図１　baPWV と eGFR の関係

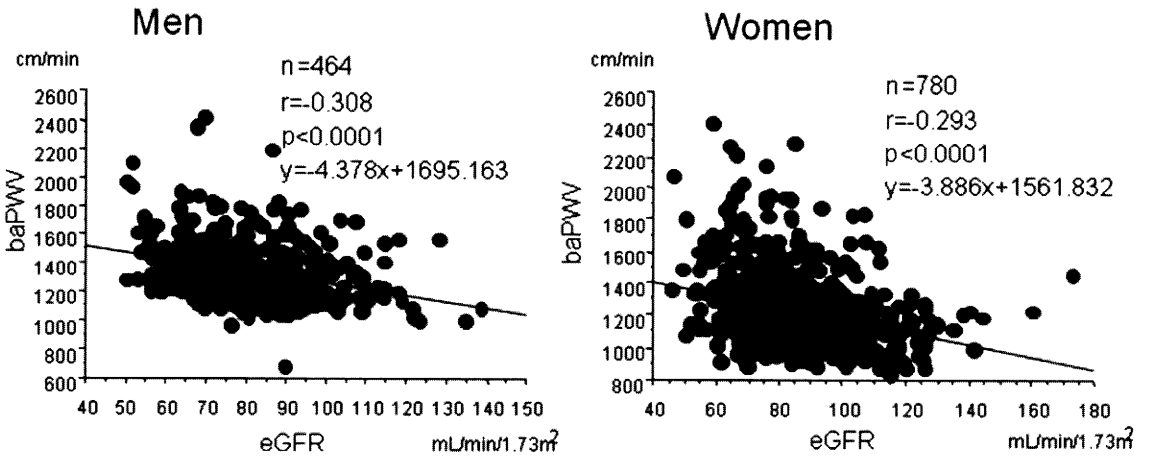
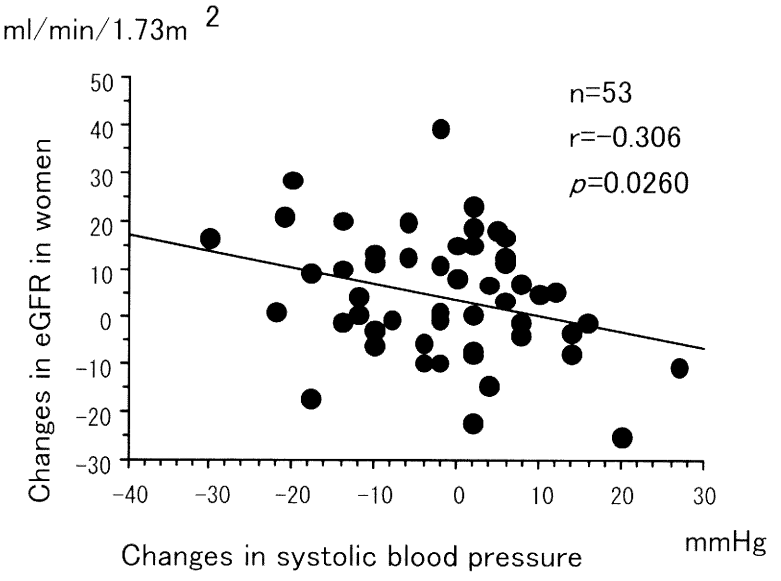


図２　収縮期血圧の変化量とeGFRの変化量との関係



厚生労働科学研究費補助金　腎疾患対策研究事業

平成22年度　分担研究報告

虚血性腎症と発症率と危険因子の同定に関する研究

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研究要旨

熊本市の特定健診のデータを用い、腎硬化症及び虚血性腎症の発症率及びリスクの解析を行う。腎硬化症は、agingとの相違を含め、概念や定義に未解決な部分が残されているため、健診データを解析し、まず腎硬化症の定義、診断にアプローチした。

A. 研究目的

CKDの中でも頻度的に重要である腎硬化症及び虚血性腎症は、agingとの相違の問題などを含め、概念や定義に未解決な部分が残されている。本研究では腎硬化症や虚血性腎症のリスク因子を解析し、CKDの早期発見、進展防止に役立てる。

B. 研究方法

熊本市の特定健診のデータ（40～74歳の国民健康保険加入者：2008年度～2010年度）の提供を受けてコホート研究を行う。また、データの信頼性を高めるため、熊本市と協力して受診率を高めるための教育活動推進を行う。(研究の倫理面への配慮）本調査研究は、個人特定不可のデータを元にしたものであり、また熊本大学倫理委員会の承諾を得て行われている。

C. 研究結果

主要データに欠落のない16527名のデータを解析した。糖尿病有病率は男性11.8%、女性6.1%、高血圧有病率は男性49.6%、女性39.8%でどちらも男性の方が多かった。尿蛋白陽性率（1＋以上）は、男性8.6%、女性4.3%であり、やはり男性の方が多かった。CKD有病率は、eGFR 60未満とすると、男性18.1%、女性10.4%、eGFR 50未満とすると男性3.9%、女性2.6%であった。またCKD有病率（eGFR<60/eGFR<50）は、糖尿病合併群では16.2/5.2 %、高血圧合併群では17.4/4.9 %、尿蛋白陽性群では25.6/12.0 %、これらのいずれも認めない群では9.8/1.6 %であり、糖尿病、高血圧、尿蛋白のeGFR低下への関与が疑われた。

D. 考察

腎硬化症を、尿蛋白±あるいはーで、腎機能低下を認める群と定義し、そのラインを①eGFR<60、②eGFR<50、あるいはagingを考慮に入れ、糖尿病、高血圧、尿蛋白を合併しない群の③1.5SD値未満、あるいは④2SD値未満とすると、腎硬化症有

病率は、それぞれ①12.5%、②2.6%、③4.8%、④1.1%となった。

E. 結論

2010 年度のデータを得てコホート解析を行うが、やはり aging の扱いが解析のポイントになると考えられる。

厚生労働科学研究費補助金　腎疾患対策研究事業

平成22年度　総括研究報告

高齢者における薬物性腎障害の調査

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研究要旨

2007年1月1日～2009年12月31日までの3年間において発生した薬物性腎障害の実態調査（アンケート調査）を、腎臓専門医が常駐する全国の主な大学病院、基幹病院、計47施設にて行った。アンケート回収状況は61.7%であり、全入院患者における薬物性腎障害の発症頻度は0.935%であった。解析症例183例における、薬物性腎障害の被疑薬は非ステロイド性抗炎症薬、抗腫瘍薬、抗菌薬の順であった。薬物性腎障害の発症機序は直接型腎障害が過半数を、過敏型腎障害が約2割を占めていた。薬物性腎障害の治療は被疑薬の中止および保存療法が多く、時にステロイド療法が用いられていた。薬物性腎障害の転帰では約 55%の症例が回復を示していた。薬物性腎障害の予後に関しては、既存の腎不全は薬物性腎障害回復の危険因子であり、発症前 eGFR と薬物性腎障害の回復期間は負の相関関係を示した。また、高齢者（65 歳以上）では腎機能回復までの期間が有意に長かった。薬物性腎障害を回避するためには、特に腎障害例に対して非ステロイド性抗炎症薬、抗腫瘍薬、抗菌薬を使用する際には格別の注意が必要であると考えられた。

A．研究目的

18歳以上を対象にした薬物性腎障害に関するアンケート調査を行い、薬物性腎障害の発生頻度、臨床的特徴、発生前推定GFR（発生前CKD病期）、基礎疾患やメタボリックシンドロームなどの合併症と予後との関連、危険因子などを中心に解析し、高齢者の薬物性腎障害の特徴を非高齢者と対比することにより明らかにすることにより、その予防法の確立につな

げる。

B．研究方法

2007年1月1日～2009年12月31日までの3年間において発生した薬物性腎障害の実態調査（アンケート調査）を、腎臓専門医が常駐する全国の主な大学病院、基幹病院、計47施設にて行った。なお、本研究は、疫学研究に関する倫理指針（平成19年度文部科学省・厚生労働省告示第1号）に則っており、また東京慈恵会医科大学倫理委員会において承認済みである。

C．研究結果

アンケート回収率は61.7%であり、全入院患者における薬物性腎障害の発症頻度は0.94%であった。解析症例183例における、薬物性腎障害の被疑薬は非ステロイド性抗炎症薬（25.1%）、抗腫瘍薬（18.0%）、抗菌薬（17.5%）の順であった。薬物性腎障害の発症機序は、直接型腎障害が54.6%と過半数を占めており、次いで過敏型腎障害が19.0%、混合型が5.7%であった。薬物性腎障害発見時の症状・所見は、急激な腎機能低下（34.8%）が最も多く、次に皮疹（12.0%）、蛋白尿（10.5%）であった。薬物性腎障害の治療は、被疑薬の中止（38.2%）、保存療法（30.4%）が多く、次にステロイド療法（11.3%）であった。薬物性腎障害の転帰は、過半数（55.1%）が回復を示した一方、非回復が36.5%を占めていた。

薬物性腎障害の予後に関しては、高齢（65歳以上）、高血圧、DM、心疾患、脳血管疾患と薬物性腎障害の回復との間には有意な関連はなかった。しかし、既存の腎不全（S-cr 2.0 mg/dl以上）は薬物性腎障害回復の危険因子であり、発症前eGFRと薬物性腎障害の回復期間は負の相関関係を示した。また、高齢者（65歳以上）では腎機能回復までの期間が有意に長かった。

D．考察・結論

今回の調査から、薬物性腎障害の危険因子としての既存の腎障害が再確認された。薬物性腎障害を回避するためには、特に腎障害例に対して非ステロイド性抗炎症薬、抗腫瘍薬、抗菌薬を使用する際には格別の注意が必要であると考えられた。

厚生労働科学研究費補助金（腎疾患対策研究事業）

研究成果の刊行物・別刷

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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.

Am J Kidney Dis 56:32-38.

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 m² (n = 206)	mGFR ≥60 mL/min/1.73 m² (n = 144)
Bias (mL/min/1.73 m²)			
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 m²)			
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 m²; 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 m² ($P < 0.001$); there was no significant difference in bias in participants with GFR <60 mL/min/1.73 m². 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

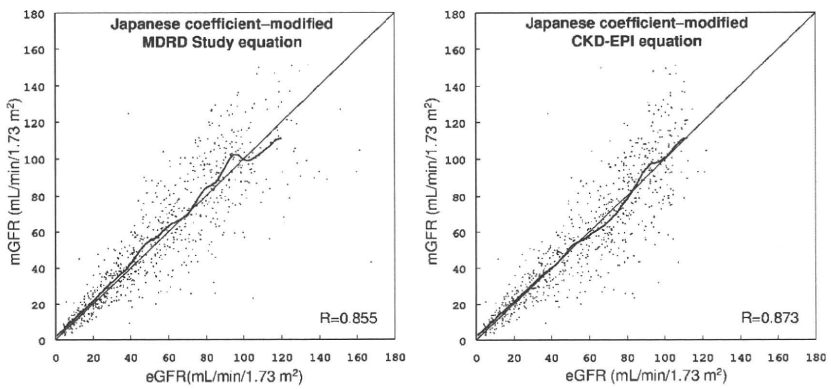

Figure 1. Correlation between estimated (eGFR) and measured glomerular filtration rate (mGFR) in the combined data set. (Left) mGFR versus eGFR obtained using the Japanese coefficient–modified Modification of Diet in Renal Disease (MDRD) Study equation. (Right) mGFR versus eGFR obtained using the Japanese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

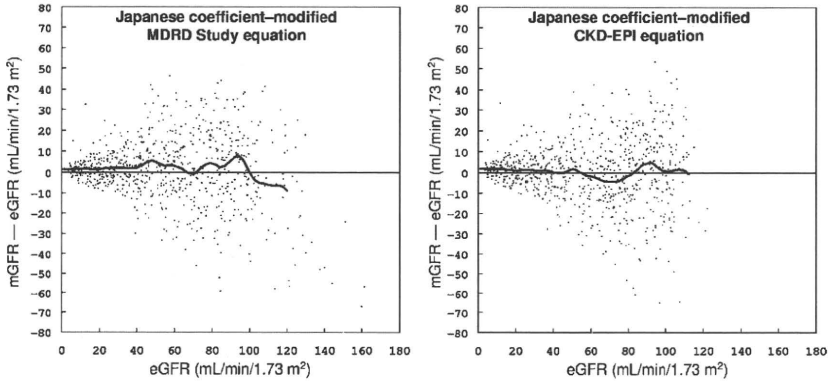

Figure 2. Difference between measured (mGFR) and estimated glomerular filtration rate (eGFR) versus eGFR in the combined data set. (Left) mGFR minus eGFR versus eGFR obtained using the Japanese coefficient–modified Modification of Diet in Renal Disease (MDRD) Study equation. (Right) mGFR minus eGFR versus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

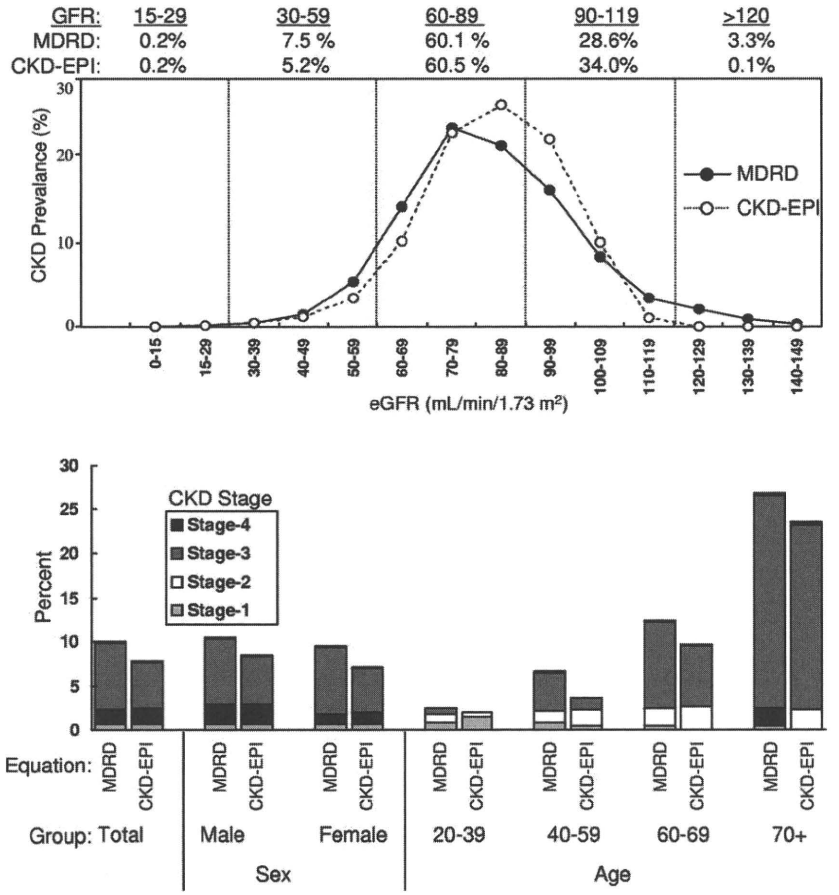

Figure 3. Comparison of distributions of estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD) prevalence. (Top) Distribution in a Japanese general adult population of eGFR obtained using the Japanese coefficient–modified Modification of Diet in Renal Disease (MDRD) Study equation (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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Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating the glomerular filtration rate in multiple ethnicities

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An equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) provides more accurate estimates of the glomerular filtration rate (eGFR) than that from the modification of diet in renal disease (MDRD) Study, although both include a two-level variable for race (Black and White and other). Since creatinine generation differs among ethnic groups, it is possible that a multilevel ethnic variable would allow more accurate estimates across all groups. To evaluate this, we developed an equation to calculate eGFR that includes a four-level race variable (Black, Asian, Native American and Hispanic, and White and other) using a database of 8254 patients pooled from 10 studies. This equation was then validated in 4014 patients using 17 additional studies from the United States and Europe (validation database), and in 1022 patients from China (675), Japan (248), and South Africa (99). Coefficients for the Black, Asian, and Native American and Hispanic groups resulted in 15, 5, and 1% higher levels of eGFR, respectively, compared with the White and other group. In the validation database, the two-level race equation had minimal bias in Black, Native American and Hispanic, and White and other cohorts. The four-level ethnicity equation significantly improved bias in Asians of the validation data set and in Chinese. Both equations had a large bias in Japanese and South African patients. Thus, heterogeneity in performance among the ethnic and geographic groups precludes use of the four-level race equation. The CKD-EPI two-level race equation can be used in the United States and Europe across a wide range of ethnicity.

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KEYWORDS: creatinine; ethnicity; glomerular filtration rate

Chronic kidney disease (CKD) is a worldwide health problem, affecting all racial and ethnic groups that have been investigated.[1] In the United States, chronic kidney failure disproportionately burdens racial and ethnic minorities. Incidence rates for chronic kidney failure treated by dialysis and transplantation are 3.6 and 1.4 times higher in Blacks and Asians, respectively, compared with Whites, and 1.5 times higher in Hispanics compared with non-Hispanics.[2] Outside of the United States, Taiwan and Japan have the highest prevalence rates of treated kidney failure.[2,3] Data on the prevalence, etiology, and outcomes of earlier stages of kidney disease in these groups are likely to be inaccurate due, at least in part, to the lack of accurate glomerular filtration rate (GFR) estimates.

The Modification of Diet in Renal Disease (MDRD) Study equation utilizes a two-level variable for race (Black vs White and other). The coefficient for Blacks leads to higher values for estimated GFR (eGFR) compared with Whites for the same level of creatinine, because of differences between Blacks vs Whites in factors other than GFR that affect the serum level of creatinine (non-GFR determinants), especially higher creatinine generation from muscle and diet.[4,5] It is widely believed that there are also differences in creatinine generation in other racial, ethnic, and geographic groups, which are not captured by current equations.[6,7] Consistent with this assumption, introduction of coefficients for use in the MDRD Study equation in China and Japan improves its performance in these populations.[8,9]

We recently reported a new equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation,

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