < 11g/dl ($P = 0.005$) and 11 g/dl ≤ Hb ($P < 0.001$) compared to that of baseline (Fig. 7). However, significant correlation was not observed among the three subsets.

Safety

With regard to patient safety, adverse events observed in the two studies were those commonly seen in this patient population. No safety difference for adverse events with the occurrence frequency of ≥5% was reported between DPO and EPO (Fig. 8). The incidence of pruritus was similar in both products, although there was a report of an increase in the DPO treatment [18]. Headache was reported only in the DPO group. Death and antibody formation with DPO or EPO were not reported in our studies.

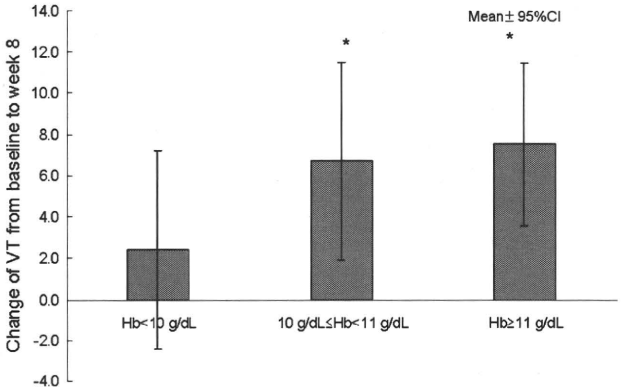

Fig. 7 Change of VT and Hb at week 8. Adjusted by sex, age, weight and baseline value, stratified into three groups. *VT* Vitality, *Hb* hemoglobin. *$P < 0.05$

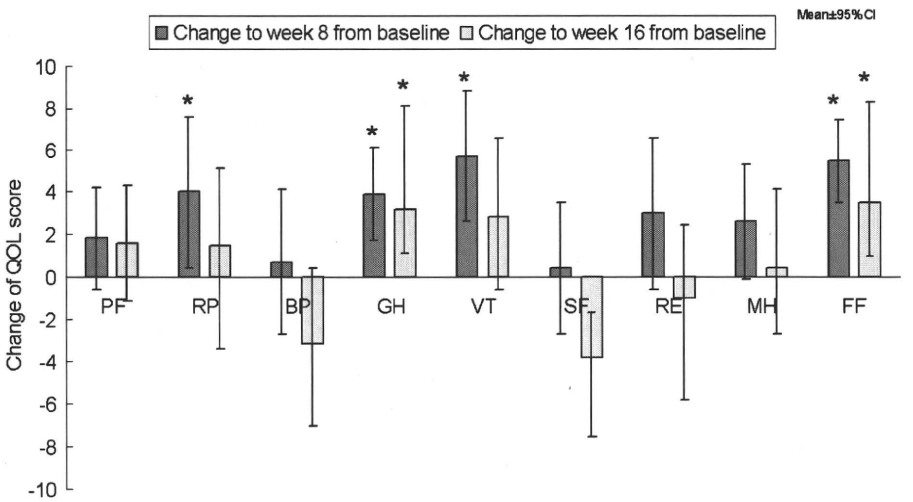

Fig. 6 QOL score changes across the treatment groups. QOL scores at week 8 and 16 (adjusted by baseline). *PF* Physical functioning, *RP* role-physical, *BP* bodily pain, *GH* general health, *VT* vitality, *SF* social functioning, *RE* role-emotional, *MH* mental health, *FF* FACIT fatigue. *$P < 0.05$

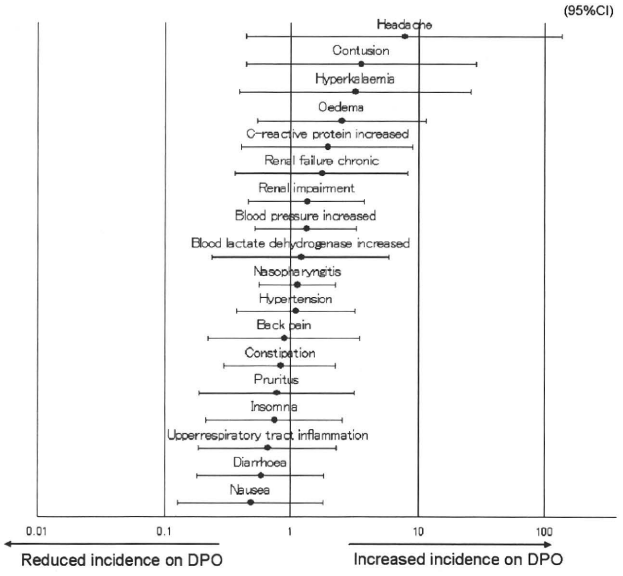

Fig. 8 Commonly observed adverse advents by treatment group. Adverse events odds ratio between DPO and EPO (95% confidence interval). Value smaller than 1 indicates reduced incidence on DPO and larger than 1 is increased incidence on DPO. *EPO* Epoetin alfa, *DPO* darbepoetin alfa

Discussion

Presently, use of epoetins, regardless of conventional EPO or the new long-acting DPO, is the routine treatment for patients with chronic anemia, especially for those with CKD, as more than 80% of the patients on hemodialysis therapy receive the treatment [19]. Currently, the purpose of anemia treatment by epoetins is not just to avoid transfusion, but also to improve QOL. Moreover, an association of higher hematocrit values with lower hospitalization and mortality in hemodialysis patients was indicated [6].

Silverberg et al. [20] reported that the use of epoetins in patients with chronic heart failure, targeting above 12 g/dl, improved not only anemia, but also the NYHA class and number of hospitalizations. Hayashi et al. [13] also concluded that from the perspective of left ventricular hypertrophy regression, normalization of the hematocrit was more effective than partial correction in Japanese CKD patients.

In this analysis, we examined the effect of anemia treatment on QOL and LVMI in Japanese patients with CKD not on dialysis. In Japan, the therapeutic Hb target for CKD patients, whether or not on dialysis, is set at around 10 g/dl for EPO, and treatment suspension is recommended if the Hb value exceeds 12 g/dl. Our result indicates that, at least for pre-dialysis CKD patients, a conventional target higher than the recommenced worldwide guidelines is beneficial. Continuous reduction of the LVMI score was observed only in the DPO group whose Hb target was set higher than the conventional one, and the decrease of LVMI was prominent in the $12 \leq$ Hb group. Also, improvement of QOL was demonstrated in our study, as observed in other reports [10, 15, 16, 21]. Although the KDOQI guideline for anemia treatment states that it lacks sufficient evidence to recommend maintaining 13 g/dl or higher, it was updated in 2006 to lift the upper side of the Hb target [2]. Recently, however, the CHOIR study revealed that targeting 13.5 g/dl was more harmful than 11.3 g/dl in pre-dialysis patients with CKD [3]. Also, the CREATE study did not demonstrate that early anemia correction targeting over 13 g/dl reduced the risk of cardiovascular events [10]. Following the publication of these studies, the guideline was revised in 2007 to reinstitute the upper limit target value of 12 g/dl [22]. In our studies, CKD patients with serious complications were excluded, while the CHOIR study included many patients with severe complications such as myocardial infarction. It suggests that caution is needed to apply a therapeutic Hb target higher than 12 g/dl to patients with a history of serious complications, especially cardiac. In the dose–response study, we enrolled patients whose Hb was less than 10 g/dl. In contrast, patients enrolled in the CREATE study had much less anemia than ours, and the mean Hb was above 11 g/dl. Early anemia correction seems to contribute to improving QOL, but the effect on cardiac functions might be obscured if patients are not too anemic at the commencement of the treatment. The effect on renal functions should be discussed further.

Our results indicate that anemia correction and maintenance up to 12 g/dl are a reasonable target for pre-dialysis CKD patients without serious complications. Even after the publications of the CHOIR and CREATE studies, it was decided to continue a much larger study, TREAT, in which targeting 13 g/dl in CKD patients with diabetes was compared to a placebo to examine patient outcome, including composite of death and hard endpoints [23, 24]. It might be appropriate to maintain the therapeutic target on a subnormal level (around 12 g/dl) until the results of this largest trial come out. With regards to the CHOIR trial, the secondary analysis was additionally published, and it suggests that the detrimental outcome of a higher target may be associated with the inability to achieve the hemoglobin target with the use of a high EPO dose [25]. Although no deaths were reported in our study, the relationship should be investigated in future studies.

There are still certain limitations to our study, and to apply the results to the general population of renally impaired patients requires caution. For many CKD patients without severe complications, twice-a-month clinical assessments might be unrealistic in daily clinical practice. In that sense, a long-acting epoetin like DPO may play an

important role in actual clinical settings, especially in countries like Japan, where self-injection of EPO is not officially authorized. Further studies for generalization are warranted.

In summary, we examined the effect of anemia correction and management, comparing groups targeting around 12 g/dl with 10 g/dl in pre-dialysis patients with CKD without severe complications. Targeting around 12 g/dl was more beneficial than 10 g/dl in terms of decreased LVMI and QOL. This indicates that higher Hb may be a more appropriate target for pre-dialysis Japanese CKD patients.

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Modification of the CKD Epidemiology Collaboration (CKD-EPI) Equation for Japanese: Accuracy and Use for Population Estimates

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Introduction: We previously reported a modification to the Modification of Diet in Renal Disease (MDRD) Study equation for use in Japan. Recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) developed a new equation that is more accurate and yields a lower CKD prevalence estimate in the United States than the MDRD Study equation. We modified the CKD-EPI equation for use in Japan, compared its accuracy with the Japanese modification of the MDRD Study equation, and compared the prevalence of CKD in Japan using both equations.

Design: A diagnostic test study comparing the Japanese coefficient–modified CKD-EPI equation and Japanese coefficient–modified MDRD Study equation and a cross-sectional study comparing distribution of estimated glomerular filtration rate and prevalence of CKD in participants in a Japanese annual health check program.

Setting & Participants: 763 Japanese patients (413 for development and 350 for validation) were included. Prevalence estimates were based on 574,024 participants from the annual health check program.

Index Test: Japanese modification of the MDRD Study and CKD-EPI equations.

Reference Test: Inulin clearance.

Results: The Japanese coefficient of the modified CKD-EPI equation was 0.813 (95% CI, 0.794-0.833). In the validation data set, the modified CKD-EPI equation performed better than the modified MDRD Study equation. Bias (measured GFR [mGFR] − eGFR) was 0.4 ± 17.8 (SD) versus 1.3 ± 19.8 mL/min/1.73 m^2 overall, respectively ($P = 0.02$); 7.3 ± 20.6 versus 7.8 ± 22.2 mL/min/1.73 m^2 for participants with mGFR ≥60 mL/min/1.73 m^2, respectively ($P < 0.001$); and −4.4 ± 13.8 versus −3.3 ± 15.6 mL/min/1.73 m^2 for participants with mGFR <60 mL/min/1.73 m^2, respectively ($P = 0.5$). The modified CKD-EPI equation yields a lower estimated prevalence of CKD than the modified MDRD Study equation (7.9% vs 10.0%), primarily because of a lower estimated prevalence of stage 3 (5.2% vs 7.5%).

Limitation: Most study participants had CKD. The study population contained a limited number of participants with mGFR ≥90 mL/min/1.73 m^2.

Conclusion: The Japanese coefficient–modified CKD-EPI equation is more accurate than the Japanese coefficient–modified MDRD Study equation and leads to a lower estimated prevalence of CKD in Japan.

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INDEX WORDS: Modification of Diet in Renal Disease (MDRD) Study equation; Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; CKD prevalence; Japanese coefficient.

Accurate estimation of glomerular filtration rate (GFR) is crucial for the detection of chronic kidney disease (CKD).[1] Calculating GFR by measuring the clearance of exogenous markers, such as inulin, is accurate, but the procedure is time consuming. The use of GFR-estimating equations has been recommended in clinical practice.[1] The Modification of Diet in Renal Disease (MDRD) Study equation[2] is the most commonly used worldwide. The equation was developed in mostly whites and African Americans. We previously reported that estimated GFR (eGFR) obtained using the isotope-dilution mass spectrometry–traceable 4-variable MDRD Study equation was significantly higher than measured GFR (mGFR) in Japanese patients.[3] Therefore, we calculated a correction coefficient of 0.808 for the MDRD

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Study equation and developed a new Japanese equation for GFR estimation.[3]

Recently, Levey et al[4] developed a more accurate new GFR estimation equation, the CKD Epidemiology Collaboration (CKD-EPI) equation, based on data from 5,504 participants. The equation yields a lower estimated prevalence of CKD than the MDRD Study equation in the United States. In this study, we explored the accuracy of this new equation in Japanese and estimated CKD prevalence in the general population in Japan using the equation. Because the CKD-EPI equation was developed mostly in whites and African Americans, we calculated a correction coefficient for the use of the CKD-EPI equation in Japanese and performed: (1) a diagnostic test study comparing the Japanese coefficient–modified CKD-EPI equation with the Japanese coefficient–modified MDRD Study equation, and (2) cross-sectional study comparing the distribution of eGFR and prevalence of CKD in participants in a Japanese annual health check program.

METHODS

Diagnostic Test Study

Participants

To perform a diagnostic test study to compare the modified CKD-EPI and modified MDRD Study equations, we used same data sets from which the Japanese coefficient of the MDRD Study equation was developed and validated. Details of participants were reported previously.[3] Briefly, 763 Japanese patients in 80 medical centers were included. They were divided into a development data set (413 participants) and a validation data set (350 participants). GFR was measured using inulin renal clearance. Serum creatinine was measured using an enzymatic method in a single laboratory. The accuracy of creatinine measurement was validated using the calibration panel of the Cleveland Clinic.[3]

Calculation of a Coefficient of the CKD-EPI Equation

A coefficient for the CKD-EPI equation appropriate for use in Japanese was calculated in the development data set in the same way the Japanese MDRD Study equation coefficient was obtained previously.[3] The coefficient was determined by minimizing the sum of squared errors between eGFR and inulin renal clearance.

Performance of the Coefficient-Modified Equation

Performance of the Japanese coefficient–modified equations was studied using the development and validation data sets. Bias, root mean square error, and accuracy within 30% (P_{30}) were analyzed.

Cross-sectional Study

Population

We previously reported the prevalence of CKD based on data from the Japanese annual health check program in 2005 using an equation for Japanese.[5] In the present study, to compare eGFR distribution and CKD prevalence in participants in this health check program, we used the same population from the Japanese annual health check program, which consisted of 574,024 participants older than 20 years. Details of the data have been reported previously.[5] We calculated CKD prevalence using the Japanese coefficient–modified MDRD Study equation and Japanese coefficient–modified CKD-EPI equation using a Japanese adult population obtained from a census in 2005.

Statistical Analysis

Data are expressed as mean ± standard deviation. Differences in clinical characteristics between the development and validation

Table 1. Clinical Characteristics of the Study Population for the Diagnostic Test Study

Characteristic	Development Data Set	Validation Data Set	*P*
No. of participants	413	350	
Men	262 (63)	203 (58)	0.1
Age (y)	51.4 ± 16.5	53.9 ± 17.5	0.04
Height (cm)	163.2 ± 8.8	161.6 ± 9.5	0.01
Weight (kg)	61.0 ± 12.9	60.4 ± 12.7	0.5
BSA (m^2)	1.65 ± 0.19	1.63 ± 0.19	0.2
BMI (kg/m^2)	22.8 ± 3.8	23.0 ± 3.8	0.4
Diabetes	82 (20)	77 (22)	0.5
Hypertension	235 (57)	202 (58)	0.8
Transplant	9 (2)	2 (1)	0.06
Kidney donor	1 (0)	10 (3)	0.003
Creatinine (mg/dL)	1.52 ± 1.59	1.88 ± 1.70	0.6
mGFR ($mL/min/1.73\ m^2$)	59.1 ± 35.4	45 ± 25	0.5

Note: Data are expressed as mean ± standard deviation or number (percentage). Conversion factor for GFR in $mL/min/1.73\ m^2$ to $mL/s/1.73\ m^2$, ×0.01667.

Abbreviations: BMI, body mass index; BSA, body surface area; mGFR, measured glomerular filtration rate.

Table 2. Performance of GFR-Estimating Equations in the Validation Data Set

Variable and Equation	All (N = 350)	mGFR <60 mL/min/1.73 m^2 (n = 206)	mGFR ≥60 mL/min/1.73 m^2 (n = 144)
Bias (mL/min/1.73 m^2)			
Japanese coefficient–modified MDRD Study equation	1.3 ± 19.4	−3.3 ± 15.6	7.8 ± 22.2
Japanese coefficient–modified CKD-EPI Study equation	0.4 ± 17.8	−4.4 ± 13.8	7.3 ± 20.6
P	0.02	0.5	<0.001
P_{30} (%)			
Japanese coefficient–modified MDRD Study equation	73 (69-78)	67 (61-74)	82 (75-87)
Japanese coefficient–modified CKD-EPI Study equation	75 (70-79)	65 (58-71)	88 (82-92)
P	0.7	0.6	0.1
Root mean square error (mL/min/1.73 m^2)			
Japanese coefficient–modified MDRD Study equation	19.4	15.9	23.5
Japanese coefficient–modified CKD-EPI Study equation	17.8	14.4	21.8

Note: Bias is mGFR minus eGFR and is reported as mean ± standard deviation; P_{30} refers to percentage of GFR estimates that are within 30% of mGFR, with 95% confidence intervals given in parentheses. The Japanese coefficient–modified MDRD Study equation is the isotope-dilution mass spectrometry–traceable 4-variable MDRD Study equation multiplied by a Japanese coefficient of 0.808: $eGFR = 0.808 \times 175 \times SCr^{-1.154} \times Age^{-0.203} \times 0.742$ (if female). The Japanese coefficient–modified CKD-EPI Study equation is multiplied by a Japanese coefficient of 0.813; $eGFR = 0.813 \times 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 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.

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate.

data sets were evaluated using χ^2 test and independent *t* test. Differences in the bias (absolute value) of eGFRs were evaluated using paired *t* test. Differences in accuracy (ie, P_{30}) were evaluated using χ^2 tests. Differences in the prevalence of specific GFR groups were evaluated using χ^2 test. A difference with $P < 0.05$ is considered statistically significant. Statview, version 4.02, and JMP 8.01 (both from SAS Institute, www.sas.com) were used for statistical analysis. JMP 8.01 was used for receiver operating characteristic curve analysis.

RESULTS

Modifying the CKD-EPI Equation for a Japanese Population

The coefficient to modify the CKD-EPI equation for Japanese, calculated from the development data set of 413 participants (for whom clinical characteristics are listed in Table 1), was found to be 0.813 (95% confidence interval, 0.794-0.833).

Diagnostic Test Study

We used a diagnostic test design to compare the Japanese coefficient–modified CKD-EPI and MDRD Study equations, which are listed in Table 2.

Comparison of Performance of Coefficient-Modified Equations

We analyzed all participants and subgroups in the validation data set, stratified by mGFR (<60 vs ≥60 mL/min/1.73 m^2; Table 2). As in the development data set, root mean square error was lower for the Japanese coefficient–modified CKD-EPI equation than the Japanese coefficient–modified MDRD Study equation in all participants and both subgroups stratified by mGFR. The coefficient-modified CKD-EPI equation had significantly less bias than the coefficient-modified MDRD Study equation in all participants ($P = 0.02$). This difference was due to improved bias in participants with GFR ≥60 mL/min/1.73 m^2 ($P < 0.001$); there was no significant difference in bias in participants with GFR <60 mL/min/1.73 m^2. Accuracy was not significantly different between equations.

Table 3 lists the performance of the equations in a validation data set (see Table 1 for details of participants in this data set) stratified by clinical characteristics. Compared with the coefficient-modified MDRD Study equation, the coefficient-modified CKD-EPI equation showed significantly lower bias in younger participants (aged

Table 3. Performance of Japanese Coefficient–Modified GFR-Estimating Equations in the Validation Data Set According to Clinical Characteristics

Clinical Characteristics	No. of Participants	Bias		*P*
		0.808 × MDRD	0.813 × CKD-EPI	
Sex				
Men	203	0.8 ± 15.8	0.4 ± 14.7	0.1
Women	147	1.9 ± 23.4	0.5 ± 21.5	0.1
Age (y)				
19-44	107	3.2 ± 18.7	−0.5 ± 17.1	0.03
45-64	130	1.0 ± 22.5	1.1 ± 20.7	0.5
≥65	113	−0.2 ± 15.9	0.5 ± 14.7	0.1
BMI (kg/m^2)				
<20	71	0.2 ± 26.4	−0.5 ± 25	0.9
20-25	190	−0.6 ± 17.2	−1.2 ± 14.8	0.01
>25	89	6.1 ± 16.2	4.6 ± 16.4	0.2
Diabetes				
Yes	83	−1.5 ± 15.2	−1.1 ± 14.5	0.9
No	264	2.2 ± 20.5	0.9 ± 18.8	0.02
Hypertension				
Yes	209	1.0 ± 15.9	0.1 ± 15.5	0.7
No	141	1.6 ± 23.6	0.9 ± 20.9	0.02
Total	350	1.3 ± 19.4	0.4 ± 17.8	0.02

Note: Unit of bias (mGFR − eGFR) is mL/min/1.73 m^2. Bias was reported as mean ± standard deviation. 0.808 × MDRD refers to the Japanese coefficient–modified isotope-dilution mass spectrometry–traceable 4-variable MDRD Study equation. 0.813 × CKD-EPI refers to the Japanese coefficient–modified CKD-EPI Study equation.

Abbreviations: BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate.

19-44 years; $P = 0.03$), those with optimal body mass index (20-25 kg/m^2; $P = 0.01$), those without diabetes ($P = 0.02$), and those without hypertension ($P = 0.02$).

Receiver operating characteristic curves to detect GFRs less than 90, 60, and 30 mL/min/1.73 m^2 did not differ between the Japanese coefficient–modified CKD-EPI and MDRD Study

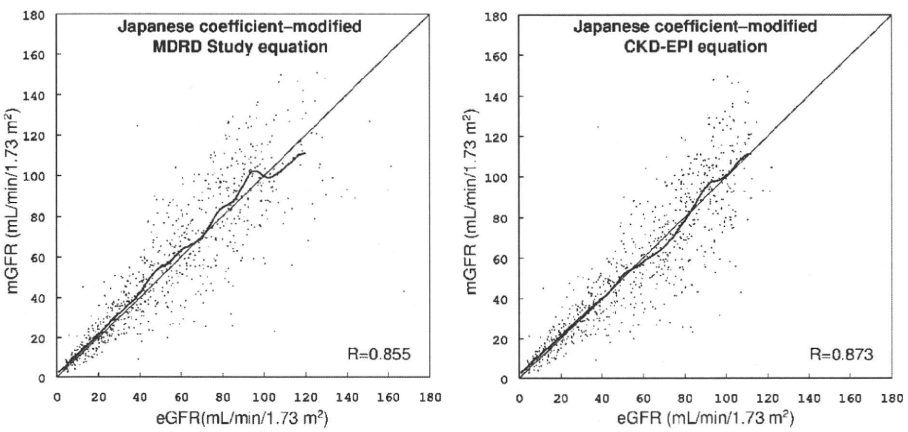

Figure 1. Correlation between estimated (eGFR) and measured glomerular filtration rate (mGFR) in the combined data set. (Left) mGFR versus eGFR obtained using the Japanese coefficient–modified Modification of Diet in Renal Disease (MDRD) Study equation. (Right) mGFR versus eGFR obtained using the Japanese coefficient–modified Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Smoothed lines show the fit of the data.

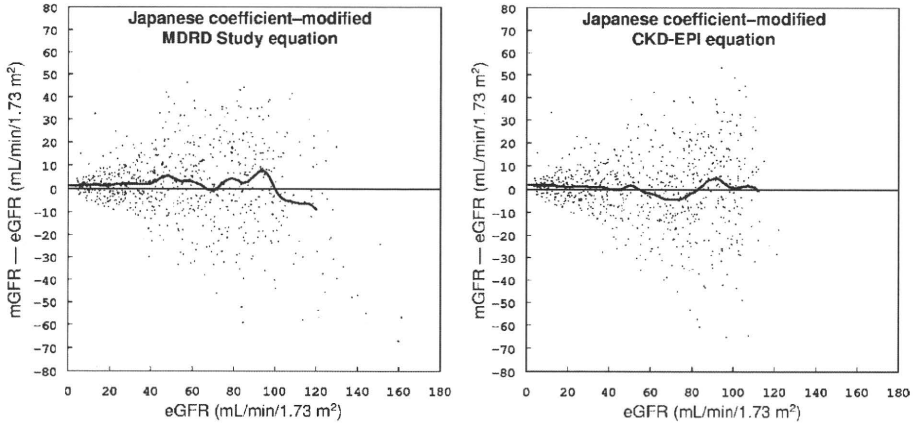

Figure 2. Difference between measured (mGFR) and estimated glomerular filtration rate (eGFR) versus eGFR in the combined data set. (Left) mGFR minus eGFR versus eGFR obtained using the Japanese coefficient–modified Modification of Diet in Renal Disease (MDRD) Study equation. (Right) mGFR minus eGFR versus eGFR obtained using the Japanese coefficient–modified Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

equations. Areas under the receiver operating characteristic curves were 0.93, 0.94 and 0.96 for both equations, respectively.

Correlation Between Modified CKD-EPI eGFR and mGFR

The correlation coefficient between mGFR and eGFR calculated using the coefficient-modified CKD-EPI equation in the combined data set was higher than the corresponding value for the coefficient-modified MDRD Study equation (0.872 vs 0.855, respectively; Fig 1). Smoothed lines show the fit of the data. Plots of mGFR minus eGFR versus eGFR were evaluated as shown in Fig 2. Smoothed lines show the fit of the data. The Japanese coefficient–modified CKD-EPI equation showed good performance.

Cross-sectional Study

We also performed a cross-sectional study to compare the eGFR distribution and CKD prevalence obtained using the Japanese coefficient–modified equations in participants in a Japanese annual health check program. Characteristics of the study population are shown in Table 4 and results of the cross-sectional analysis are shown in Fig 3. Percentages of specific GFR ranges (15-29, 30-59, 60-89, 90-119, and ≥120 mL/min/1.73 m^2) indicated that the coefficient-modified CKD-EPI equation increased the prevalence of GFR within the range of 90-119 mL/min/1.73 m^2 from 28.6% to 34.0% and decreased the prevalence of GFR within the range of 30-59 mL/min/1.73 m^2 from 7.5% to 5.2%. The coefficient-modified CKD-EPI equation yields a lower estimated prevalence of CKD than the coefficient-modified MDRD Study equation (7.9% vs 10.0%), primarily because of a lower estimated prevalence of stage 3 (5.2% vs 7.5%).

Table 4. Characteristics of the Study Population in the Annual Health Check Program

	Men	Women
No. of participants	240,594	333,430
Age (y)	57.8	58.6
Creatinine (mg/dL)	0.86	0.63
Mean eGFR (mL/min/1.73 m^2)		
0.808 × MDRD	78.5	81.9
0.813 × CKD-EPI	77.5	79.6
Median eGFR (mL/min/1.73 m^2)		
0.808 × MDRD	77 (68-88)	79 (70-93)
0.813 × CKD-EPI	78 (70-86)	80 (73-87)
Prevalence (%)		
Diabetes	5.9	3.5
Hypertension	30.3	24.7
Proteinuria	4.7	2.5

Note: Values in parentheses are interquartile ranges. 0.808 × MDRD refers to the Japanese coefficient–modified isotope-dilution mass spectrometry–traceable 4-variable MDRD Study equation. 0.813 × CKD-EPI refers to the Japanese coefficient–modified CKD-EPI Study equation.

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

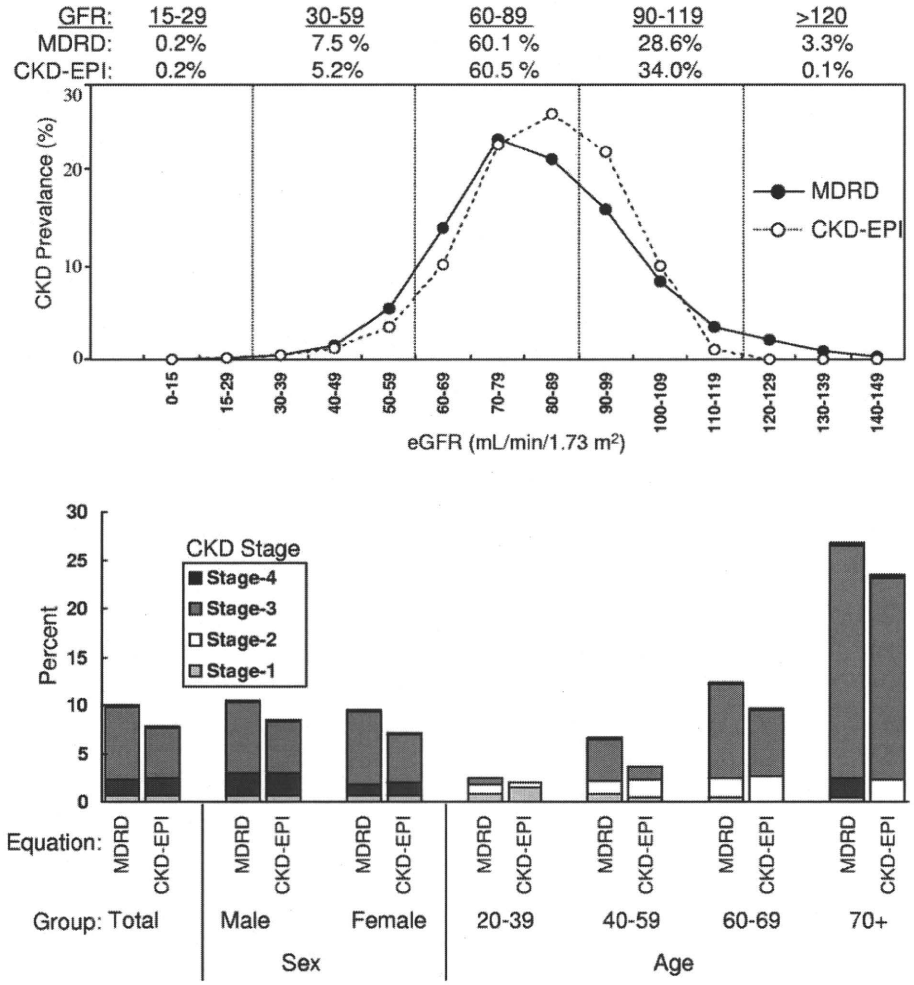

Figure 3. Comparison of distributions of estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD) prevalence. (Top) Distribution in a Japanese general adult population of eGFR obtained using the Japanese coefficient–modified Modification of Diet in Renal Disease (MDRD) Study equation (solid line) compared with eGFR obtained using the Japanese coefficient–modified Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (dotted line). Percentages of specific GFR ranges (15-29, 30-59, 60-89, 90-119, and ≥120 mL/min/1.73 m^2) are shown. (Bottom) Estimated prevalence of CKD by sex and age when GFRs are obtained using either the Japanese coefficient–modified MDRD Study or CKD-EPI equation.

DISCUSSION

We previously reported a Japanese coefficient of 0.808 for the MDRD Study equation.[3] In the present study, we obtained the Japanese coefficient of 0.813 (95% confidence interval, 0.794-0.833) for the CKD-EPI equation. The values are similar in both equations. The observation that correction coefficients are less than 1.0 indicates lower serum creatinine levels in Japanese than in whites with equivalent GFRs, probably because of the lower skeletal muscle mass found in Japanese compared with North Americans.[3]

The coefficient-modified CKD-EPI equation had lower bias (P = 0.02) than the coefficient-modified MDRD Study equation because of lower bias in participants with mGFR ≥60 mL/min/1.73 m^2. As reported by Levey et al,[4] the improvement in bias likely depends on the use of a 2-slope linear spline with sex-specific knots to model the relationship between log(GFR) and log(serum creatinine), which allows for a steeper slope of GFR versus serum creatinine at creatinine levels above the knots and a less steep slope at creatinine levels below the knots.[4] Differences in bias between subgroups defined by age, body mass index, diabetes, and hypertension also were noted, but larger studies are needed to confirm these results.

The eGFR distribution and CKD prevalence indicated that the Japanese coefficient–modified CKD-EPI equation increased the prevalence of GFR within the range of 90-119 mL/min/1.73 m^2 even as it decreased the prevalence of GFR

within the range of 30-59 mL/min/1.73 m^2. The coefficient-modified CKD-EPI equation yields a lower estimated prevalence of CKD than the coefficient-modified MDRD Study equation (7.9% vs 10.0%), primarily because of a lower estimated prevalence of stage 3 (5.2% vs 7.5%). This result may be explainable by the characteristics of the coefficient-modified CKD-EPI equation that increased eGFR in participants stratified by mGFR >60 or <60 mL/min/1.73 m^2 compared with the coefficient-modified MDRD Study equation. Levey et al[4] reported that the CKD-EPI equation decreased the prevalence estimate for CKD in the United States from 13.1% to 11.5% compared with the MDRD Study equation. These results are consistent with our results.

Limitations of the present study are as follows. (1) We obtained and validated the Japanese coefficient for the CKD-EPI equation from 763 participants. Most study participants had CKD. The study population contained a limited number of participants with mGFR ≥90 mL/min/1.73 m^2, and performance of the coefficient-modified equation was not studied sufficiently in the healthy population. (2) We compared performances between coefficient-modified equations, but the best performance of the equations may not be shown by a simple coefficient correction. The CKD-EPI equation uses log(serum creatinine) with 2-slope linear spline with sex-specific knots at 0.7 mg/dL in women and 0.9 mg/dL in men. That the coefficient was found to be less than 1.0 indicates lower serum creatinine levels in Japanese than in whites with equivalent GFRs. It is unknown whether creatinine values for sex-specific knots are suitable for Japanese.

In conclusion, the CKD-EPI equation modified with the Japanese coefficient performed better than the Japanese coefficient–modified MDRD Study equation. The Japanese coefficient–modified CKD-EPI equation yields a lower estimated prevalence of CKD than the Japanese coefficient–modified MDRD Study equation, primarily because of a lower estimated prevalence of CKD stage 3.

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ORIGINAL ARTICLE

Reference serum cystatin C levels in Japanese children

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Abstract
Background Single measurements of serum cystatin C (cysC) concentration have generally been used to determine glomerular filtration rate (GFR) in adults. Since GFR varies to some extent among children, we attempted to determine reference serum cysC concentrations for Japanese children.
Methods Serum cysC concentrations were determined by a latex particle-enhanced turbidimetric immunoassay in children who did not present with kidney disease or infectious disease, and the relationship between age and serum cysC level was assessed.
Results We found that reference serum cysC levels gradually decreased during the first year after birth, thereafter becoming constant. Mean serum cysC concentration in children aged 1 year (0.76 ± 0.10 mg/L) was slightly higher than in children aged ≥2 years (0.70 ± 0.09 mg/L).
Conclusion Our reference values will be applicable for screening renal function in Japanese children.

Keywords Reference serum cystatin C level · Japanese children · Cystatin C · Creatinine · Glomerular filtration rate

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Introduction

Glomerular filtration rate (GFR) is used universally as a measure of kidney function. A single measurement of serum concentration of cystatin C (cysC), an endogenous proteinase inhibitor, has commonly been used to determine GFR. CysC is produced at a constant rate in the body, freely filtered by the glomerulus, not secreted or reabsorbed by kidney tubules, and excreted only by the kidneys. We previously found a significant positive correlation between serum creatinine (SCr) concentration and body length in children aged 1–12 years, with body length (m) × 0.30 yielding a value similar to reference SCr level [1]. Thus, normal SCr value is limited as a tool for estimating GFR in that it gradually increases with body length. GFR varies to some extent among children, increasing from about 30–100% of the level in adults during the year after birth. Moreover, serum cysC concentrations in normal children aged ≥1 year are thought to remain constant. We therefore attempted to derive reference serum cysC values for Japanese children.

Materials and methods

A total of 154 children (73 males and 81 females), aged 16 days–18 years, who attended the outpatient clinic of Aichi Children's Health and Medical Center between April 2004 and March 2005, and who did not present with kidney disease or infectious disease, were initially included in this study. Data of patients from whom consent was not received for inclusion in a clinical report were excluded. Serum cysC concentrations obtained from daily laboratory tests were analyzed. Study participants were classified as being <1 year (n = 52; 34 males, 18 females), ≥1 to

<2 years ($n = 23$; 11 males, 12 females), ≥2 to <7 years ($n = 48$; 21 males, 27 females), ≥7 to <13 years ($n = 18$; 5 males, 13 females), and ≥13 years ($n = 12$; 2 males, 10 females) old. Serum concentrations of cysC were determined by a latex particle-enhanced turbidimetric immunoassay (Mitsubishi Chemical Medience Corp.) using a Hitachi 7170S automated analyzer (Hitachi High-Technologies Corp.). The coefficients of inter- and intraassay variance were 1.14% and 1.25%, respectively. The average cysC concentration and its standard deviation (SD) were determined for each group. The relationship between age and serum cysC level was plotted by scattergram, and the average cysC concentrations in each age group were compared using one-way factorial analysis of variance (ANOVA). In the case of a significant ANOVA, the Tukey–Kramer post hoc test and Scheffe's multiple contrasts were used to make multiple pairwise comparisons. Differences in average cysC between males and females were compared using unpaired t tests. A p value <0.05 was defined as statistically significant.

Results

We examined the correlations between serum cysC concentration and age in all participants (Fig. 1) and in children aged <1 year (Fig. 2) and ≥1 year (Fig. 3). These scattergrams show that reference serum cysC concentrations gradually decreased, from about 1.5 to 0.8 mg/L, during the year after birth, and then remained relatively constant at about 0.7 mg/L. When we compared average cysC concentration in subgroups of children aged ≥1 year, i.e., ≥1 to <2, ≥2 to <7, ≥7 to <13, and ≥13 years, we observed statistically significant differences between children aged ≥1 to <2 and ≥2 to <7 years (0.76 ± 0.10 vs. 0.69 ± 0.08 mg/L, $p < 0.05$; Table 1) using ANOVA.

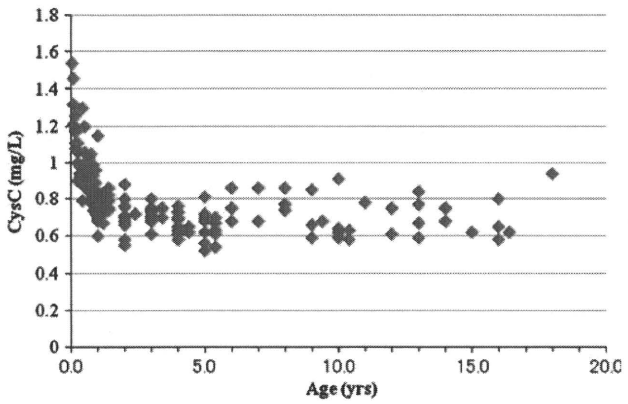

Fig. 1 Reference serum cystatin C (cysC) levels over time from birth, showing a gradual decrease during the year after birth but then remaining relatively constant

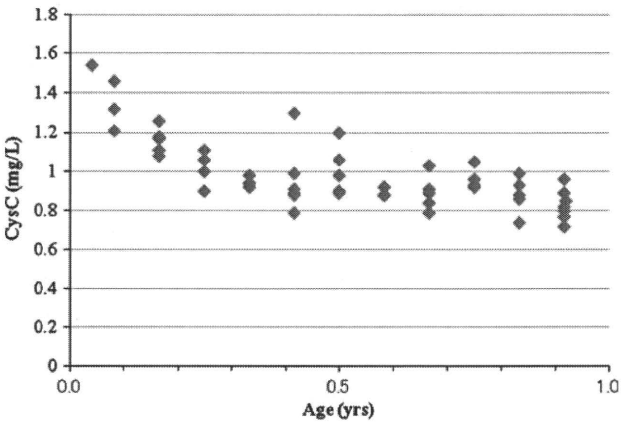

Fig. 2 Reference serum cystatin C (cysC) levels during the year after birth, showing a gradual decrease from about 1.5 to 0.8 mg/L

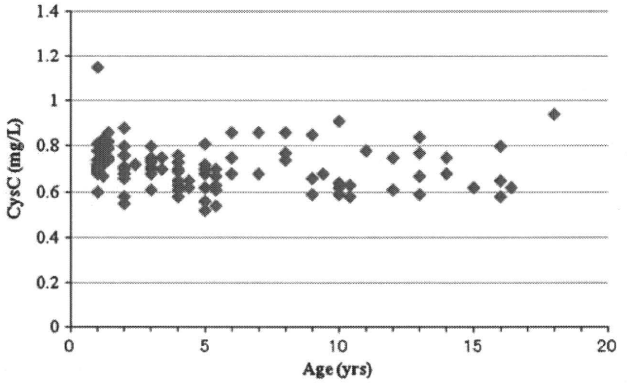

Fig. 3 Reference serum cystatin C (cysC) levels in children aged ≥1 year, showing a relatively constant level of about 0.7 mg/L

Table 1 Mean and median cystatin C (cysC) level by age

Age (years)	Number	Mean	SD	Median	Range
≥1 to <2	23	0.76	0.10	0.74	0.60–1.15
≥2 to <7	48	0.69	0.08	0.70	0.52–0.88
≥7 to <13	18	0.71	0.11	0.68	0.58–0.91
≥13	12	0.71	0.11	0.68	0.58–0.94
≥2	78	0.70	0.09	0.68	0.52–0.94

We observed significant differences between children aged ≥1 to <2 years and those aged ≥2 to <7 and ≥2 years ($p < 0.05$ each), but no significant difference among children aged ≥2 to <7, ≥7 to <13, and ≥13 years

SD standard deviation

However, we did not observe significant differences among groups of children aged ≥2 to <7 years, ≥7 to <13 years (0.71 ± 0.11 mg/L), and ≥13 years (0.71 ± 0.11 mg/L) old. When we combined the latter groups into one group (≥2 years old), we found that their average serum cysC concentrations (0.70 ± 0.09 mg/L) differed significantly from that of children aged ≥1 to 2 years ($p < 0.05$;

Table 1). We did not observe significant differences between males and females in children aged ≥1 to <2 years (0.80 ± 0.13 vs. 0.73 ± 0.07 mg/L) and those aged ≥2 years (0.68 ± 0.10 vs. 0.71 ± 0.08 mg/L).

Discussion

GFR reflects kidney function and is measured by assessments of renal clearance techniques. Although inulin clearance is the gold standard for evaluation of kidney function, it cannot be measured easily. Therefore, other methods have been used, including cysC concentration. Factors such as renal transplantation, glucocorticoid use, and malignancy may affect serum cysC concentration independently of GFR [2–6]. Nevertheless, cysC concentration is regarded as more accurate than SCr levels for determining kidney function, because SCr level has shown a significant positive correlation with body length in children [1] and because low SCr concentrations have been reported in selected populations of children with low muscle mass. In contrast, cysC concentration was found not to vary by age, height, or sex [7–9]. Moreover, cysC-based equations may more precisely estimate GFR than Cr-based equations in pediatric patients [2, 10–12]. These equations may be cumbersome to use in clinical practice, however, because of their complicated formulae and the need for logarithmic transformation of variables.

There have been a few previous reports of reference serum cysC levels in Japanese children. The mean serum cysC concentration in 135 healthy Japanese children aged 1–15 years was reported to be 0.67 ± 0.19 mg/L and was not influenced by age [9]. In contrast, a review of several studies of children in different age groups found that 1-year-old children had a higher serum cysC concentration than older children [13]. A study in 136 Japanese children with various renal diseases and with normal renal function, as assessed by Cr concentration, reported that cysC concentration decreased rapidly during the first 3 years of life but remained constant thereafter [14], a finding in agreement with previous reports [15]. Other studies in Japanese children with normal and decreased renal function have reported that serum cysC concentration is a more effective and accurate marker for evaluating renal function than other markers, including SCr and β2 microglobulin concentrations [16, 17], and that reference values for serum cysC were constant, regardless of age, in children aged >1 year [16].

We found that reference serum cysC concentrations gradually decreased, from about 1.5 to 0.8 mg/L, during the first year after birth and then remained relatively constant, at about 0.7 mg/L. However, we found a significant difference in serum cysC concentrations between children aged ≥1 to <2 years (0.76 ± 0.10 mg/L) and those aged and ≥2 to <7 years (0.69 ± 0.08 mg/L). Infants younger than 18 months were found to have a higher mean serum cysC concentration (0.94 ± 0.24 mg/L) than older children (0.65 ± 0.19 mg/L), as determined by the nephelometric method; in that study, however, it was difficult to accurately assess the age cutoff point at 18 months [18]. We found that serum cysC concentrations of normal children aged ≥2 years were relatively constant (0.70 ± 0.09 mg/L), indicating that serum cysC is more useful than SCr in diagnosing whether children aged ≥2 years do or do not have normal renal function. Additional research is required to compare the utility of serum cysC with SCr in estimating renal function in Japanese pediatric CKD patients.

Conclusion

We found that reference serum cysC levels gradually decreased during the year after birth, with children aged 1 having a slightly higher concentration (0.76 ± 0.10 mg/L) than children aged ≥2 years (0.70 ± 0.09 mg/L). Our reference values will therefore be applicable for the screening of renal function in Japanese children.

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