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Estimating GFR by Serum Creatinine, Cystatin C, and β2-Microglobulin in Older Adults: Results From the Canadian Study of Longevity in Type 1 Diabetes

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Introduction: Glomerular filtration rate (GFR) is routinely used for clinical assessment of kidney function. However, the accuracy of estimating equations in older adults is uncertain.

Methods: In 66 adults with ≥50 years type 1 diabetes (T1D) duration and 73 nondiabetic controls from age/sex-matched subgroups (65 ± 8 years old and 77[55%] were women) we evaluated the performance of estimated GFR (eGFR) by creatinine (Modification of Diet and Renal Disease [MDRD], Chronic Kidney Disease–Epidemiology [CKD-EPI]$_{cr}$), cystatin C (CKD-EPI$_{cys}$, CKD-EPI$_{cr\text{-}cys}$), and β_2-microglobulin (β2M) compared with measured GFR by inulin clearance (mGFR). Performance was evaluated using metrics of bias (mean difference), precision (SD), and accuracy (proportion of eGFR that differed by >20% of mGFR).

Results: Mean mGFR was 104 ± 18 ml/min per 1.73 m^2 (range: 70–154 ml/min per 1.73 m^2) and was not different between T1D and controls (103 ± 17 vs. 105 ± 19 ml/min per 1.73 m^2, $P = 0.39$). All equations significantly underestimated mGFR (bias: −15 to −30 ml/min per 1.73 m^2, $P < 0.001$ for all comparisons) except for β2M, which had bias of 1.9 ml/min per 1.73 m^2 ($P = 0.61$). Bias was greatest in cystatin C–based equations. Precision was lowest for β2M (SD: 43.5 ml/min per 1.73 m^2, $P < 0.001$ for each comparison). Accuracy was lowest for CKD-EPI$_{cysC}$ (69.1%, $P < 0.001$ for each comparison). Cystatin C–based equations demonstrated greater bias and lower accuracy in older age subgroups (<60, 60–69, ≥70 years). All equations demonstrated greater bias across higher ranges of mGFR (60–89, 90–119, ≥120 ml/min per 1.73 m^2). Results were similar between T1D and controls except that β2M had lower performance in T1D.

Conclusion: Better estimates of GFR in older adults are needed for research and clinical practice, as this subgroup of the population has an amplified risk for the development of chronic kidney disease (CKD) that requires accurate GFR estimation methods.

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GFR has long been considered the best overall index of kidney function and is included as criterion in the definition and staging of CKD.[1,2] Gold standard measures of GFR (mGFR) using exogenous iothalamate, iohexol, or inulin clearance remain

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expensive and impractical, and consequently these techniques are not routinely performed in clinical research or practice.[3,4] Clinicians must therefore rely on eGFR to identify CKD and evaluate renal function. The most widely used clinical laboratory reported eGFR equations are based on standardized serum creatinine assays and include the MDRD creatinine equation,[5] and the CKD-EPI Collaboration creatinine equation (CKD-EPI_{cr}).[6] In general, creatinine-based equations for GFR can be confounded by muscle mass, the main determinant of creatinine generation.[4] Although MDRD and CKD-EPI_{cr} include age as a surrogate marker, age-related reductions in muscle mass may lead to biased, imprecise, and inaccurate estimates of GFR in older adults.[7,8] The uncertainty around using creatinine-based eGFR in older adults has led to an interest in use of alternative filtration markers for clinical evaluation of kidney function.

Cystatin C is an endogenous 13-kDa protein that is produced at a stable rate by all nucleated cells and is filtered by the glomeruli and reabsorbed by epithelial cells of the proximal tubule.[9] Its production is less confounded by ethnicity, age, or sex compared with creatinine.[10,11] The most widely used cystatin C–based equations include the CKD-EPI cystatin C equation (CKD-EPI_{cys}) and the CKD-EPI creatinine–cystatin C equation (CKD-$EPI_{cr\text{-}cys}$).[12] Use of cystatin C in combination with creatinine has been shown to improve the accuracy of eGFR compared with using either marker alone,[12,13] and it has also demonstrated a stronger association between decreased eGFR and subsequent risk of death, and cardiovascular and kidney disease outcomes.[14,15] However, use of eGFR by creatinine and cystatin C for clinical decision making, such as staging of early CKD, drug dosing, and prediction of adverse outcomes remains suboptimal due to a lack of precision and accuracy.

β2M is a low molecular weight protein component of class I major histocompatibility molecules and is found on the surface of nucleated cells; it is filtered by the glomerulus and retained in the blood as GFR declines.[16] Similar to cystatin C, β2M has been shown to be less affected by age, sex, and ethnicity and has stronger associations with death, cardiovascular disease, and kidney disease outcomes compared with creatinine.[10,17] An equation has recently been developed for eGFR by β2M,[18] but it has not been extensively evaluated.

A lack of precision and accuracy of eGFR may be of particular concern in older adults with longstanding diabetes duration who are at elevated risk of developing diabetic nephropathy,[19] and who have additional eGFR confounders such as hyperglycemia.[20] Even though diabetes is the leading cause of CKD, end-stage renal disease (ESRD), and dialysis in the western world,[21] the accuracy of eGFR equations to assess renal function in those with longstanding T1D has not been evaluated. Studies to date that have evaluated the accuracy of CKD-EPI_{cr}, CKD-EPI_{cys}, and CKD-$EPI_{cr\text{-}cys}$ in older adults have been limited to elderly individuals without T1D,[22–27] and the accuracy of β2M has not been evaluated in older adults or in T1D.

Accordingly, our aim was to evaluate the performance of eGFR by serum creatinine, cystatin C, and β2M compared with mGFR by inulin clearance in older adults with and without T1D.

METHODS

Study Population

This was a cross-sectional study involving patients who were recruited for the second phase of the Canadian Study of Longevity in Type 1 Diabetes.[28] Between February 2015 and September 2016, a total of 75 participants with ≥50 years of T1D and 75 age- and sex-matched nondiabetic controls underwent extensive phenotyping procedures over the course of 2 clinical visits set 2 to 4 weeks apart. Participants with T1D were recruited from the nationwide registry of approximately 450 Canadians with ≥50 years of T1D established during the first phase of the study,[29–33] and nondiabetic controls were friends or family members of T1D participants, or were recruited through community advertisement. Search criteria for the second phase included residence in the Greater Toronto Area (e.g., proximity to the University Health Network and Mount Sinai Hospital in Toronto, Ontario, Canada), or a willingness to travel for 2 requisite study days. Inclusion criteria for T1D participants was ≥50 years of T1D duration, and inclusion criteria for nondiabetic controls was any race and sex-matched 1:1 within 5 years of age of a T1D participant. Inclusion criteria common to both nondiabetic controls and T1D participants was the ability to understand and cooperate with study procedures. Exclusion criteria for controls was the presence of diabetes mellitus. Exclusion criteria common to both nondiabetic controls and T1D participants were specific to phenotyping procedures not discussed in this article and included (i) any current eye infection, corneal damage, severe movement disorder, or proparacaine allergy to preclude safe corneal confocal microscopy examination; and (ii) blood pressure >140/90 mm Hg to preclude angiotensin II infusion procedures. All participants provided written informed consent, and the study and its procedures were approved by the institutional ethics board at the University Health Network and Mount Sinai Hospital in Toronto, ON, Canada.

Laboratory Methods

mGFR was determined by the mean of 2 plasma inulin clearances and was expressed per 1.73 m^2 body surface area,[34] and details of this procedure can be found in the Supplementary Methods. Creatinine was measured using the Abbott Architect chemistry analyzer using manufacturer's reagents with the Modified Jaffe Kinetic method (coefficients of variation of 2.8% and 1.8% at 1.4 and 6.6 mg/dl, respectively), which is traceable to National Institute Standardized Technology creatinine standard reference material 967. Cystatin C was measured on an immunoturbidimetric assay kit (Kamiya Biomedical Company, Seattle, WA) (coefficient of variation 6.5%). Cystatin C values were adjusted so that they could be traceable to the International Federation of Clinical Chemistry and Laboratory Medicine Working Group for the Standardization of Serum Cystatin C and the Institute for Reference Materials and Measurements certified reference materials.[12,35,36] β2M was measured using the Meso Scale Discovery Human Kidney Injury Panel Assay Kits (Gaithersburg, MD) (coefficient of variation 3.5%).

eGFR Equations

eGFR by creatinine and cystatin C was calculated from equations developed by the MDRD and CKD-EPI groups.[5,6,12] eGFR by β2M was calculated using the equation developed by Inker *et al.*[18] Supplementary Table S1 presents the equations in detail.

Statistical Analyses

All analyses were performed using SAS 9.4 for Windows (SAS Institute, Cary, NC). An α-level of 0.05 (2-tailed) was used for tests of statistical significance. Comparisons of the clinical characteristics between controls and T1D were made using Student *t*-test, the Wilcoxon rank-sum test, or the χ^2 test, depending on variable distribution. Correlation and agreement between mGFR and eGFR were assessed using the method of Bland and Altman.[37] Spearman's rank correlation coefficients (r_s), the mean difference, and the 95% limits of agreement (2.5th and 97.5th percentiles of the mean difference) were used to assess correlation, magnitude, and direction of agreement between eGFR and mGFR.

Equation Performance

The performance of eGFR was assessed using metrics for bias, precision, and inaccuracy.[38] Bias was assessed using the mean difference between eGFR and mGFR (eGFR − mGFR) and precision was assessed using the SD of the difference. Relative bias and relative precision were assessed using the mean and SD of the % difference, respectively; higher SDs represented lower precision. Accuracy was assessed using $1-P_{30}$ (the proportion of eGFR that differed by more than 30% of mGFR) and $1-P_{20}$ (the proportion of eGFR that differed by more than 20% of mGFR); higher percentages represented lower accuracy. The 95% confidence intervals around bias, precision, relative bias, relative precision, $1-P_{30}$, and $1-P_{20}$ were calculated using the bootstrap method (2000 bootstraps, with replacement). In addition to control and T1D subgroups, other subgroups were defined from the total study population according to age range (<60, 60–69, ≥70 years), sex (male or female), body mass index range (<25, 25–29, ≥30 kg/m^2), diabetes duration (50–52, 53–56, ≥57 years) in those with T1D, and mGFR range (60–89, 90–119, ≥120 ml/min per 1.73 m^2). Bias, precision, and accuracy metrics were used to assess eGFR performance in the study population and within subgroups.

The significance of differences between equations was determined with the use of a paired *t*-test for bias, a 2-tailed F-test for precision, and the McNemar test for $1-P_{30}$ and $1-P_{20}$. The significance of differences between subgroups were determined with the use of analysis of variance or Student *t*-test for bias, a 2-tailed F-test for precision, and the χ^2 test for $1-P_{30}$ and $1-P_{20}$.

RESULTS

Characteristics of the Study Population

Among eligible participants enrolled in the Canadian Study of Longevity in Type 1 Diabetes, 66 of 75 (88%) participants with ≥50 years of T1D and 73 of 75 (97%) age- and sex-matched nondiabetic controls underwent both measures: mGFR and eGFR. Clinical characteristics of the 139 participants are shown in Table 1. Controls and patients with T1D were similar age (65 ± 8 vs. 66 ± 7 years, $P = 0.54$) and the proportion of participants who were female sex was similar (56% vs. 55%, $P = 0.85$). T1D participants had mean HbA1c of 7.4 ± 0.8% (57 ± 8.7 mmol/mol) and had median (interquartile range) diabetes duration of 54 (52,58) years. Serum creatinine was lower in controls compared with patients with T1D (0.7 ± 0.1 vs. 0.8 ± 0.2 mg/dl, $P = 0.048$). Serum cystatin C was similar between controls and patients with T1D (1.1 ± 0.3 vs. 1.1 ± 0.3 mg/l, $P = 0.91$). Serum β2M was similar between controls and patients with T1D (1.6 ± 0.5 vs. 1.5 ± 0.8 mg/l, $P = 0.68$).

GFR Measures and Classification of GFR Range Subgroups

Mean measures of GFR and the proportion of participants in GFR range subgroups (<60, 60–89, 90–119, ≥120 ml/min per 1.73 m^2) are displayed in Table 2. There were no differences in mean GFR between controls versus patients with T1D, except for CKD-EPI_{cr} (90 ± 10 vs. 86 ± 15 ml/min per 1.73 m^2, $P = 0.040$) and β2M (98 ± 26 vs. 114 ± 53 ml/min per

Table 1. Baseline characteristics of the 139 study participants

Characteristic	Study population (N = 139)	Controls (n = 73)	T1D (n = 66)	P
Clinical characteristics				
Age, yr	65 ± 8	65 ± 8	66 ± 7	0.54
Women, *n* (%)	77 (55)	41 (56)	36 (55)	0.85
T1D duration, yr	—	—	54 [52, 58]	—
Weight, kg	74.5 ± 14.5	75.7 ± 16.2	73.2 ± 12.3	0.31
Height, m	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	0.59
BMI, kg/m^2	26.9 ± 4.8	27.2 ± 5.5	26.6 ± 3.9	0.45
Systolic blood pressure, mm Hg	130 ± 16	128 ± 18	133 ± 14	0.10
Diastolic blood pressure, mm Hg	74 ± 10	78 ± 9	70 ± 9	<0.001
HbA_{1c}, %	6.5 ± 1.1	5.5 ± 0.3	7.4 ± 0.8	<0.001
HbA_{1c}, mmol/mol	48.0 ± 12.0	37 ± 3.3	57 ± 8.7	<0.001
Urine ACR, mg/mmol	1.3 [0.7, 2.8]	0.9 [0.6, 2.2]	1.6 [0.9, 7.2]	0.035
Serum creatinine, mg/dl	0.8 ± 0.2	0.7 ± 0.1	0.8 ± 0.2	0.048
Serum cystatin C, mg/l	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.91
Serum β2M, mg/l	1.5 ± 0.6	1.6 ± 0.5	1.5 ± 0.8	0.68
Medications				
RAAS inhibitor, *n* (%)	64 (46)	10 (14)	54 (82)	<0.001
Calcium channel blocker, *n* (%)	25 (18)	8 (11)	17 (26)	0.023
Diuretic, *n* (%)	22 (16)	9 (12)	13 (20)	0.23
Statin, *n* (%)	70 (50)	18 (25)	52 (79)	<0.001

ACR, albumin-creatinine ratio; B2M, β2-microgobulin; BMI, body mass index; RAAS, renin-aldosterone-angiotensin system; T1D, type 1 diabetes.
Data are mean ± SD, median [interquartile range], or *n* (%).

Table 2. GFR measures of the 139 study participants

Measure	Study population (N = 139)	Controls (n = 73)	T1D (n = 66)	P
mGFR				
Mean, ml/min per 1.73 m^2	104 ± 18	105 ± 19	103 ± 17	0.39
Range, ml/min per 1.73 m^2	70–154	70–154	70–142	
<60, *n* (%)	0 (0)	0 (0)	0 (0)	0.095
60–89, *n* (%)	31 (22)	12 (16)	19 (29)	
90–119, *n* (%)	78 (56)	41 (56)	37 (56)	
≥120, *n* (%)	30 (22)	20 (27)	10 (15)	
MDRD creatinine equation				
Mean, ml/min per 1.73 m^2	89 ± 17	91 ± 14	87 ± 19	0.12
Range, ml/min per 1.73 m^2	45–127	46–127	44–124	
<60, *n* (%)	9 (6)	1 (1)	8 (12)	0.044
60–89, *n* (%)	62 (45)	32 (44)	30 (45)	
0–119, *n* (%)	64 (46)	38 (52)	26 (39)	
≥120, *n* (%)	4 (3)	2 (3)	2 (3)	
CKD-EPI creatinine equation				
Mean, ml/min per 1.73 m^2	88 ± 13	90 ± 10	86 ± 15	0.040
Range, ml/min per 1.73 m^2	48–108	49–108	48–105	
<60, *n* (%)	8 (6)	1 (1)	7 (11)	0.052
60–89, *n* (%)	52 (37)	27 (37)	25 (38)	
90–119, *n* (%)	79 (57)	45 (62)	34 (51)	
≥120, *n* (%)	0 (0)	0 (0)	0 (0)	
CKD-EPI cystatin C equation				
Mean, ml/min per 1.73 m^2	74 ± 22	73 ± 21	75 ± 23	0.56
Range, ml/min per 1.73 m^2	24–120	29–115	24–120	
<60, *n* (%)	42 (30)	25 (34)	17 (26)	0.25
60–89, *n* (%)	60 (43)	33 (45)	27 (41)	
90–119, *n* (%)	33 (24)	15 (21)	21 (31)	
≥120, *n* (%)	1 (1)	0 (0)	1 (2)	
CKD-EPI creatinine–cystatin C equation				
Mean, ml/min per 1.73 m^2	81 ± 17	81 ± 16	81 ± 19	0.81
Range, ml/min per 1.73 m^2	33–117	38–114	33–117	
<60, *n* (%)	16 (12)	6 (8)	10 (15)	0.19
60–89, *n* (%)	78 (56)	46 (63)	32 (48)	
90–119, *n* (%)	45 (32)	21 (29)	24 (36)	
≥120, *n* (%)	0 (0)	0 (0)	0 (0)	
β2M equation				
Mean, ml/min per 1.73 m^2	106 ± 42	98 ± 26	114 ± 53	0.025
Range, ml/min per 1.73 m^2	36–302	46–207	36–302	
<60, *n* (%)	13 (9)	6 (8)	7 (11)	<0.001
60–89, *n* (%)	44 (32)	23 (32)	21 (32)	
90–119, *n* (%)	43 (31)	34 (47)	9 (14)	
≥120, *n* (%)	39 (28)	10 (14)	29 (44)	

β2M, β2-microgobulin; CKD-EPI, Chronic Kidney Disease–Epidemiology; GFR, glomerular filtration rate; MDRD, Modification of Diet and Renal Disease; mGFR, measures of GFR; T1D, type 1 diabetes.
Data are mean ± SD, range [min–max], or *n* (%).

1.73 m^2, $P = 0.025$). Although no participants were classified as having stage 3 CKD (<60 ml/min per 1.73 m^2) according to mGFR,[2] 6% of participants were misclassified as having CKD by the MDRD and CKD-EPI$_{cr}$ equations, 30% by CKD-EPI$_{cys}$, 12% by CKD-EPI$_{cr-cys}$, and 9% by β2M. Compared with mGFR, 53% of participants were misclassified into a different GFR range subgroup by MDRD, 50% were misclassified by CKD-EPI$_{cr}$, 78% were misclassified by CKD-EPI$_{cys}$, 70% were misclassified by CKD-EPI$_{cr-cys}$, and 60% were misclassified by β2M.

Comparisons of Agreement and Equation Performance

Figure 1 (Scatter and Bland-Altman plots) demonstrates the correlation and agreement for each equation compared with mGFR. On inspection of these plots, all equations had weak-moderate positive relationships with mGFR and agreement between eGFR and mGFR was poor. The corresponding performance metrics of each equation in the study population and in the control and T1D subgroups are presented in Table 3. Creatinine- and cystatin C–based equations significantly underestimated mGFR with bias −14.9 ml/min per 1.73 m^2 for MDRD, −15.9 ml/min per 1.73 m^2 for CKD-EPI$_{cr}$, −30.3 ml/min per 1.73 m^2 for CKD-EPI$_{cys}$, and −23.2 ml/min per 1.73 m^2 for CKD-EPI$_{cr-cys}$ ($P <$ 0.001 for each equation compared with mGFR). β2M had bias of 1.9 ml/min per 1.73 m^2 ($P = 0.61$). Bias was greater in cystatin C–based eGFR compared with equations that did not include cystatin C, and was greatest for CKD-EPI$_{cys}$ ($P < 0.001$ for comparison with each equation). Precision was similar between creatinine- and cystatin C–based equations, but was lowest for β2M (43.5 ml/min per 1.73 m^2, $P < 0.001$ for comparison with each equation). Accuracy ($1-P_{20}$) was highest for eGFR by creatinine (MDRD 32.4%, CKD-EPI$_{cr}$ 37.4%), was lower for CKD-EPI$_{cr-cys}$ (52.5%) and

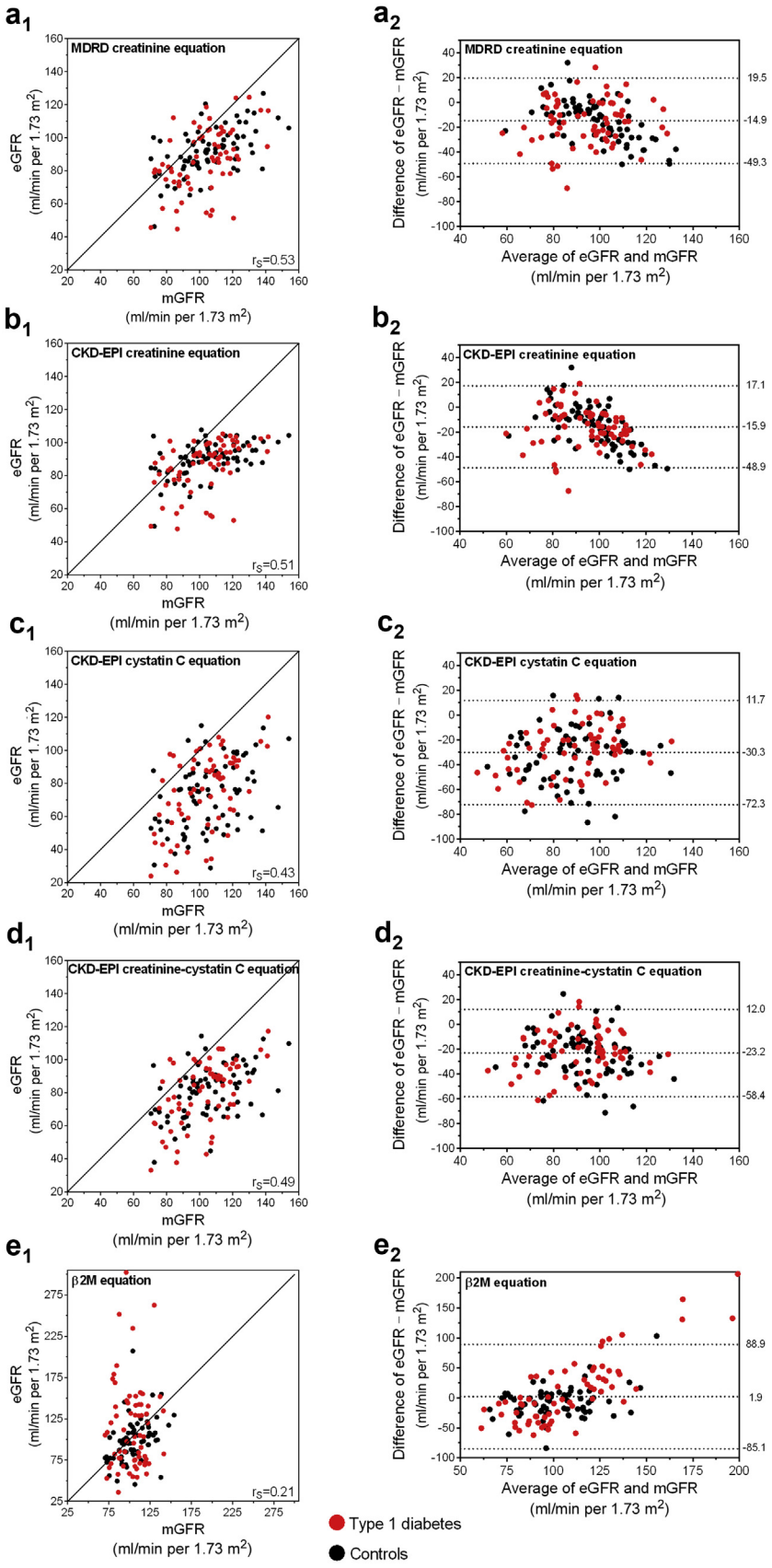

Figure 1. Scatterplots and Bland-Altman plots comparing measures of glomerular filtration rate (mGFR) with the estimated GFR (eGFR) determined by the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease–Epidemiology (CKD-EPI), and β2-microgobulin (β2M) equations. a_1, b_1, c_1, d_1, and e_1 display the scatterplots of the MDRD creatinine equation (a_1), the CKD-EPI creatinine (b_1), (continued)

β2M (52.5%), and was lowest for CKD-EPI$_{cys}$ (69.1%, $P < 0.05$ for all comparisons). Results were similar for 1−P$_{30}$. No differences in performance metrics were observed between controls and T1D for creatinine- or cystatin C–based eGFR. Compared with controls, patients with T1D had a greater magnitude for bias (−7.2 vs. 11.6 ml/min per 1.73 m^2, $P = 0.014$), lower precision (25.4 vs. 55.5 ml/min per 1.73 m^2, $P < 0.001$), and lower accuracy (1−P$_{20}$ 35.6% vs. 71.2%, $P < 0.001$) for β2M.

Subgroup Comparisons

We evaluated the performance of eGFR in subgroups based on demographic and clinical characteristics. The bias and 95% confidence interval between eGFR and mGFR according to age range, sex, body mass index range, T1D duration, and mGFR range are displayed in Figure 2; the corresponding quantitative values for each subgroup are presented in Supplementary Table S2. Bias was greater in older age groups (<60, 60–69, ≥70 years) for CKD-EPI$_{cys}$ and CKD-EPI$_{cr\text{-}cys}$ and the accuracy (1−P$_{20}$) was lower in older age groups for CKD-EPI$_{cys}$ (53%, 71%, 80%, $P = 0.039$) and CKD-EPI$_{cr\text{-}cys}$ (35%, 49%, 61%, $P = 0.042$). Bias was greater in women versus men for MDRD, CKD-EPI$_{cys}$, and CKD-EPI$_{cr\text{-}cys}$ and the accuracy (1−P$_{20}$) was lower in women versus men for MDRD (39% vs. 22%, $P = 0.046$), CKD-EPI$_{cys}$ (79% vs. 56%, $P = 0.004$), and CKD-EPI$_{cr\text{-}cys}$ (61% vs. 42%, $P = 0.030$). The bias across mGFR 60–89, 90–119, and ≥120 ml/min per 1.73 m^2 subgroups was greater for all equations; accuracy (1−P$_{20}$) was lower at higher ranges of mGFR for MDRD (16%, 26%, 65%, $P < 0.001$), CKD-EPI$_{cr}$ (13%, 26%, 77%, $P < 0.001$), CKD-EPI$_{cys}$ (52%, 65%, 83%, $P < 0.001$), and CKD-EPI$_{cr\text{-}cys}$ (35%, 49%, 77%, $P < 0.001$).

CONCLUSION

Accurate estimation of GFR is an important tool for clinicians to routinely identify kidney disease, to monitor changes in renal function, to estimate prognosis for ESRD, and for selection of appropriate use and dosing of pharmacotherapies. We found that in older adults with and without T1D, who had preserved renal function according to mGFR, eGFR by serum creatinine, cystatin C, and β2M did not accurately ascertain GFR. Cystatin C–based eGFR performed worse than creatinine-based eGFR and had lower performance in older subgroups, and the combination of both creatinine and cystatin C did not outperform creatinine alone. β2M was the least biased, but was the least precise and had lower performance in patients with T1D. In addition, all equations had lower performance at higher ranges of mGFR. Due to poor performance, eGFR by creatinine was associated with 6% false-positive rate for stage 3 CKD (mGFR <60 ml/min per 1.73 m^2), eGFR by cystatin C was associated with 30% false-positive rate, eGFR by β2M was associated with 9% false-positive rate, and all equations had more than 50% misclassification of GFR range subgroups overall.

Creatinine is the most widely used and readily available endogenous filtration marker to estimate GFR in research and clinical settings.[2,6] Age-related reductions in muscle mass have long been hypothesized to reduce serum creatinine concentrations in older adults.[8] This could result in systematic bias of mGFR by creatinine-based eGFR and therefore misclassify CKD in older patients. Consequently, serum cystatin C, an endogenous filtration marker that is not confounded by muscle mass, has been hypothesized to be the preferred filtration marker in older adults. In external validation cohorts of younger adults,[1,12] eGFR by combination of cystatin C and creatinine has been shown to be more accurate than using either marker alone. Interestingly, in our study population of older adults with and without T1D, and without CKD, eGFR by cystatin C performed worse than creatinine, had lower performance in older subgroups, and the combination of cystatin C and creatinine had lower performance than creatinine alone. These findings suggest that eGFR by creatinine, although itself associated with limited accuracy, may provide benefit over cystatin C in older adults with preserved renal function. The finding that cystatin C did not improve on creatinine-based eGFR is consistent with one recent study that evaluated eGFR performance in elderly Malaysian adults (≥65 years old) who had a mean mGFR of 41 ± 19 ml/min per 1.73 m^2 according to 51 chromium EDTA.[39] However, the findings of both our study and the Malaysian study are inconsistent with results from a recent study of Icelandic adults aged 74 to 93 years who had a mean mGFR of 62 ± 16 ml/min per 1.73 m^2 by plasma clearance of iohexol.[40] In this study, cystatin C improved on all creatinine-based equations. One other key study determined that eGFR by combination

Figure 1. (continued) cystatin C (c_1), and creatinine–cystatin C (d_1) equations, and the β2M equation (e_1) compared with mGFR determined by plasma inulin clearance; r_s refers to Spearman's rank correlation coefficient, and the solid diagonal line represents the line of unity (x=y). a_2, b_2, c_2, d_2, and e_2 display the Bland-Altman plots demonstrating the difference between eGFR − mGFR for the MDRD creatinine equation (a_2), the CKD-EPI creatinine (b_2), cystatin C (c_2), and creatinine–cystatin C (d_2) equations, and the β2M equation (e_2); points above or below zero on the y-axis represent overestimation and underestimation of mGFR by eGFR, respectively. The dotted lines correspond to, from top to bottom, the 97.5th percentile of differences, the mean difference (bias metric), and the 2.5th percentile of differences.

Table 3. Comparison of the performance of the MDRD, CKD-EPI, and β2M equations in the 139 study participants

Variable	Study population (N = 139)	Controls (n = 73)	T1D (n = 66)
Bias, mean difference (95% CI)[a]			
MDRD creatinine equation	−14.9 (−17.8 to − 12.0)	−14.1 (−17.8 to −10.4)	−15.8 (−20.4 to −11.3)
CKD-EPI creatinine equation	−15.9 (−18.6 to −13.1)	−15.0 (−18.8 to −11.1)	−16.8 (−20.9 to −12.7)
CKD-EPI cystatin C equation	−30.3 (−33.8 to −26.7)	−32.6 (−37.7 to −27.4)	−27.7 (−32.6 to −22.9)
CKD-EPI creatinine–cystatin C equation	−23.2 (−26.2 to −20.3)	−24.1 (−28.4 to −19.9)	−22.2 (−26.4 to −18.0)
β2M equation	1.9 (−5.5 to 9.2)	−7.2 (−13.2 to −1.4)	11.6 (−2.1 to 25.2)
Precision, SD of difference (95% CI)			
MDRD creatinine equation	17.2 (15.4 to 19.5)	15.9 (13.6 to 19.0)	18.6 (15.9 to 22.5)
CKD-EPI creatinine equation	16.5 (14.8 to 18.7)	16.5 (14.2 to 19.7)	16.6 (14.2 to 20.0)
CKD-EPI cystatin C equation	21.0 (18.8 to 23.8)	21.9 (18.9 to 26.2)	19.8 (16.9 to 23.9)
CKD-EPI creatinine–cystatin C equation	17.6 (15.7 to 20.0)	18.1 (15.6 to 21.7)	17.0 (14.6 to 20.6)
β2M equation	43.5 (38.9 to 49.4)	25.4 (21.8 to 30.5)	55.5 (47.4 to 67.0)
Relative bias, mean % difference (95% CI)[a]			
MDRD creatinine equation	−13.2 (−15.9 to −10.4)	−11.9 (−15.4 to −8.5)	−14.5 (−18.9 to −10.1)
CKD-EPI creatinine equation	−13.6 (−16.2 to −11.1)	−12.3 (−15.7 to −8.9)	−15.1 (−19.0 to −11.3)
CKD-EPI cystatin C equation	−28.6 (−31.9 to −25.3)	−30.0 (−34.5 to −25.6)	−27.0 (−32.0 to −22.1)
CKD-EPI creatinine–cystatin C equation	−21.4 (−24.2 to −18.7)	−21.7 (−25.3 to −18.0)	−21.2 (−25.4 to −17.1)
β2M equation	4.0 (−3.5 to 11.5)	−5.6 (−11.3 to −0.0)	14.3 (0.2 to 28.4)
Relative precision, SD of % difference (95% CI)			
MDRD creatinine equation	16.3 (14.6 to 18.5)	14.8 (12.7 to 17.7)	17.9 (15.3 to 21.6)
CKD-EPI creatinine equation	15.2 (13.6 to 17.2)	14.7 (12.6 to 17.6)	15.7 (13.4 to 19.0)
CKD-EPI cystatin C equation	19.6 (17.6 to 22.3)	19.2 (16.5 to 23.0)	20.2 (17.2 to 24.3)
CKD-EPI creatinine–cystatin C equation	16.3 (14.5 to 18.4)	15.8 (13.5 to 18.8)	16.9 (14.4 to 20.4)
β2M equation	44.3 (39.6 to 50.3)	23.7 (20.3 to 28.4)	57.5 (49.0 to 69.4)
Accuracy, % (95% CI)[b]			
$1-P_{30}$			
MDRD creatinine equation	16.6 (10.8 to 23.4)	13.7 (6.8 to 23.8)	19.7 (10.9 to 31.3)
CKD-EPI creatinine equation	13.7 (8.4 to 20.5)	12.3 (5.8 to 22.1)	15.1 (7.5 to 26.1)
CKD-EPI cystatin C equation	43.2 (34.8 to 51.8)	48.0 (36.1 to 60.0)	37.9 (26.2 to 50.7)
CKD-EPI creatinine–cystatin C equation	28.8 (21.4 to 37.1)	30.1 (19.9 to 42.0)	27.3 (17.0 to 39.6)
β2M equation	34.5 (26.7 to 43.1)	17.8 (9.8 to 28.5)	53.0 (40.3 to 65.4)
$1-P_{20}$			
MDRD creatinine equation	32.4 (24.7 to 40.8)	26.0 (16.5 to 37.6)	39.4 (27.6 to 52.2)
CKD-EPI creatinine equation	37.4 (29.4 to 46.0)	38.4 (27.2 to 50.5)	36.4 (24.9 to 49.1)
CKD-EPI cystatin C equation	69.1 (60.7 to 76.6)	71.2 (59.5 to 81.2)	66.7 (54.0 to 77.8)
CKD-EPI creatinine–cystatin C equation	52.5 (43.9 to 61.1)	54.8 (42.7 to 66.5)	50.0 (37.4 to 62.6)
β2M equation	52.5 (43.9 to 61.1)	35.6 (24.8 to 47.7)	71.2 (58.8 to 81.7)

[a]Bias and relative bias are expressed as estimated glomerular filtration rate (eGFR) − measures of GFR (mGFR), where negative values represent an underestimation of mGFR by eGFR.
[b]Accuracy was calculated as the proportion of eGFR that differed from mGFR by more than 30% ($1-P_{30}$) and the proportion that differed by more than 20% ($1-P_{20}$).
β2M, β2-microgobulin; CI, confidence interval; CKD-EPI, Chronic Kidney Disease–Epidemiology; MDRD, Modification of Diet and Renal Disease; T1D, type 1 diabetes.

of cystatin C and creatinine performed better than eGFR by either marker alone in 805 adults with mean age 80 ± 4 years and mean mGFR of 62.4 ± 16.5 ml/min per 1.73 m^2 according to plasma clearance of iohexol.[22] These findings are inconsistent with our study, the Malaysian study, and the Icelandic study. Overall, the poor performance of eGFR by creatinine and cystatin C in the present study, and the inconsistency of findings across multiple studies is problematic because these equations are commonly applied to this population and inaccurate estimates of CKD prevalence and renal function can lead to disparities in treatment decisions, incorrect selection of interventions, and unnecessary health care costs.[41,42] Our study was able to provide a novel evaluation of eGFR by β2M, an equation for which accuracy had yet to be evaluated in older adults or in patients with T1D. GFR estimated by β2M had the lowest magnitude of bias but was highly imprecise when compared with eGFR by creatinine and cystatin C. We also found that performance of β2M was lower in patients with T1D compared with nondiabetic controls, which should be confirmed in younger adults with T1D. The identification of filtration and nonfiltration factors that may be associated with imprecision of eGFR by β2M is needed, specifically in T1D.

Annual reports from the US Renal Data System have confirmed that diabetes is the leading cause of CKD and ESRD, and that the age/sex/race-adjusted prevalence of ESRD has risen over time, with steeper increases among older adults.[21] Given that the general population is aging,[43] and prevalence of diabetes is increasing,[44] it is important to accurately identify kidney disease in older adults,

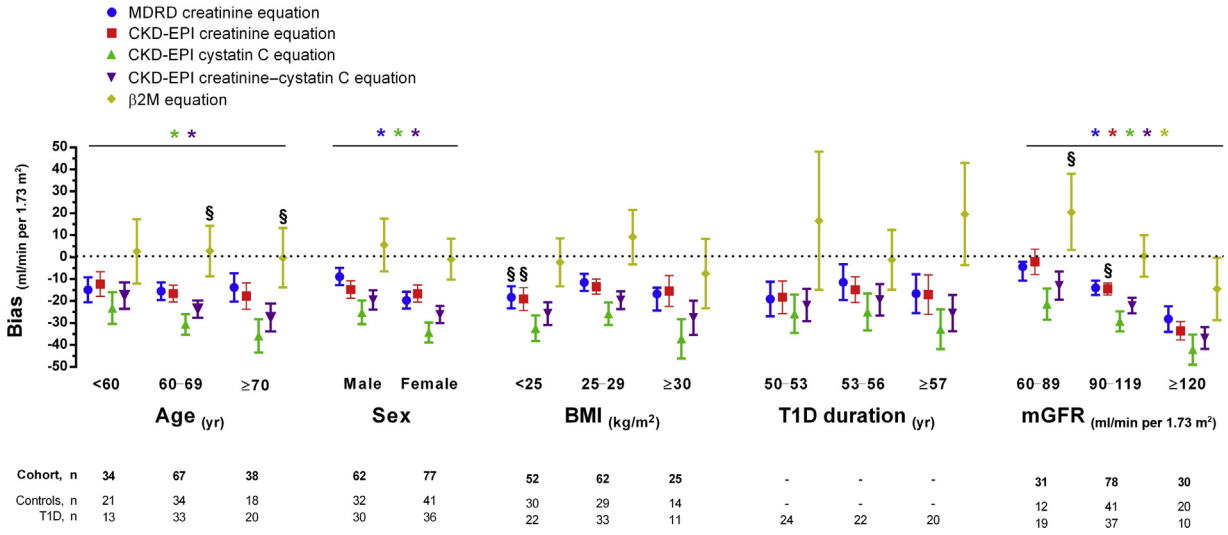

Figure 2. Comparison of the bias of the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease–Epidemiology (CKD-EPI), and β2-microgobulin (β2M) equations in participant subgroups. Bias is calculated as the mean difference between estimated glomerular filtration rate (eGFR) – measures of GFR (mGFR) where values below 0 represent an underestimation of mGFR. Bars indicate the 95% confidence intervals and *n* indicates the sample size. The mean bias and 95% confidence interval values for each subgroup are presented in Supplementary Table S2. **P* < 0.05 across subgroups. §*P* < 0.05 between patients with type 1 diabetes (T1D) and controls. BMI, body mass index.

especially in those with diabetes. Findings from the DCCT/EDIC study have demonstrated that eGFR may not accurately reflect changes over time in GFR in those with T1D.[45] Similarly, the significant underestimation, imprecision, and inaccuracy found in the present study has implications on the ability eGFR to accurately detect CKD in older adults with T1D. Although the poor performance of eGFR was nondifferential between older adults with and without T1D, except for β2M in which performance was lower in T1D, the inaccurate and imprecise ascertainment of eGFR in those with longstanding T1D is highly concerning because this subgroup of the population has an amplified risk for the development of CKD that requires accurate GFR estimation methods that are not susceptible to misclassification.[19]

Rapid GFR decline has been established as one of the earlier phenotypes of CKD, and has been strongly associated to risk of ESRD, and cardiovascular and all-cause mortality.[46–48] Ideally, eGFR equations should be able to detect early declines in GFR when interventions may be most effective in preserving renal structure and function.[49] The prevailing lack of precision and accuracy of eGFR when GFR >60 ml/min per 1.73 m^2 may hinder the ability to accurately detect these early changes, although inaccuracy in cross-sectional measures may not translate to inaccuracies in the change in values over time. In this study, we found greater bias at higher ranges of mGFR (60–89, 90–119, ≥120 ml/min per 1.73 m^2) for all 5 equations. This finding highlights the limitations of current eGFR equations for the cross-sectional identification of early renal function loss in older adults with preserved renal function.

The Kidney Disease Improving Global Outcomes guidelines recommend that clinical laboratories report eGFR by serum creatinine in adults, and to use either serum cystatin C–based eGFR or mGFR as a confirmatory test if a more accurate assessment is required for clinical decision making.[2] Although the CKD-EPI equations have demonstrated better accuracy than MDRD when GFR >60 ml/min per 1.73 m^2,[6,12,50] both sets of equations are still routinely applied in research and clinical practice across adult populations. One recent study evaluated the use of cystatin C to confirm a CKD diagnosis in a primary care cohort of older adults and demonstrated that eGFR by cystatin C did not result in a significant reduction of CKD diagnosis, did not improve risk prediction, and was associated with increased cost.[51] Similarly, another study demonstrated that declines in mGFR over a 2-year period did not show enhanced association with risk of ESRD, cardiovascular events, or death compared with eGFR by creatinine.[52] In the current study of eGFR accuracy, MDRD and CKD-EPI_{cr} had similar, but poor performance, whereas cystatin C–based eGFR had greater bias and lower accuracy, and misclassified a larger proportion of the participants into different, clinically significant, GFR range subgroups. The evaluation of the novel β2M equation did demonstrate stronger operating characteristics than creatinine- and cystatin C–based eGFR with respect to bias, but its usefulness was limited by a lack of precision and accuracy. Importantly, the MDRD, CKD-EPI, and β2M equation development studies were limited in their inclusion of older adults in both internal derivation and external

validation datasets.[5,6,18] These limitations support the concerns raised by the findings of the current study: current eGFR equations are not accurate or precise in older adults with preserved renal function.

Strengths of our study include use of a unique cohort of older adults with and without T1D, measurement of creatinine, cystatin C, and β2M using standardized assays, performance of an inulin clearance during a euglycemic clamp after maintaining a standard diet for a week subsequent to washing out antihypertensive medications, and extensive statistical analyses including agreement estimates, performance metrics, and 95% confidence intervals for testing performance of eGFR in the overall cohort and subgroups defined by demographic and clinical characteristics. However, this study has limitations. First, none of the study participants had mGFR <60 ml/min per 1.73 m^2 and we were therefore not able to evaluate eGFR performance in older adults with CKD. Second, the study recruited participants with ≥50 years of T1D, and there is a potential incidence-prevalence (survivorship) bias toward exclusion of participants with more severe complications. Third, our study population was primarily white (90%) and our results may not extend to other ethnic groups. Fourth, eGFR equations were generated from ^{125}I-iothalamate data,[5,6] rather than inulin clearance, which may in part explain the inaccuracy and imprecision we observed between eGFR and mGFR. Finally, although 2 clearance measures were used calculate eGFR and mGFR according to reference standard methods, they are susceptible to measurement error, which may in part explain inaccuracy and imprecision.

In conclusion, eGFR by serum creatinine, cystatin C, and β2M did not accurately or precisely ascertain GFR in older adults with and without T1D who had preserved renal function according to mGFR. Cystatin C had lower performance than creatinine as a filtration marker of GFR and had lower performance in older subgroups, and the combination of both markers did not outperform creatinine alone. The novel β2M equation did demonstrate stronger operating characteristics than creatinine- and cystatin C–based eGFR with respect to bias, but was limited by a lack of precision and accuracy and had lower performance in T1D. For clinical care, greater bias and lower accuracy at higher GFR ranges may hinder the ability to detect early phenotypes of kidney disease in older adults when interventions may be most effective and may lead to false-positive identification of CKD. Better estimates of GFR are needed for research and clinical practice in older adults, an important subgroup of the population who are at greater risk for development of CKD and its sequelae, and for whom accurate classification of renal function is essential for clinical care.

DISCLOSURE

JAL has received speaker honoraria from Novo Nordisk, Merck Sharp Dohme, Eli Lilly, Intarcia Therapeutics, and AstraZenca. GB has received speaker honoraria from Johnson & Johnson. HAK has received support from Sanofi. NP has received support from Toshiba Medical. DZIC has received speaker honoraria from Janssen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, and Merck and has received research grant support from AstraZeneca, Merck, and Boehringer Ingelheim. BAP has received speaker honoraria from Medtronic, Johnson & Johnson, Roche, GlaxoSmithKline Canada, Novo Nordisk, and Sanofi; has received research grant support from Medtronic and Boehringer Ingelheim; and serves as a consultant for NeuroMetrix. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary Methods. Pre-study procedures and GFR measurement protocol.

Table S1. GFR estimating equations.

Table S2. Comparison of the mean bias between eGFR–mGFR for the MDRD, CKD-EPI, and β2M equations in the 139 participants by subgroups.

Supplementary material is linked to the online version of the paper at www.kireports.org.

REFERENCES

1. Levey AS, Inker LA. GFR as the "gold standard": estimated, measured, and true. *Am J Kidney Dis*. 2016;67:9–12.

2. Kidney Disease: Improving Global Outcomes (KDIGO). Clinical practice guidelines for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1–150.
3. Traynor J, Mactier R, Geddes CC, Fox JG. How to measure renal function in clinical practice. *BMJ*. 2006;333:733–737.
4. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function — measured and estimated glomerular filtration rate. *N Engl J Med*. 2006;354:2473–2483.
5. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145(4):247–254.
6. Levey AS, Stevens LA, Schmid CH, et al. A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med*. 2009;150(9):604–612.
7. Coresh J, Astor BC, Greene T, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis*. 2003;41:1–12.
8. Stevens LA, Levey AS. Chronic kidney disease in the elderly–how to assess risk. *N Engl J Med*. 2005;352:2122–2124.
9. Filler G, Bokenkamp A, Hofmann W, et al. Cystatin C as a marker of GFR–history, indications, and future research. *Clin Biochem*. 2005;38:1–8.
10. Foster MC, Levey AS, Inker LA, et al. Non-GFR determinants of low-molecular-weight serum protein filtration markers in the elderly: AGES-Kidney and MESA-Kidney. *Am J Kidney Dis*. 2017;70:406–414.
11. Stevens LA, Schmid CH, Greene T, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int*. 2009;75:652–660.
12. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367:20–29.
13. Schaeffner ES, Ebert N, Delanaye P, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. *Ann Intern Med*. 2012;157:471–481.
14. Peralta CA, Shlipak MG, Judd S, et al. Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *JAMA*. 2011;305:1545–1552.
15. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med*. 2013;369:932–943.
16. Winchester JF, Salsberg JA, Levin NW. Beta-2 microglobulin in ESRD: an in-depth review. *Adv Ren Replace Ther*. 2003;10:279–309.
17. Astor BC, Shafi T, Hoogeveen RC, et al. Novel markers of kidney function as predictors of end-stage kidney disease, cardiovascular disease and mortality in the general population. *Am J Kidney Dis*. 2012;59:653–662.
18. Inker LA, Tighiouart H, Coresh J, et al. GFR estimation using β-trace protein and β(2)-microglobulin in CKD. *Am J Kidney Dis*. 2016;67:40–48.
19. Pambianco G, Costacou T, Ellis D, et al. The 30-year natural history of type 1 diabetes complications: The Pittsburgh Epidemiology of Diabetes Complications Study Experience. *Diabetes*. 2006;55:1463–1469.
20. Cherney DZ, Sochett EB, Dekker MG, Perkins BA. Ability of cystatin C to detect acute changes in glomerular filtration rate provoked by hyperglycaemia in uncomplicated Type 1 diabetes. *Diabet Med*. 2010;27:1358–1365.
21. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2016 Annual Data Report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2016;69:S1–S688.
22. Fan L, Levey AS, Gudnason V, et al. Comparing GFR estimating equations using cystatin C and creatinine in elderly individuals. *J Am Soc Nephrol*. 2015;26:1982–1989.
23. Earley A, Miskulin D, Lamb EJ, et al. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. *Ann Intern Med*. 2012;156:785–795.
24. Bevc S, Hojs R, Ekart R, et al. Simple cystatin C formula compared to sophisticated CKD-EPI formulas for estimation of glomerular filtration rate in the elderly. *Ther Apher Dial*. 2011;15:261–268.
25. Carter JL, Stevens PE, Irving JE, Lamb EJ. Estimating glomerular filtration rate:comparison of the CKD-EPI and MDRD equations in a large UK cohort with particular emphasis on the effect of age. *QJM*. 2011;104:839–847.
26. Gaspari F, Ruggenenti P, Porrini E, et al. The GFR and GFR decline cannot be accurately estimated in type 2 diabetics. *Kidney Int*. 2013;84:164–173.
27. Murata K, Baumann NA, Saenger AK, et al. Relative performance of the MDRD and CKD-EPI equations for estimating glomerular filtration rate among patients with varied clinical presentations. *Clin J Am Soc Nephrol*. 2011;6:1963–1972.
28. Lovshin JA, Boulet G, Lytvyn Y, et al. Renin-angiotensin-aldosterone system activation in long-standing type 1 diabetes. *JCI Insight*. 2018;3:96968.
29. Boulet G, Halpern EM, Lovblom LE, et al. Prevalence of insulin pump therapy and its association with measures of glycemic control: results from the Canadian Study of Longevity in Type 1 Diabetes. *Diabetes Technol Ther*. 2016;18:298–307.
30. Bai JW, Lovblom LE, Cardinez M, et al. Neuropathy and presence of emotional distress and depression in longstanding diabetes: results from the Canadian study of longevity in type 1 diabetes. *J Diabetes Complications*. 2017;31:1318–1324.
31. Weisman A, Rovinski R, Farooqi MA, et al. Commonly measured clinical variables are not associated with burden of complications in long-standing type 1 diabetes: results from the Canadian Study of Longevity in Diabetes. *Diabetes Care*. 2016;39:e67–e68.
32. Bai JW, Boulet G, Halpern EM, et al. Cardiovascular disease guideline adherence and self-reported statin use in long-standing type 1 diabetes: results from the Canadian study of longevity in diabetes cohort. *Cardiovasc Diabetol*. 2016;15:14.
33. Weisman A, Lovblom LE, Keenan HA, et al. Diabetes care disparities in long-standing type 1 diabetes in Canada and the U.S.: a cross-sectional comparison. *Diabetes Care*. 2018;41:88–95.
34. Schnurr E, Lahme W, Kuppers H. Measurement of renal clearance of inulin and PAH in the steady state without urine collection. *Clin Nephrol*. 1980;13:26–29.
35. Inker LA, Eckfeldt J, Levey AS, et al. Expressing the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) cystatin C equations for estimating GFR with standardized serum cystatin C values. *Am J Kidney Dis*. 2011;58:682–684.

36. Grubb A, Blirup-Jensen S, Lindstrom V, et al. First certified reference material for cystatin C in human serum ERM-DA471/IFCC. *Clin Chem Lab Med*. 2010;48:1619–1621.
37. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1:307–310.
38. Stevens LA, Zhang Y, Schmid CH. Evaluating the performance of GFR estimating equations. *J Nephrol*. 2008;21:797–807.
39. Jalalonmuhali M, Elagel SMA, Tan MP, et al. Estimating renal function in the elderly Malaysian patients attending medical outpatient clinic: a comparison between creatinine based and cystatin-C based equations. *Int J Nephrol*. 2018;2018:3081518.
40. Bjork J, Grubb A, Gudnason V, et al. Comparison of glomerular filtration rate estimating equations derived from creatinine and cystatin C: validation in the Age, Gene/Environment Susceptibility-Reykjavik elderly cohort. *Nephrol Dial Transplant*. 2018;33:1380–1388.
41. Standards of medical care in diabetes–2013. *Diabetes Care*. 2013;36(Suppl 1):S11–S66.
42. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60:850–886.
43. Lutz W, Sanderson W, Scherbov S. The coming acceleration of global population ageing. *Nature*. 2008;451:716–719.
44. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2010;87:4–14.
45. de Boer IH, Sun W, Cleary PA, et al. Longitudinal changes in estimated and measured GFR in type 1 diabetes. *J Am Soc Nephrol*. 2014;25:810–818.
46. Al-Aly Z, Zeringue A, Fu J, et al. Rate of kidney function decline associates with mortality. *J Am Soc Nephrol*. 2010;21:1961–1969.
47. Rifkin DE, Shlipak MG, Katz R, et al. Rapid kidney function decline and mortality risk in older adults. *Arch Intern Med*. 2008;168:2212–2218.
48. Krolewski AS, Skupien J, Rossing P, Warram JH. Fast renal decline to end-stage renal disease: an unrecognized feature of nephropathy in diabetes. *Kidney Int*. 2017;91:1300–1311.
49. Bjornstad P, Cherney DZ, Maahs DM. Update on estimation of kidney function in diabetic kidney disease. *Curr Diab Rep*. 2015;15:57.
50. Stevens LA, Schmid CH, Greene T, et al. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. *Am J Kidney Dis*. 2010;56:486–495.
51. Shardlow A, McIntyre NJ, Fraser SDS, et al. The clinical utility and cost impact of cystatin C measurement in the diagnosis and management of chronic kidney disease: a primary care cohort study. *PLoS Med*. 2017;14:e1002400.
52. Ku E, Xie D, Shlipak M, et al. Change in measured GFR versus eGFR and CKD outcomes. *J Am Soc Nephrol*. 2016;27:2196–2204.