Received: 21 March 2018 | Revised: 25 June 2018 | Accepted: 27 July 2018

DOI: 10.1002/hsr2.85

RESEARCH ARTICLE

WILEY Health Science Reports Open Access

Improvement of renal function estimation equations for elderly Japanese people

Soyoko Kaburaki[1] | Eri Yoshimura[2] | Nozomi Kojima[2] | Hidefumi Ueno[2] | Mitsuru Sugawara[3] | Yoh Takekuma[3]

[1] Graduate School of Life Science, Hokkaido University, Sapporo, Japan

[2] Department of Pharmacy, Sunagawa City Medical Center, Sunagawa, Japan

[3] Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

Correspondence
Yoh Takekuma, PhD, Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12-jo, Nishi-6-chome, Kita-ku, Sapporo 060-0812, Japan.
Email: y-kuma@pharm.hokudai.ac.jp

Funding information
The Japan Foundation for Aging And Health

Abstract

Background and aim: The Cockcroft-Gault (C-G) equation for estimation of creatinine clearance (CCr) is still used in a clinical setting for drug dosage adjustment. Because differences between measured and estimated CCr values have been reported, particularly for Japanese elderly people, the aim of this study was to improve the accuracy of CCr estimation equations, such as C-G and Orita-Horio, by fitting to newly obtained data. Also, glomerular filtration rate (GFR) estimation equations, such as the Modification of Diet in Renal Disease (MDRD), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and the eGFR equation for Japanese people, were studied to compare with measured CCr.

Method: Data from 313 subjects over the age of 40 years with laboratory data available were used for analysis in this study. Special attention was paid to elderly people, and approximately 70% of the subjects were over the age of 65 years.

Results: The accuracy of estimation by the two conventional (C-G, Orita-Horio) CCr estimation equations was greatly improved by introducing adjusted body weight for which the degree of obesity is over 30% instead of measured body weight. By fitting the coefficients of the estimation equations to the present population, the mean error was reduced by almost half, particularly for people over the age of 75. Although all the values calculated by the GFR estimation equations were underestimated compared with measured CCr due to secretion, a coefficient of determination of above 0.65 was obtained for all GFR estimation equations.

Conclusions: Improvement of the fitted CCr estimation equations suggests that reconstruction of renal function estimation equations is required, especially for old people. Further work is required to find optimal renal function (CCr and/or GFR) estimation equations for drug dosage adjustment.

KEYWORDS

Cockcroft-Gault equation, creatinine clearance, elderly people, glomerular filtration rate, newly fitted equations, renal function estimation equation

1 | INTRODUCTION

1.1 | Background

People over the age of 65 account for 27.3% of the total population of Japan, and 13.4% are over 75 years of age.[1] These percentages are higher than those in other developed countries.[1] To establish appropriate pharmaceutical therapy for elderly people, physiological functions need to be evaluated properly. However, clinical trials for developing new drugs have mainly focused on younger adults. Thus, there is little knowledge about the design of drug administration for elderly people. Because physiological functions decline with age, fine adjustment depending on each function is required in pharmaceutical therapy for elderly people. The effects of renal excretion-type drugs on pharmacokinetics are particularly important for elderly people, because the renal function of elderly people, even those without any kidney disease, tends to be deteriorated.[2,3] Accurate evaluation of renal function is required to decide the doses of renal excretion-type drugs. Although the 24-hour urine collection method is the most common method to determine CCr,[4] its use is sometimes difficult for infants and elderly people, and in an emergency.[5] Therefore, a method for a quick and precise estimation of renal function is needed for deciding the doses of drugs. For adjusting drug dosage in a clinical setting, the Cockcroft-Gault (C-G) equation is used to predict kidney function by inputting parameters including sex, age, body weight, and serum creatinine (sCr) concentration.[6] However, this equation was established from a population of 249 male Westerner patients aged 18 to 92 years, in which the number of elderly patients aged over 75 years was small. Moreover, sCr values are affected by various factors, including muscle mass, exercise, and nutrition, and it has been reported that estimated CCr values calculated by the C-G equation tend to deviate from the values measured in elderly people.[7-9] In addition, attention should be given to body weight (kg), one of the input parameters for the C-G equation, because it has been reported that a difference between measured and estimated CCr values in many elderly people resulted from the use of the real body weight value.[10,11] In the last decade, there is a general trend of employing GFR instead of CCr for evaluating kidney function. However, in reference to drug dosage adjustment, whether GFR or CCr should be used, is not yet clear.[12] In any case, special attention should be paid to the administration of drugs for elderly people, because pharmacokinetics is considered to be significantly different from that in healthy adults due to various factors, such as a decline in bodily function, morbidity of several diseases, and polypharmacy.[13] In Japan, it is common to employ CCr estimation equations for the purpose of estimating kidney function and drug dosage adjustment.[14,15] Therefore, in this study, we compared the differences between measured CCr values and CCr values calculated by conventional renal function estimation equations such as the C-G equation. The measured data, almost 70% of which were from elderly patients, were used to modify the estimation equations by fitting the parameters. In the analysis of the C-G equation, accuracy of estimation was examined by using the adjusted body weight for which the degree of obesity is over 30%[16,17] instead of real body weight, and correction was made for the intercept value of the regression line in the fitting process. Along with the C-G equation, the Orita-Horio equation,[18] which was established for Japanese people to estimate CCr, was also studied to check its predictability. In this study, two modified estimation equations, the C-G equation and the Orita-Horio equation, were proposed to improve their predictive accuracies by fitting the coefficients to the present population. For the purpose of estimating renal function through the glomerular filtration rate (GFR), GFR estimation equations such as the Modification of Diet in Renal Disease (MDRD) equation[19] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations,[20] and the eGFR equation for Japanese people,[21] were calculated to evaluate correlations with measured CCr.

The aim of this study was to understand pharmacokinetics by comparing and improving renal function estimation equations with measured CCr data derived particularly from elderly subjects, over the age of 75 years.

2 | METHODS

2.1 | Study population

The data used in this study were obtained from patients over the age of 20 years who were hospitalized at Sunagawa City Medical Center, Hokkaido, Japan, during the period from January 2013 to June 2016. This population consists of hospitalized patients because accurate kidney function estimation is particularly needed for hospitalized patients. The data included only patients for whom the following laboratory data were available: CCr, sCr (enzymatic method), blood urea nitrogen (BUN), serum albumin (Alb), urinary volume, and urinary creatinine concentration (see Table 1). Patients receiving renal dialysis were excluded from this study. Only the first measurement data were used for patients who had CCr measured multiple times. The medical history of each patient was also scrutinized in detail. Attention was paid to diseases that may affect kidney functions, such as renal disease, prostatomegaly, heart failure, hepatopathy, cancer, and lifestyle-related diseases including high blood pressure, hyperlipidemia, and diabetes mellitus, and the number of patients and the percentage of the total number of patients in each generation (age group) for each of their morbidities are summarized in Table 2. Subjects were classified into the following four groups according to age: generation I (age: 20-39 years), generation II (age: 40-64 years), generation III (age: 65-74 years), and generation IV (age: over 75 years). We classified patients into these specific groups because elderly people are defined to be over the age of 65, the period of which is divided into generations III and IV, in Japan. These generations are the main target of our study. We also considered people over the age of 20, in particular generation II, 40 to 64 years, to study a change in pharmacokinetics due to aging.

2.2 | Anthropometric measurements

Height and weight of the patients were measured by hospital staff at the time of hospitalization and on the day of CCr measurement. According to the World Health Organization (WHO) classification, values for body mass index (BMI), defined as body weight (kg)/height^2 (m^2), were categorized as underweight (BMI < 18.50), normal

TABLE 1 Baseline characteristics of the subjects[a]

	All (n = 313)	Men (n = 167)	Women (n = 146)	Range
Age, y	71 (63-76.3)	71 (65.5-77)	68.47 ± 10.5	40-89
Height, m	1.58 ± 0.09	1.64 ± 0.064	1.54 ± 0.061	1.4-1.8
Body weight, kg	57.6 (51-66)	61.1 (55.85-69.08)	52.15 (46.4-60.23)	31.4-132.8
Adjusted body weight, kg	55.0 (47.6-60.1)	60.8 (55.4-67.08)	48.15 (43.12-54)	31.4-95.8
Body surface area, m^2	1.58 (1.47-1.71)	1.65 (1.58-1.78)	1.47 (1.38-1.57)	1.13-2.31
BMI, kg/m^2	23.19 (20.8-25.9)	23.22 (21.2-25.7)	23.16 (20.3-26.2)	14.81-50.0
Measured CCr, mL/min/1.73 m^2	82.18 ± 35.35	77.72 ± 34.28	87.29 ± 35.97	3.9-197.2
Urinary volume, mL	1800 (1400-2500)	1900 (1500-2600)	1700 (1300-2188)	400-6700
Urinary creatinine conc., mg/dL	50.4 (37-67.7)	56.1 (40.4-72)	44.5 (33-58.1)	11.7-253.5
Serum creatinine conc., mg/dL	0.85 (0.68-1.13)	1.01 (0.79-1.32)	0.67 (0.6-0.95)	0.33-11.6
Blood urea nitrogen, mg/dL	15.3 (11.5-19.2)	16.0 (12.5-20.9)	14.5 (10.7-18.1)	5.9-109
Serum albumin, g/dL	3.3 (2.9-3.7)	3.3 (2.9-3.6)	3.4 (3.1-3.8)	0.7-4.6

Abbreviation: BMI, body mass index.

[a]The data are represented as mean and standard deviation (mean ± S.D.) for normally distributed variables and as median and interquartile range for nonnormally distributed variables.

(18.50-24.99), overweight (25.00-29.99), and obese (≧30.00).[22] Body surface area (BSA) was calculated by the Du Bois equation: BSA (m^2) = body weight (kg)$^{0.425}$ × height (cm)$^{0.725}$ × 0.007184.[23] Taking the degree of obesity into consideration, body weights were adjusted by the following formulae:

$$\mathrm{IBW(Men)} = 50 + 2.3\times\frac{\mathrm{Height(cm)}-150}{2.5}$$
$$\mathrm{IBW(Women)} = 45 + 2.3\times\frac{\mathrm{Height(cm)}-150}{2.5}$$
$$\mathrm{ABW} = \mathrm{IBW} + 0.4\times(\mathrm{TBW}-\mathrm{IBW}).$$

Here, IBW, ABW, and TBW indicate ideal body weight, adjusted body weight, and total body weight, respectively. The degree of obesity is defined as (TBW-IBW) ×100/IBW (%). Generally, body weight was adjusted to IBW for subjects for whom the degree of obesity was between 30% and 100%. Adjusted body weight (ABW) was used for weight when the degree of obesity was over 100%.[16,17]

2.3 | Measurements of CCr and biochemical parameters

Creatinine clearance (CCr) was measured by 24-hour urine collection. Serum creatinine (sCr) and urinary creatinine concentration were measured by the enzymatic method used in Japan.[24] Clinical histories used in this study were only those for patients who showed morbidity on the day of the medical examination. Creatinine excretion per body weight was calculated by the following formula: Creatinine excretion (mg/BWkg/day) = urinary creatinine concentration (mg/dL) × 1/100 × urinary volume (mL) × body weight (kg).

All the data are presented in Table 1 using standard descriptive statistics as mean and standard deviation for normally distributed variables, and median and interquartile range for nonnormally distributed variables. The Jarque-Bera test was used to check the normality of distribution for each variable, with a critical value of $p = 0.05$.

2.4 | Renal function estimation equations

We focused on the following renal function estimation equations. The Cockcroft-Gault equation,[3] the MDRD equation,[19] and the CKD-EPI equation[20] were proposed in Canada or the United States and have been widely used in Japan. The Orita-Horio equation[18] was proposed mainly for Japanese people and was, thus, also used to analyze the data in this study. In addition, the CKD-EPI equation[17] and the eGFR equation for Japanese people,[21] both of which have been adjusted to Japanese people, were employed to analyze the present population. In this study, all of the estimations by the equations were represented on a per BSA basis.

*Cockcroft-Gault (C-G) equation[6]

$$\mathrm{Men:\ CCr(mL/min)} = \frac{(140-\mathrm{Age})\times\mathrm{Body\ Weight(kg)}}{72\times\mathrm{sCr}}$$
$$\mathrm{Women:\ CCr(mL/min)} = \frac{(140-\mathrm{Age})\times\mathrm{Body\ Weight(kg)}}{72\times\mathrm{sCr}}\times 0.85$$

*Orita-Horio equation[18]

$$\mathrm{Men:\ CCr(mL/min)} = \frac{(33-0.065\times\mathrm{Age}-0.493\times\mathrm{BMI})\times\mathrm{Body\ Weight(kg)}}{\mathrm{sCr}\times 14.4}$$
$$\mathrm{Women:\ CCr(mL/min)} = \frac{(21-0.030\times\mathrm{Age}-0.216\times\mathrm{BMI})\times\mathrm{Body\ Weight(kg)}}{\mathrm{sCr}\times 14.4}$$

*MDRD equation[19]

$$\mathrm{Men:\ GFR\ (mL/min/1.73m^2)} = 170\times\mathrm{sCr}^{-0.999}\times\mathrm{Age}^{-0.176}\times\mathrm{BUN}^{-0.170}\times\mathrm{Alb}^{0.318}$$
$$\mathrm{Women:\ GFR\ (mL/min/1.73m^2)} = 170\times\mathrm{sCr}^{-0.999}\times\mathrm{Age}^{-0.176}\times\mathrm{BUN}^{-0.170}\times\mathrm{Alb}^{0.318}\times 0.762$$

TABLE 2 Clinical histories of subjects. The number in () indicates of the disease based on the total number of subjects (n) of each generation (%)

	Generation			
	II (n=88)	III (n=122)	IV (n=103)	all (n=313)
Kidney disease				
Nephrotic Syndrome	0 (0)	3 (2.46)	1 (0.97)	4 (1.28)
IgA nephropathy	0 (0)	0 (0)	0 (0)	0 (0)
Diabetic nephropathy	2 (2.27)	0 (0)	3 (2.91)	5 (1.60)
Cystitis	0 (0)	1 (0.82)	0 (0)	1 (0.32)
Overactive Bladder	0 (0)	1 (0.82)	5 (4.85)	6 (1.92)
Hydronephrosis	1 (1.14)	3 (2.46)	4 (3.88)	8 (2.56)
Kidney failure	5 (5.68)	10 (8.20)	5 (4.85)	20 (6.39)
Others	8 (9.09)	9 (7.38)	12 (11.65)	29 (9.27)
Genital Disease				
Prositatic hypertrophy	1 (1.14)	9 (7.38)	14 (13.59)	24 (7.67)
Heart failure				
Heart failure	4 (4.55)	9 (7.38)	15 (14.56)	28 (8.95)
Myocardial infraction	0 (0)	1 (0.82)	3 (2.91)	4 (1.28)
Arrhythmia	1 (1.14)	0 (0)	2 (1.94)	3 (0.96)
Liver disease				
Hepstic cirrhosis	1 (1.14)	0 (0)	1 (0.97)	2 (0.64)
Hepatitis	7 (7.95)	5 (4.10)	4 (3.88)	16 (5.11)
Hyperammonemia	2 (2.27)	1 (0.82)	4 (3.88)	7 (2.24)
Hyperammonemia	0 (0)	0 (0)	0 (0)	0 (0)
Cancer				
Kidney				
Kidney	10 (11.36)	14 (11.48)	10 (9.71)	34 (10.86)
Nephrocyte	1 (1.14)	0 (0)	1 (0.97)	2 (0.64)
Pelvis renalis	2 (2.27)	4 (3.28)	9 (8.74)	15 (4.79)
Bladder	4 (4.55)	17 (13.93)	5 (4.85)	26 (8.31)
Ureter, Urethra	0 (0)	0 (0)	0 (0)	0 (0)
Genitalia				
Prostate	0 (0)	6 (4.92)	8 (7.77)	14 (4.47)
Tumour				
Kidney	3 (3.41)	0 (0)	0 (0)	3 (0.96)
Adrenal gland	0 (0)	0 (0)	3 (2.91)	3 (0.96)
Lifestyle-related disease				
Hypertension	18 (20.45)	23 (18.85)	27 (26.21)	68 (21.73)
Hyperlipidemia	4 (4.55)	13 (10.66)	14 (13.59)	31 (9.90)
Diabetes mellitus	13 (14.77)	18 (14.75)	11 (10.68)	36 (11.50)

*CKD-EPI equation for Japanese people[20]

$$\text{Men: } GFR = 144\times(sCr/0.9)^{-0.411}\times0.993^{Age}\times0.813 \quad (sCr\leqq0.9)$$

$$GFR = 144\times(sCr/0.9)^{-1.209}\times0.993^{Age}\times0.813 \quad (sCr>0.9)$$

$$\text{Women: } GFR = 144\times(sCr/0.9)^{-0.329}\times0.993^{Age}\times0.813 \quad (sCr\leqq0.7)$$

$$GFR = 144\times(sCr/0.9)^{-1.209}\times0.993^{Age}\times0.813 \quad (sCr>0.7)$$

*eGFR equation for Japanese people[21]

$$\text{Men: } eGFR = 194\times sCr^{-1.094}\times Age^{-0.287}$$

$$\text{Women: } eGFR = 194\times sCr^{-1.094}\times Age^{-0.287}\times0.739$$

2.5 | Statistical analysis

Measured and estimated values of CCr were plotted on the ordinate and abscissa, respectively, and the regression equation was derived for each generation. Regression lines were derived by the Deming regression method. Differences between the measured and estimated values of CCr were analyzed by using the following mean prediction error (ME%) and mean absolute prediction error (MAE%) indices[25]:

$$ME(\%) = \frac{1}{n}\sum_{i=1}^{n}\left[\frac{\text{predicted CCr-CCr}}{CCr}\times100\right],$$

$$MAE(\%) = \frac{1}{n}\sum_{i=1}^{n}\left[\frac{|\text{predicted CCr-CCr}|}{CCr}\times100\right].$$

New coefficients were derived for the C-G and Orita-Horio equations by fitting to the measured data of CCr. All of the statistical analyses, including fitting, were performed by using Origin2017 (OriginLab Corp., Massachusetts, USA). In this study, all two-sided p values were calculated by the t test. The coefficient of determination (R^2), which is

the square of the Pearson correlation coefficient, was used to study correlations between measured CCr values and GFR estimation equations. A Bland-Altman plot for a difference versus an average for measured and estimated CCr values with 95% confidence interval (CI), was done for the fitted C-G and Orita-Horio equation, and the figures are shown in Supporting Information.

2.6 | Ethics guidelines

Researchers in this study complied with the Declaration of Helsinki and ethics guidelines for human clinical trials. This study was approved by the Ethics Committee of the Faculty of Pharmaceutical Sciences, Hokkaido University (2016-004). All the patients enrolled in this study were informed that their data could be used for research and that they could opt out, and that this protocol was approved by the Institutional Review Board (IRB) of Sunagawa City Medical Center.

3 | RESULTS

3.1 | Study population

Data from 313 subjects, including 167 men and 146 women, were used for analysis. Data for generation I were excluded from the analysis due to the small number of subjects (one man and six women). Generation II included 88 subjects (38 men and 50 women), generation III included 122 (69 men and 53 women), and generation IV included 103 (60 men and 43 women). Baseline characteristics of the subjects are summarized in Table 1. Overall, sCr and weight for women were significantly lower than those for men ($p < 0.05$, t test). In the present population, women showed a significantly higher CCr level than that in men ($p < 0.05$, t test). The clinical histories of subjects are shown in Table 2. In the clinical histories, the following diseases that may influence kidney function were considered: renal disease, prostatomegaly, heart failure, hepatopathy, cancer, and lifestyle-related diseases including high blood pressure, hyperlipidemia, and diabetes mellitus. Figure 1 shows CCr changes with aging. It can be seen in Figure 1 that CCr decreased with age at a rate of 1.17 mL/min/1.73m^2 per year over the age of 40 years. We observed that generation IV showed the largest reduction in CCr per year compared with other generations.

3.2 | Comparison of renal function estimation equations

The mean value (±SD) of measured CCr was 90.48 ± 40.38 mL/min/1.73m^2. The mean values (±SD) of CCr estimated by the C-G and Orita-Horio equations were 64.25 ± 26.99 mL/min/1.73m^2 and 78.33 ± 29.33 mL/min/1.73m^2, respectively. In addition, the mean values of GFR estimated by MDRD, CKD-EPI, and eGFR equation for Japanese people were 77.30 ± 31.92 mL/min/1.73m^2, 65.55 ± 23.05 mL/min/1.73 m, and 59.72 ± 23.95 mL/min/1.73m^2, respectively. Figure 2 shows a plot of measured values versus values estimated by each of the kidney function estimation equations. The

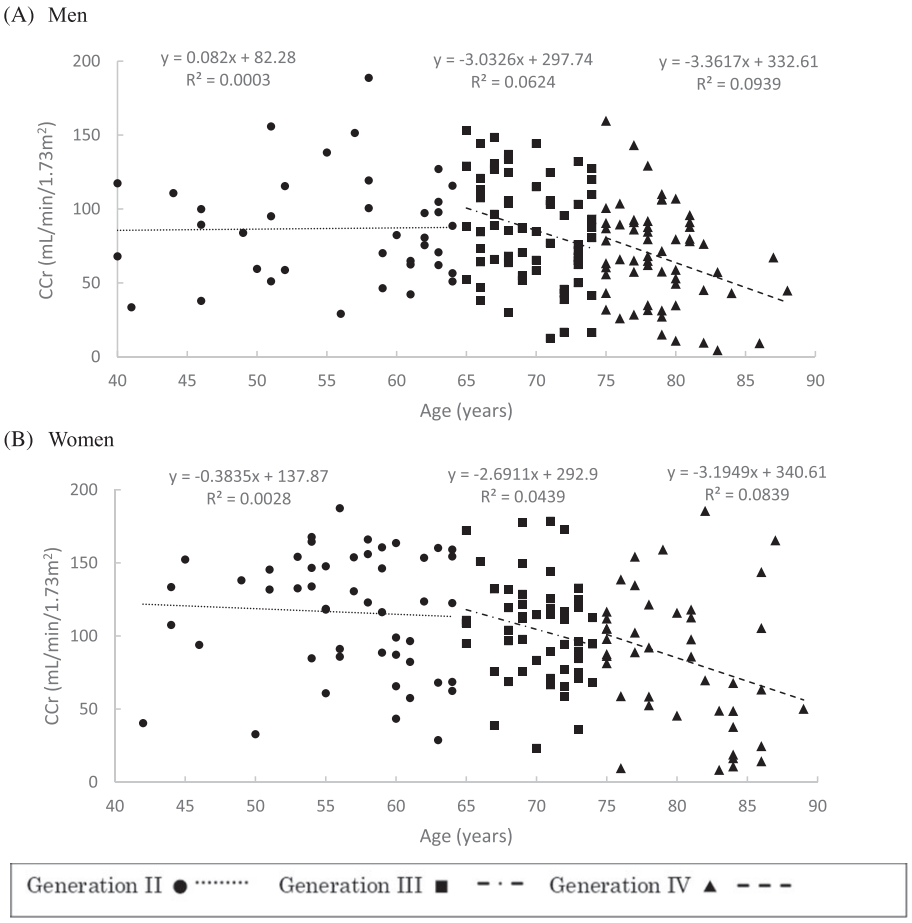

FIGURE 1 Changes in creatinine clearance with age (A: men, B: women)

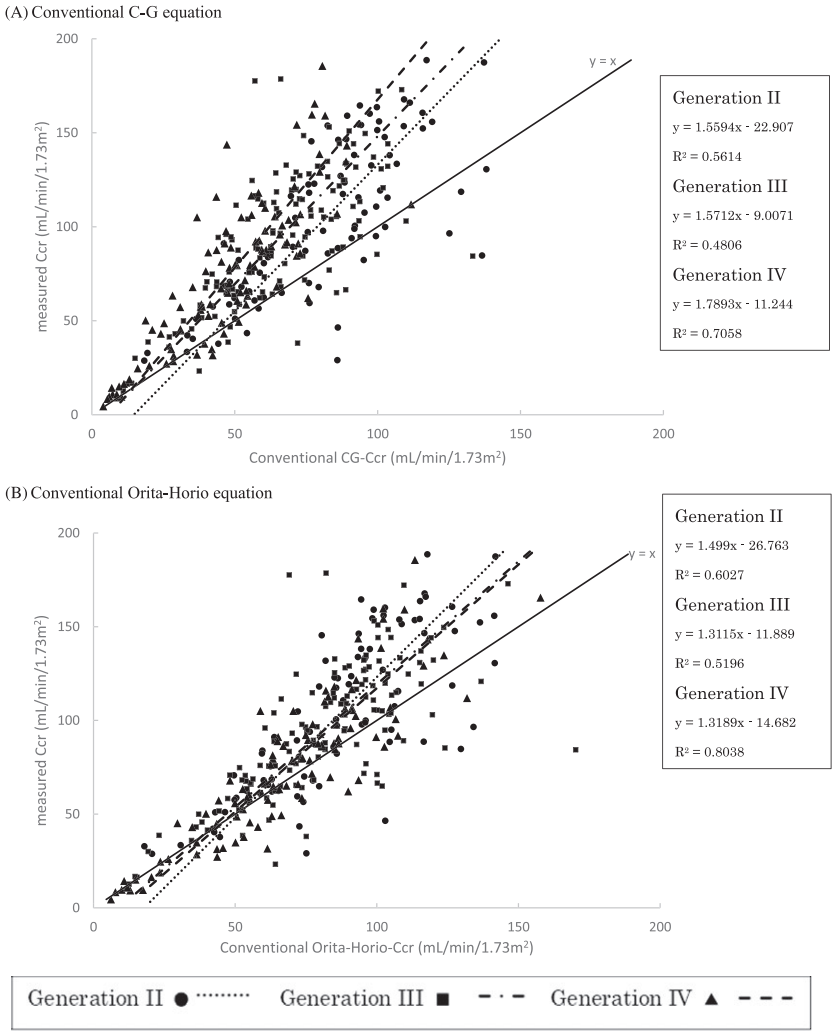

FIGURE 2 Relationship between measured CCr and estimated CCr by (A) conventional C-G equation and (B) conventional Orita-Horio equation. If the plot falls on the ideal line ($y = x$), the estimated value coincides with the measured value. The formula results in underestimation or overestimation when the slope of the regression line is greater or smaller than one, respectively

regression lines are also shown. It can be seen in Figure 2 that the two estimation equations, the conventional C-G and Orita-Horio equations, resulted in underestimation of kidney function (CCr) for people over the age of 40 years. All the GFR values estimated by the MDRD, CKD-EPI, and eGFR equation for Japanese people were lower than measured CCr due to secretion rates (data not shown). The results presented in Figure 2A,B show that all of the conventional estimation equations underestimated values of CCr for subjects over the age of 40 years. Therefore, we studied in detail the extents of the deviation of the estimated values from the measured values. The values of ME (%) and MAE (%) in terms of the two estimation equations are summarized in Table 3. The values of ME (%) and MAE (%) for the C-G equation were higher than those for the Orita-Horio equation across all generations, and the deviations were particularly large for generation IV. On the other hand, the values predicted by the Orita-Horio equation were closest to the measured values across all generations. The coefficient of determination (R^2) between measured CCr and estimated GFR calculated by the MDRD, CKD-EPI, and eGFR equation for Japanese people are shown in Table 4. Figure 3A-C shows the relationship between measured CCr and GFR estimated by the MDRD, CKD-EPI equation, and eGFR equation for Japanese people. The results indicate that, when the value of measured CCr was 100 mL/min/1.73m^2, the corresponding estimated values of GFR were 79.41 mL/min/1.73m^2 for MDRD, 71.09 mL/min/1.73m^2 for CKD-EPI, and 65.36 mL/min/1.73m^2 for eGFR equation for Japanese people. All the values of the GFR estimation equations were underestimated compared with measured CCr due to creatinine secretion. In the case of CKD-EPI, a reduction of almost 30% was observed.

TABLE 3 ME (%) and MAE (%) values for overall subjects and subjects in generations II-IV in reference to three kidney function estimation equations

	Cockcroft-Gault		Orita-Horio	
	ME (%)	MAE (%)	ME (%)	MAE (%)
All (n = 313)	−44.42	48.32	−14.96	24.96
Generation II (n = 88)	−28.65	35.25	−19.31	28.15
Generation III (n = 122)	−46.51	50.20	−18.29	26.56
Generation IV (n = 103)	−55.40	57.25	−7.31	20.36

Abbreviations: MAE, mean absolute prediction error; ME, mean prediction error.

3.3 | Reconstruction of CCR estimation equations by fitting

The subjects in this study cover a wide range of ages, and include elderly subjects with various diseases. Therefore, we tried to derive a new set of coefficients by fitting the two CCr estimation equations to the

TABLE 4 The coefficient of determination (R^2) in each estimation equation

	R^2			
	All	Generation II	Generation III	Generation IV
C-G	0.59694166	0.56136058	0.48059556	0.70581842
Orita-Horio	0.66264484	0.60268827	0.51963914	0.80381983
MDRD	0.66497501	0.59079208	0.53418557	0.8120533
CKD-EPI	0.66745632	0.57191406	0.5929308	0.74540776
eGFR	0.6566185	0.61268191	0.50515135	0.79652055

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

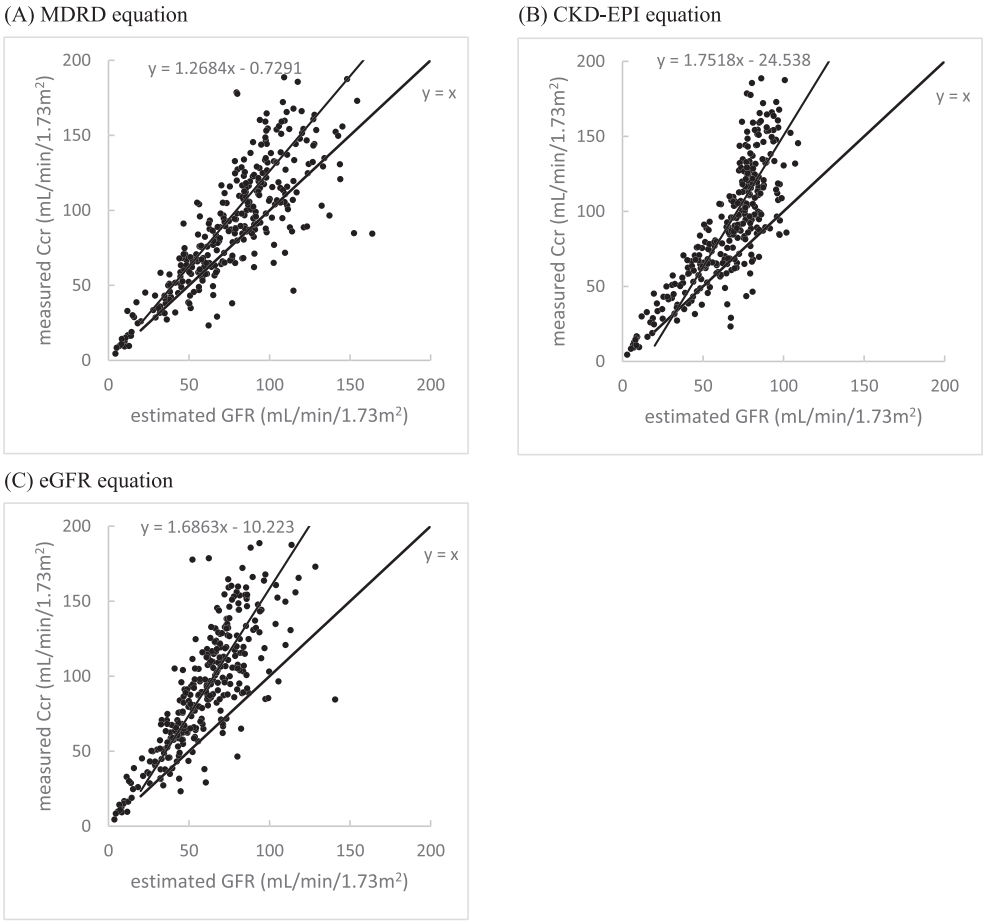

FIGURE 3 Relationship between measured CCr and GFR estimated by GFR estimation equations. A, Modification of Diet in Renal Disease (MDRD) equation. B, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. C, glomerular filtration rate (GFR) estimation equation

present population of subjects. The equation forms before and after the fitting process are summarized below. The values of ME (%) and MAE (%) for the C-G and Orita-Horio equations after the fitting are shown in Table 5. Figure 4A,B shows the relationship between measured and estimated values of CCr after the fitting process. Compared with Figure 2A,B, the regression line of each estimation equation after the fitting was closer to the ideal line ($y = x$). It can also be seen in Table 5 that the difference between measured and estimated values of CCr was substantially reduced for all equations after the fitting. The ME (%) and MAE (%) values of the C-G equation were reduced to less than half after the fitting, particular for generation IV.

The results of the Bland-Altman plot with 95% CI for the fitted C-G and Orita-Horio equations (see the figures in Supporting Information) showed that no systematic errors were observed, and the extent of scatters was small for the fitted Orita-Horion equation compared with the C-G equation.

TABLE 5 ME (%) and MAE (%) values of estimation equations after fitting

	Cockcroft-Gault		Orita-Horio	
	ME (%)	MAE (%)	ME (%)	MAE (%)
All (n = 313)	−5.50	20.85	−1.24	17.69
Generation II (n = 88)	−3.34	19.58	−1.43	18.18
Generation III (n = 122)	−5.73	20.81	−4.02	18.45
Generation IV (n = 103)	−1.68	19.32	2.12	16.54

Abbreviations: MAE, mean absolute prediction error; ME, mean prediction error.

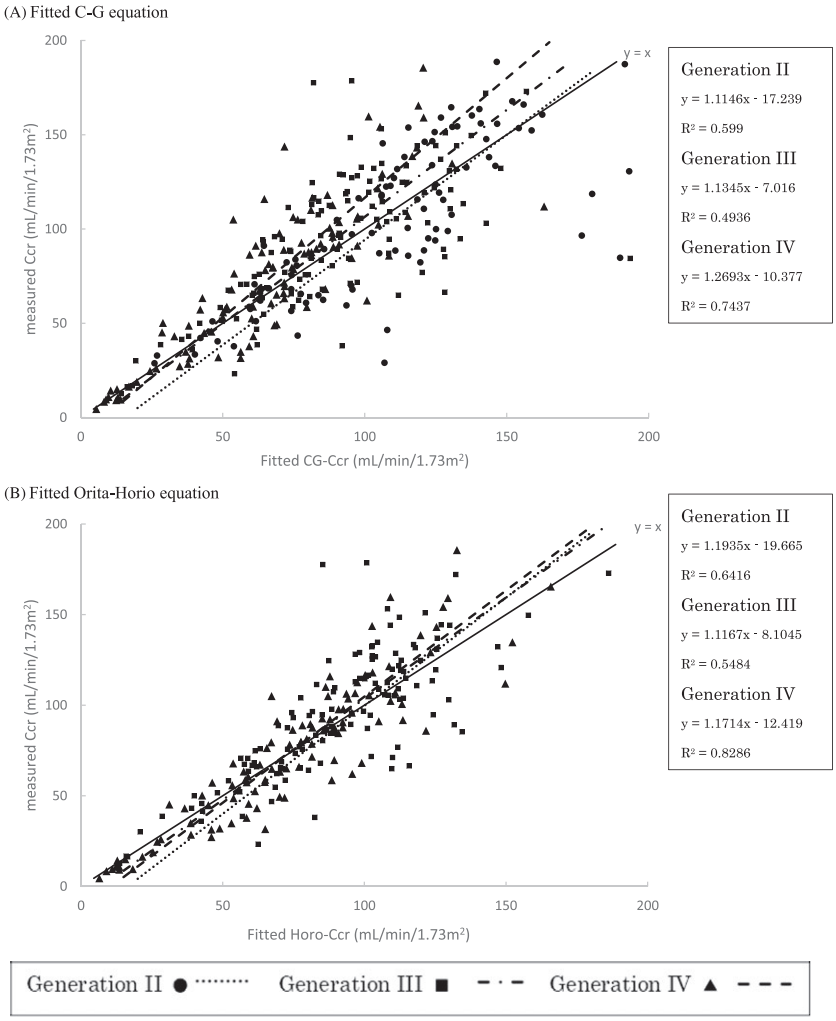

FIGURE 4 Relationship between measured CCr and estimated CCr by the newly fitted estimation equations. A, Fitted C-G equation. B, Fitted Orita-Horio equation

Fitted renal function (CCr) estimation equations

- C-G equation

After fitting

$$\text{Men: } Ccr = \frac{(160-Age)\times ABW(kg)}{72\times sCr}$$

$$\text{Women: } Ccr = \frac{(155-Age)\times ABW(kg)}{72\times sCr} = \frac{(160-Age)\times ABW(kg)}{72\times sCr}\times 0.96$$

- Orita-Horio equation

After fitting

$$\text{Men: } Ccr = \frac{(38-0.112\times Age-0.509\times BMI)\times BW(kg)}{14.4\times sCr}$$

$$\text{Women: } Ccr = \frac{(32-0.086\times Age-0.418\times BMI)\times BW(kg)}{14.4\times sCr}$$

3.4 | Relationship between age and creatinine excretion

The mean values of creatinine excretion were 0.96 ± 0.35 g/day (mean ± SD) for the entire cohort, 1.12 ± 0.35 g/day for men and 0.78 ± 0.24 g/day for women. It was found that creatinine excretion decreased 0.019 g/day per year with age. Creatinine excretion for men was significantly different from that for women ($p < 0.05$, t test). Figure 5 shows the relationship between creatinine excretion (mg/day/BWkg) and age. The reduction of creatinine excretion was more conspicuous for generation IV (over 75 years old) than for other generations.

3.5 | Relationship between creatinine excretion and BMI

The relationship between creatinine excretion (mg/day/BWkg) and BMI is shown in Figure 6. The measured values of creatinine excretion were found to be inversely proportional to BMI. There seemed to be no correlation between BMI and age (data not shown).

4 | DISCUSSION

The cohort in the present study consisted of 313 Japanese people over the age of 40 years, with a tendency for the morbidity rate to increase with age. According to the Ministry of Health, Labour, and Welfare of Japan, the number of people over the age of 65 years who receive medical examinations and require hospitalization is increasing compared with the numbers in other age groups.[26] It is

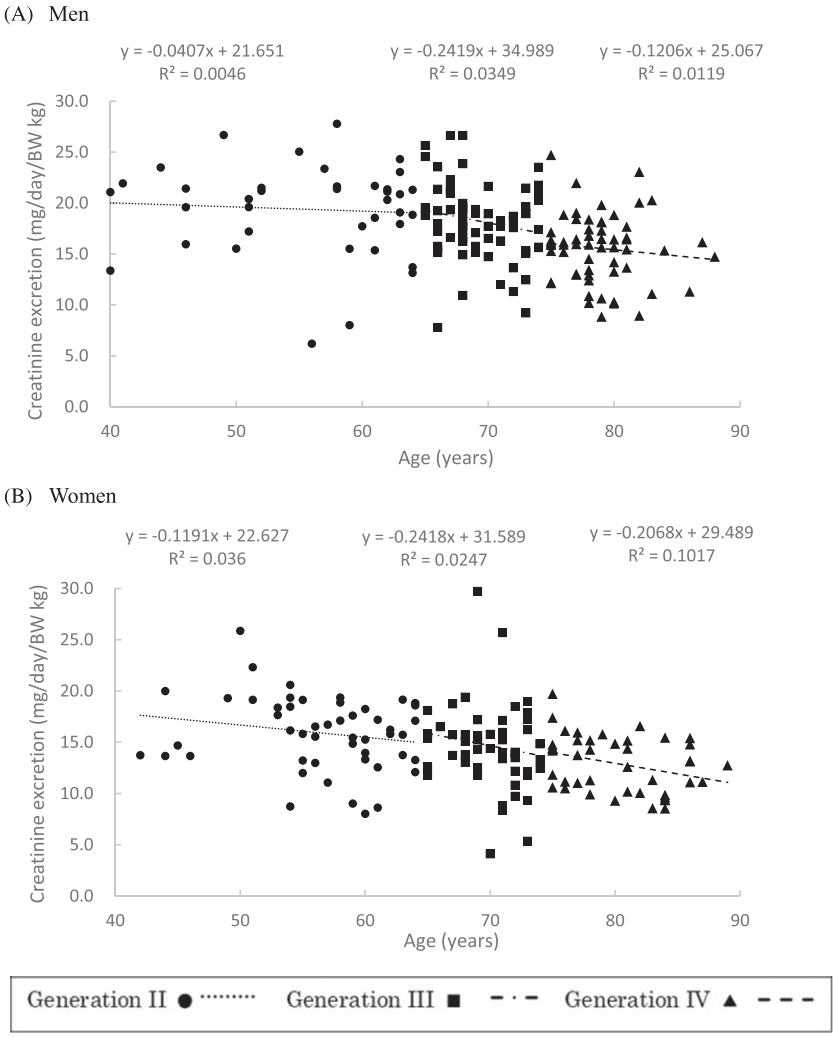

FIGURE 5 Relationship between creatinine excretion (mg/day/BWkg) and age (A: men, B: women)

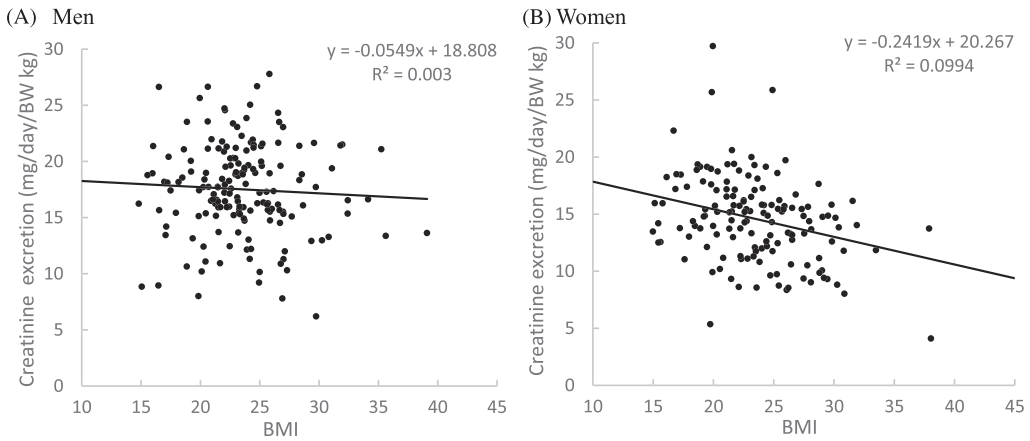

FIGURE 6 Relationship between creatinine excretion (mg/day/BWkg) and BMI (A: men, B: women)

obvious that bodily functions decline with age and that renal function differs depending on age even in the same ethnic group.[27] Thus, an appropriate kidney function estimation equation is needed for improvement of therapeutic efficacy and for prevention of drug adverse effects due to high or low dosages.

Table 1 shows the laboratory data for subjects in this study. Because the present population covered a wide range of sCr, the results of this study should be useful for estimating renal function of patients, such as a decrease and increase of sCr due to the reduction of muscle mass with age and renal failure, respectively.

The relationship between measured CCr and age is shown in Figure 1. The figure shows a reduction of renal function with age. In the United States, it has been reported that the GFR decreases 4 mL/min/1.73m^2 per 10 years in persons under 45 years old, while it decreases twice as fast (8 mL/min/1.73m^2 per 10 years) in persons over 45 years old.[28] A recent report shows that the decrease in GFR

starts around the age of 40 years, with a rate of approximately 1 mL/min/1.73m^2 per year.[29] The present study also showed that the measured values of CCr were almost constant up to the age of 64 years and started to decrease with age, with reductions of 3.0 mL/min/1.73m^2 per year for men and 2.7 mL/min/1.73m^2 per year for women between 65 and 74 years of age, and 3.4 mL/min/1.73m^2 per year for men and 3.2 mL/min/1.73m^2 per year for women of over 75 years of age. Thus, CCr values tend to decrease with age for both men and women. The reduction of CCr becomes noticeable after 65 years of age and reaches a maximum after 75 years of age. Considering the above findings, caution is needed in the direct application of the empirical renal function estimation equations, which were established on the basis of populations in the United States and Europe, to the Japanese population, due to ethnic and age differences as well as differences in medical history. In the present study, there were few patients with a renal disorder included in generation II (age: 40-64 years). Therefore, there seems to be no need to correct the C-G equation for generation II. However, correction of the C-G equation is required for generations III and IV (over the age of 65 years) due to the sharp reduction of renal function, as shown above.

Among the two CCr estimation equations considered in this study, the estimated values of CCr using the C-G equation deviated the most from the measured values, and the deviations increased gradually with advance age. The ME (%) and MAE (%) values for the C-G equation reached maximum values in generation IV (age: over 75 years) before the fitting process, when the MAE (%) value was 57.5%. Therefore, the conventional C-G equation should not be used for estimating renal function in people over 75 years of age. Because the C-G equation is convenient in a clinical setting, a new set of parameters was derived by fitting it to the present population for respective generations. Notably, the MAE (%) value of generation IV was decreased from 57.5% to 19.32%. With the newly adjusted C-G equation, the design of drug administration will be improved drastically, especially in estimating renal function for generation IV, which may lead to an understanding of pharmacokinetics for older generations. In this study, we fit the C-G equation to the partial data corresponding to respective generations; however, few differences were found between the fit to the whole data and the fits to the partial data (data not shown). Therefore, for the convenient use in a clinical setting, we employed the C-G equation fitted to the whole data including all generations. Instead of the coefficient value of 140 in the conventional C-G generation, accurate prediction of renal function for men in the present study was achieved by using the fitted value of 160. In the case of women, the coefficient value for men multiplied by 0.96 was found by fitting. The difference between renal function in men and women was, thus, found to be minor. The fact that the intercept value of the C-G equation was increased from 140 to 160 in the present population indicated that the reduction of renal function with age for Japanese is likely be less than that for Americans and Europeans. The C-G equation is generally used in a clinical setting for simply estimating renal function. This equation was originally derived in reference to Americans and Europeans, and it was not particularly adapted for elderly people.[6] A difference in estimated values of renal function is likely to occur due to ethnic differences in body composition, such as the mass of muscle, fat, and body water.[30] Because the form and input parameters for the C-G equation are simple and useful for easy estimation of renal function in a clinical setting, modification of the equation, as conducted in this study, will enhance its usability.

One of the features of this study is that the subjects had a wide range of sCr values compared with the values for subjects in other studies. It is predicted that sCr values depend greatly on pathological conditions and body compositions of subjects.[31,32] Determination of the effect of pathological conditions and body compositions on values estimated by the C-G equation will contribute to an understanding of the difference in sCr values.

In the Orita-Horio equation, which was established for Japanese people, BMI was incorporated as an additional parameter into the C-G equation. Horio et al showed by multiple regression analysis that BMI, which is an index of the degree of obesity, is a controlling factor of creatinine excretion/BW (kg), and they proposed a formula by introducing BMI to correct the age factor.[18] However, BMI only indicates the degree of obesity calculated from height and body weight. It is generally predicted that elderly people develop edema due to disease or decline of renal function with age.[33] In people who gain weight due to edema, BMI may not be a controlling factor for sCr because of the loss of muscle mass. Correction is required for a parameter concerning physical condition in an estimation equation for subjects whose body composition is extremely deviated from the average value. Adjusted body weight (ABW) was used in the C-G equation, as in this study, while BMI was incorporated in the Orita-Horio equation. In other studies, lean body mass (LBM) has been used.[31,34]

The slope of the regression line was larger for generation II (40-64 years old) than for other generations in the relation between creatinine excretion and age (Figure 5). Thus, over the age of 65, creatinine excretion started to decrease in the older generations. Horio et al reported that the decrease in creatinine excretion with age is less for Japanese than for Americans and Europeans, and the same trend was also found in the present study.[18] Also, in the present study, the change in BMI with age was found to be relatively small (data not shown). We showed that urinary creatinine excretion/BW (kg) tends to decrease as BMI increases (Figure 6), as was pointed out by The Ministry of Health, Labour and Welfare of Japan.[13] However, focusing more on the change of body composition with age along with BMI is considered to lead to an accurate estimation of renal function, in particular in latter-stage elderly people.[31,35]

Bretagne et al reported that there is a possibility of overestimation of renal function using the C-G equation for patients with low LBM, which is determined by a Tomography, X-Ray Computed (CT) scan, and that the method using the cystatin C, which is independent of muscle mass, is better suited for such patients.[31] However, in the process of estimating renal function using cystatin C, it is not clear how factors such as adrenocortical steroid, medicine, and pregnancy affect measured data. On the other hand, this method is considered to be effective for people, particularly elderly people, whose muscle mass has been extremely decreased or whose body composition has been substantially altered. The applicability of the renal function estimation method using cystatin C for elderly people should continue to be studied in future works.

The MDRD equation was developed for staging chronic kidney disease (CKD) rather than adjusting drug dosage. In Japan, Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012[28] recommends the use of the MDRD equation for staging CKD. In this study, it was found that an improved correlation with measured CCr was achieved by using GFR estimated by the MDRD equation compared with using CCr estimated by the conventional C-G equation. However, it has been reported that the C-G equation is better suited for predicting renal function in early stage CKD patients and elderly people.[36] On the other hand, in the case of an obese population, the MDRD equation is found to be better for drug dosage adaptation.[37] Therefore, for drug dosage adjustment, whether we should employ the C-G equation or the MDRD equation depends on the target population.

The correlation between measured CCr and estimated GFR calculated by the CKD-EPI equation adjusted for Japanese people was found to be almost the same as that by the MDRD equation. The difference between the CKD-EPI equation designed for Japanese people and the MDRD equation designed for Westerners was small because the CKD-EPI equation used here was not particularly adjusted for elderly people. Because the values of sCr for elderly patients vary significantly depending on the pathology of the disease, the criteria of the sCr values for the CKD-EPI equation should be adjusted.

In the same way, the correlation between measured CCr and estimated GFR calculated by the eGFR equation for Japanese people was found to be the same as that between measured CCr and estimated CCr calculated by the fitted C-G equation. A better correlation was obtained by the fitted Orita-Horio equation, because this equation contains BMI as a parameter to correct body composition. Further work should focus on such factors that affect the pharmacodynamics of elderly people, such as body composition and sarcopenia.

It is difficult at this point to establish the index of kidney function for drug dosage adjustment. Further study is needed to clarify the relation between CCr and GFR and to establish the optimal use of each kidney function estimation equation.

5 | CONCLUSION

The accuracy of data obtained by two conventional creatinine clearance (CCr) estimation equations was investigated by comparison with measured data from 313 subjects over the age of 40 years. The subjects, which included a large number of elderly subjects, were divided into three generation groups, and a detailed comparison of data in the generation groups was made. Both renal function estimation equations, the Cockcroft-Gault (C-G) and Orita-Horio equations, were greatly improved by fitting the coefficients of the estimation equations, particularly for the elderly subjects. The results suggest that the newly fitted Cockcroft-Gault equation incorporating adjusted body weight instead of measured body weight should be used for estimating creatinine clearance as renal function due to its usability. In addition, for the purpose of estimating renal function through GFR, three GFR estimation equations, the MDRD, the CKD-EPI, and eGFR equation for Japanese people, were studied by comparing with measured CCr, and a coefficient of determination of above 0.65 was obtained. Further work should explore the optimal renal function estimation equations for drug dosage adjustment.

ACKNOWLEDGMENTS

Funding from the Japan Foundation For Aging And Health is gratefully acknowledged.

CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Yoh Takekuma
Data Curation: Eri Yoshimura, Nozomi Kojima, Hidefumi Ueno
Formal Analysis: Soyoko Kaburaki
Funding Acquisition: Yoh Takekuma
Investigation: Soyoko Kaburaki
Supervision: Hidefumi Ueno, Mitsuru Sugawara
Visualization: Soyoko Kaburaki
Writing-original draft: Soyoko Kaburaki
Writing-review and editing: Soyoko Kaburaki

ORCID

Soyoko Kaburaki http://orcid.org/0000-0002-0798-5274
Mitsuru Sugawara http://orcid.org/0000-0001-5350-2950
Yoh Takekuma http://orcid.org/0000-0002-4325-0785

REFERENCES

1. Ministry of Internal Affairs and Communications of Japan Department of Statistics. Statistics Topics No.97 (September 18, 2016). http://www.stat.go.jp/data/topics/topi971.htm
2. Won HJ, Chung G, Lee KJ, et al. Evaluation of medication dosing errors in elderly patients with renal impairment. *Int Journal of Clinical Pharmacology and Therapeutics*. 2018;56(08):358-365. https://doi.org/10.5414/CP203258
3. Chung SM, Lee DJ, Hand A, Young P, Vaidyanathan J, Sahajwalla C. Kidney function changes with aging in adults: comparison between cross-sectional and longitudinal data analyses in renal function assessment. *Biopharm Drug Dispos*. 2015;36(9):613-621.
4. Kumar BV, Mohan T. Retrospective comparison of estimated GFR using 2006 MDRD, 2009 CKD-EPI and Cockcroft-Gault with 24 hour urine creatinine clearance. *J Clin Diagn Res*. 2017;5(11):BC09-BC12.
5. Aizawa M, Hayashi K, Shimaoka T, Yamaji K, Horikoshi S, Tomino Y. Comparison of prediction equations of glomerular filtration rate of Japanese adults. *Jpn J Nephrol*. 2006;48(2):62-66.
6. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
7. Drusano GL, Muncie HL, Hoopes JM, Damron DJ, Warren JW. Commonly used methods of estimating creatinine clearance are inadequate for elderly debilitated nursing home patients. *J Am Geriatr Soc*. 1988;36(5):437-441.
8. Iijima H, Tamano T, Imai Y, et al. Discrepancy between the estimated and actual survey of creatinine clearance. *Jpn J Med Technol*. 2008;57(5):828-835.
9. Dowling TC, Wang ES, Ferrucci L, Sorkin JD. Glomerular filtration rate equations overestimate creatinine clearance in older individuals enrolled in the Baltimore longitudinal study on aging (BLSA): impact on renal drug dosing. *Pharmacotherapy*. 2013;33(9):912-921.
10. Chaverri-Ferandez JM, Zavaleta-Monestel E, Diaz-Madriz JP, Ortiz-Urena A, Ramirez-Hernandez M, Trejos-Morales K. Analysis of the

concordance between the estimated values of creatinine clearance using the Cockcroft-Gault equation and the real value determined in patients from the Hospital Clinica Biblica. *Farm Hosp*. 2016; 40(1):3-13.

11. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clin J Am Soc Nephrol*. 2010;5(6):1003-1009.
12. Stevens LA, Nolin TD, Richardson MM, et al. Comparison of drug dosing recommendations based on measured GFR and kidney function estimation equations. *Am J Kidney Dis*. 2009;54(1):33-42.
13. Ministry of Health, Labour and Welfare of Japan. Survey of Medical Care Activities in Public Health Insurance. (July 25, 2017) http://www.mhlw.go.jp/toukei/saikin/hw/sinryo/tyosa16/dl/gaikyo2016.pdf
14. Yajima A, Ogawa C, Yatabe M, et al. Reliability of predicted renal function in Japanese patients on cisplatin therapy. *Pharmazie*. 2013;68(9):777-781.
15. Yajima A, Uesawa Y, Ogawa C, et al. Construction of a model for predicting creatinine clearance in Japanese patients treated with cisplatin therapy. *Anticancer Res*. 2015;35(5):2909-2914.
16. Echizen H. Yakubutsu touyo keikaku manual. (in Japanese) IGAKU-SHOIN Japan, 1986;21–23.
17. Kanno T. Wakaru Rinsyou yakubutsudoutai Riron no Ouyou. (in Japanese) Iyaku (Medicine and Drag) Journal Co., Ltd. Japan, 1998;45–47.
18. Horio M, Orita Y, Manabe S, Sakata M, Fukunaga M. Formula and nomogram for predicting creatinine clearance from serum creatinine concentration. *Clin Exp Nephrol*. 1997;1(2):110-114.
19. Levey AS, Bosch JP, Lewis JB, Greece T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999;130(6):461-470.
20. Terawaki H, Nakayama M, Asahi K, et al. Comparison of predictive value for first cardiovascular event between Japanese GFR equation and coefficient-modified CKD-EPI equation. *Clin Exp Nephrol*. 2015;19(3):387-394.
21. Matsuo S, Imai E, Horio M, et al. Revised equations for estimating glomerular filtration rate (GFR) from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53(6):982-992.
22. World Health Organization. Body mass index (BMI). http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi
23. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition*. 1989;5:303-311-313.
24. Horio M, Orita Y. Comparison of Jaffe rate assay and enzymic method for the measurement of creatinine clearance. *Jpn J Nephrol*. 1996;38(7):296-299.
25. Toda T, Watanabe H, Kurosawa N, et al. Limited sampling strategy for estimating area under the concentration curve for mycophenolic acid in renal transplant recipients with co-administration of tacrolimus. *Jpn J Pharm Health Care Sci*. 2004;30(1):1-7.
26. Ministry of Health, Labour and Welfare of Japan. Overview of Patient Survey 2014, 2014. http://www.mhlw.go.jp/toukei/saikin/hw/kanja/14/dl/01.pdf
27. Riccobene T, Jakate A, Rank D. A series of pharmacokinetic studies of ceftaroline fosamil in select populations: normal subjects, healthy elderly subjects, and subjects with renal impairment or end-stage renal disease requiring hemodialysis. *J Clin Pharmacol*. 2014;54(7):742-752.
28. Japanese Society of Nephrology. Clinical practice guidebook for diagnosis and treatment of chronic kidney disease 2012. *Nephrol Dial Transplant*. 2012;32:798-806.
29. Pottel H, Hoste L, Dubourg L, et al. An estimated glomerular filtration rate equation for the full age spectrum. *Nephrol Dial Transplant*. 2016;31(5):798-806.
30. Gunnarsson SI, Palsson R, Sigurdsson G, Indridason OS. Relationship between body composition and glomerular filtration rate estimates in the general population. *Nephron Clin Pract*. 2013;123(1-2):22-27.
31. Bretagne M, Jouinot A, Durand JP, et al. Estimation of glomerular filtration rate in cancer patients with abnormal body composition and relation with carboplatin toxicity. *Cancer Chemother Pharmacol*. 2017;80(1):45-53. https://doi.org/10.1007/s00280-017-3326-5
32. Donadio C. Body composition analysis allows the prediction of urinary creatinine excretion and of renal function in chronic kidney disease patients. *Nutrients*. 2017;9(6):533. https://doi.org/10.3390/nu9060553
33. Ebah LM, Wiig H, Dawidowska I, et al. Subcutaneous interstitial pressure and volume characteristics in renal impairment associated with edema. *Kidney Int*. 2013;84(5):980-988. https://doi.org/10.1038/ki.2013.208
34. Janmahasatian S, Duffull SB, Chagnac A, Kirkpatrick CMJ, Green B. Lean body mass normalizes the effect of obesity on renal function. *Br J Clin Pharmacol*. 2008;65(6):964-965.
35. Ma X, Zhang C, Su H, Gong X, Kong X. Increasing body mass index predicts rapid decline in renal function: a 5 year retrospective study. *Horm Metab Res*. 2018;50(07):556-561. https://doi.org/10.1055/a-0599-6360
36. Helou R. Should we continue to use the Cockcroft-Gault formula? *Nephron Clin Pract*. 2010;116:172-186.
37. Bouquegneau A, Vidal-Petiot E, Moranne O, et al. Creatinine-based equations for the adjustment of drug dosage in an obese population. *Br J Clin Pharmacol*. 2015;81(2):349-361.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Kaburaki S, Yoshimura E, Kojima N, Ueno H, Sugawara M, Takekuma Y. Improvement of renal function estimation equations for elderly Japanese people. *Health Sci Rep*. 2018;1:e85. https://doi.org/10.1002/hsr2.85