Clinical Kidney Journal, 2020, vol. 13, no. 3, 397–401

doi: 10.1093/ckj/sfz083
Advance Access Publication Date: 23 July 2019
Original Article

ORIGINAL ARTICLE

Validation of a simple equation for glomerular filtration rate measurement based on plasma iohexol disappearance

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ABSTRACT

Background. A simple equation for glomerular filtration rate (GFR) measurement based on only plasma samples during the slow compartment after injection of iohexol was previously developed among children with chronic kidney disease and adult men with or at risk of HIV infection [Chronic Kidney Disease in Children (CKiD)-Multicenter AIDS Cohort Study (MACS) equation], but has not been externally validated. We aimed to evaluate the performance of the CKiD-MACS equation among elderly participants in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort who underwent directly measured iohexol GFR.

Methods. Using data from 287 participants of the MESA-Kidney study who underwent a five-sample measured iohexol GFR (two and three samples in the fast and slow compartments, respectively), we assessed the performance of the CKiD-MACS equation using only plasma samples in the slow compartment by sex, race and age. Agreement was assessed by bias, correlation, proportion within 5 and 10%, and the root mean square error (RMSE).

Results. The average age and GFR of the participants were 71 years and 70.8 mL/min/1.73 m^2, respectively, and 46% were black. The equation yielded excellent agreement within stratified groups with high correlation (>0.96), low bias (≤1.2 mL/min/1.73 m^2) and low RMSE (<4.2 mL/min/1.73 m^2).

Conclusions. The CKiD-MACS equation demonstrated valid GFR measurement using only samples in the slow compartment in this racially diverse, elderly population. While the equation yielded practically the same results as the original Brochner-Mortensen equation, the CKiD-MACS equation conforms to theoretical principles embedded in the two-compartment model of direct GFR measurement.

Keywords: clinical nephrology, glomerular filtration rate, plasma disappearance of iohexol

Received: 21.1.2019; Editorial decision: 2.6.2019

INTRODUCTION

Directly measured glomerular filtration rate (GFR) by plasma clearance of iohexol is typically based on a two-compartment model, which corresponds to plasma samples taken within 60 min of iohexol injection (often referred to as fast compartment) and samples taken after 120 min of iohexol injection (often referred to as slow compartment). With the aim to reproduce the directly measured GFR by plasma disappearance of iohexol from the slow compartment only, a simple universal equation yielding $\widehat{GFR}$ was developed for diverse populations [1]. This equation was developed in a cohort of children with chronic kidney disease (the Chronic Kidney Disease in Children cohort: CKiD) and adult men with normal GFR (the Multicenter AIDS Cohort Study: MACS), representing disparate clinical populations. However, the iohexol measurements were conducted in the absence of proficiency standards. Recently, a multicenter comparison assessed the agreement of iohexol measurement across laboratories and described calibration methods for valid measurement of iohexol [2]. This analysis demonstrated that iohexol concentrations from CKiD and MACS samples required calibration by multiplication of 0.89. Since the data used to develop the proposed equation were not calibrated to external laboratories, the multiplicative factor of 0.89 resulted in the key equation parameter being equal to 0.135 (= 0.12/0.89). Thus, the equation calibrated to external laboratories is of the form $\widehat{GFR} = \text{slowGFR}/(1 + 0.135 \times \text{slowGFR}/100)$, where slowGFR refers to GFR calibrated to body surface area (BSA) from the slow compartment only (see Materials and methods section for notation).

While this equation performed well in these two cohorts and has strong theoretical principals, it has not been well validated in external populations [3]. To test the validity of this calibrated equation, we evaluated its application in a subpopulation of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort who underwent a directly measured iohexol protocol [4] (MESA-Kidney) similar to the CKiD and MACS protocols. The MESA-Kidney comprised an elderly population that was balanced by sex and race (black and white).

Specifically, we aimed to assess agreement of the equation in this population of older adults, overall and when stratified by sex, race and age. We hypothesized that the calibrated equation to calculate full GFR from iohexol measurements in the slow (second) compartment would demonstrate good agreement in the MESA-Kidney population.

MATERIALS AND METHODS

Study population

The MESA study is a longitudinal cohort of four racial and ethnic groups designed to describe the prevalence of subclinical cardiovascular disease (CVD), its risk factors and progression to clinical CVD. A selected subgroup of the larger MESA cohort participated in the MESA-Kidney GFR study, provided directly measured GFR data and was located at the Johns Hopkins University field center in Baltimore, MD. The recruitment in MESA-Kidney occurred between May 2012 and April 2014. A full description of the MESA study has been previously published [5], as well as the MESA-Kidney study [4].

Direct measurement of GFR

GFR was measured from an initial intravenous injection of 5 mL solution containing ~3200 mg of iohexol (Omnipaque 300; GE Healthcare). Subsequent blood samples were obtained at ~10, 30, 120, 240 and 300 min for measurement of plasma concentrations of iohexol. Exact timings of each blood sample were recorded and used to calculate GFR in mL/min/1.73 m^2 from a two-compartment model, with BSA based on the Haycock formula [6]. This two-compartment model comprised the fast compartment based on the early time points at 10 and 30 min; and the slow compartment based on the late time points at 120, 240 and 300 min. Generally, the slow compartment is operationally defined as sampling time points after about 60 min for normal to high GFR [3, 7]. All GFR measures reported here are BSA-calibrated to 1.73 m^2. For this protocol, the previously used notation [1] $GFR_{x,y}$ (in which x is the number of blood samples in the fast compartment and y is the number of blood samples in the slow compartment) is $GFR_{2,3}$. We also refer to $GFR_{0,3}$ as the slow GFR as this metric of plasma disappearance is based on only time points in the slow compartment (i.e. zero time points in the fast compartment). The GFR based on the CKiD-MACS equation is denoted as $\widehat{GFR}_{2,3}$ ('$GFR_{2,3}$ hat'). Details of the mathematical derivation of the two-compartment GFR have been previously described [1, 4, 7, 8]. Of 294 participants who underwent an iohexol injection, 7 had missing data in the fast compartment ($n = 6$) or extreme fast and slow compartment data ($n = 1$). The analytic dataset comprised 287 participants with a valid $GFR_{2,3}$.

Statistical analyses

Statistical analyses included quantifying agreement of the calibrated equation [$\widehat{GFR}_{2,3} = GFR_{0,3}/(1 + 0.135 \text{ x } GFR_{0,3}/100)$] with measured (observed) $GFR_{2,3}$. Agreement plots in the log scale visually depicted the concordance between the two measures and were stratified by key characteristics. Specifically, the MESA-Kidney population was stratified by men and women, non-black and black, and age <70 years and ≥70 years. Within each group, the root mean square error (RMSE), proportion within 5% (P5%) and 10% (P10%), concordance correlation coefficient and average bias (mL/min/1.73 m^2) were calculated, and 95% confidence ellipses were derived from a bivariate normal distribution (in the log scale). Traditional Bland–Altman agreement plots were constructed and presented as Supplementary material. Additionally, we replicated the analysis that derived the original equation in the overall (i.e. non-stratified) MESA-Kidney population. Here, the ratio of fast area to slow area (in the log scale) was regressed on $GFR_{0,3}/100$ (in the log scale), with the slope enforced to be equal to 1. The exponentiated intercept of this model was compared with the coefficient of 0.135 in the calibrated equation.

RESULTS

Table 1 presents the demographic and clinical characteristics of the 287 MESA participants who underwent GFR measurement by iohexol plasma disappearance and had valid data for both the fast and slow compartments. The median age was 71 years, 49% were women ($n = 137$) and 46% were black ($n = 133$); the median GFR was 70.8 mL/min/1.73 m^2. In contrast, the MACS and CKiD populations were younger (median age = 50 and 11 years), 0% and 38% were female, and 35% and 23% were black, with a median GFR of 97.2 and 39.2 mL/min/1.73 m^2, respectively (Table 1). A description of the characteristics of the MESA participants stratified by sex, race, and age <70 and ≥70 years is presented in Supplementary data, Table S1.

Figure 1 presents the agreement plots of GFR calculated from all measurements in both compartments with GFR calculated

Table 1. Demographic and clinical characteristics of the MESA-Kidney cohort and the original CKiD and MACS contributing iohexol GFR data for universal GFR determination

Variable	MESA-Kidney ($n = 287$)	MACS ($n = 527$)	CKiD ($n = 514$)
Age, years	71 (64–78)	50 (46–57)	11 (7–14)
Female	137 (48)	0 (0)	195 (38)
Black race	133 (46)	184 (35)	118 (23)
Height, m	1.68 (1.61–1.75)	1.76 (1.71–1.80)	1.40 (1.20–1.58)
Weight, kg	84 (73–95)	81 (73–90)	36 (24–55)
BMI, kg/m^2	29.4 (26.1–33.0)	26.2 (23.9–28.8)	18.3 (16.2–22.0)
BSA, m^2 (Haycock)	2.01 (1.83–2.17)	2.00 (1.87–2.14)	1.19 (0.89–1.57)
HIV-infected	0 (0)	369 (70)	0 (0)
Laboratory	University of Minnesota	University of Rochester	University of Rochester
Full iohexol GFR, mL/min/1.73 m^2	70.8[a] (58.6–81.9)	97.2[b] (84.5–111.4)	39.2[c] (29.2–49.8)

Median (interquartile range) or *n* (%). BMI, body mass index.
[a]Based on plasma samples at 10 and 30 min (fast compartment), and 120, 240 and 300 min (slow compartment) after iohexol injection ($GFR_{2,3}$).
[b]Based on plasma samples at 10 and 30 min (fast compartment), and 120 and 240 min (slow compartment) after iohexol injection ($GFR_{2,2}$).
[c]Based on plasma samples at 10 and 30 min (fast compartment), and 120 and 300 min (slow compartment) after iohexol injection resulting ($GFR_{2,2}$).

from measurements in the slow compartment only (i.e. $\widehat{GFR}_{2,3}$ as the equation-based GFR compared with the observed $GFR_{2,3}$; see Materials and methods section for explanation of nomenclature) among the MESA-Kidney participants, stratified by sex, race and age. Overall, the concordance correlation coefficient was 0.981 and 82% [95% confidence interval (CI) 77–87%] were within 5% of $GFR_{2,3}$ and 96% (95% CI 93–98%) were within 10% of $GFR_{2,3}$. This estimate of accuracy was similar to that observed in the original CKiD and MACS validation (79% and 96%, respectively). By subgroups (sex, race and age), the P5% ranged from 76% to 87%, the P10% ranged from 95% to 97% and the RMSE was between 2.4 and 4.2 mL/min/1.73 m^2. The concordance correlation coefficient was high for all subgroups, ranging from 0.961 (participants <70 years) to 0.989 (participants ≥70 years). Notably, these values were similar to those reported in the original equation development (0.996 for CKiD and 0.980 for MACS). The average overall bias was negligible (+0.75 mL/min/1.73 m^2; 95% CI +0.36 to +1.15), and this was consistent with all subgroup (biases ≤1.2 mL/min/1.73 m^2). While the minimal biases were significantly different from 0, this was due to the exceedingly high correlation. The ellipsoids, which represent 95% of data, were narrow and nearly bisected by the agreement line depicting very high concordance. We also evaluated agreement by obesity status and found similar excellent agreement (bias within 1 mL/min/1.73 m^2, correlation >0.980 and RMSE = 3.3 mL/min/1.73 m^2 for both groups; not graphically shown). To visualize bias, traditional Bland–Altman agreement plots are presented in Supplementary data, Figure S1.

Lastly, we replicated the original CKiD-MACS analysis to derive the coefficient for the correction equation using the MESA data. Specifically, we regressed the logarithm of $(GFR_{0,3} - GFR_{2,3})/GFR_{2,3}$ [=log of (fast area/slow area)] on the logarithm of $GFR_{0,3}$ to derive a MESA-specific coefficient for this equation. From this regression, the parameter was estimated as 0.138 (95% CI 0.131–0.145), and the 95% CI encompassed the calibrated parameter of 0.135.

DISCUSSION

An equation to determine GFR based on time points only in the slow compartment was previously published based on the data from children with chronic kidney disease, and HIV-infected and uninfected men. This equation has since been calibrated to external laboratories. The present analysis used data from MESA-Kidney to validate this equation in an elderly population balanced by sex and race. The results demonstrate that the calibrated equation performed well at approximating the two-compartment GFR from the one-compartment data only, overall and when stratified by sex, race and age. The simple equation derived in two disparate populations (adult and pediatric) demonstrated excellent agreement in this third disparate (older) population, which provides evidence for its validity outside the populations in which it was developed [3]. This equation has applications in research by reducing participant burden with fewer plasma samples and corresponding lowering laboratory costs. In addition, if samples in the fast compartment cannot be obtained, or are lost, damaged or measured incorrectly, the GFR measurement may be recovered with this equation. These benefits extend toward clinical applications as well.

The calibration of iohexol data [2] modified the equation modestly and was consistent with the parameter estimated from the MESA-Kidney data. This gives confidence toward the applicability of the equation in other populations, including older individuals. Since the results from the MESA-Kidney study were very close to the calibrated CKiD-MACS equation, we recommend the calibrated CKiD-MACS equation for clinical or research purposes.

We also evaluated the original 1972 Brochner-Mortensen (BM) adult equation [9] and found that this equation yielded similar $\widehat{GFR}_{2,3}$ values to the CKiD-MACS equation. This agreement is not surprising as the BM equation corresponds to the simplest (linear) Taylor expansion of the CKiD-MACS equation. Specifically, GFR/slowGFR = 1/[1 + 0.135 × (slowGFR/100)] is approximated by 1−0.135 × (slowGFR/100) by Taylor expansion, which is very similar to the BM equation of GFR/slowGFR = 0.9908−0.1218 × (slowGFR/100). It is apparent that from the BM equation that when slowGFR approaches 0, the ratio of GFR/slowGFR is 0.9908, which is a theoretical weakness since this ratio must be 1 (which is the case in the CKiD-MACS equation). While both equations are functionally equivalent, the CKiD-MACS equation conforms to the mathematical principles embedded within the two-compartment model of GFR. Furthermore, while the difference is small, the BM equation for GFR/slowGFR is systematically lower than the CKiD-MACS equation at all the possible values of slowGFR.

A similar equation was also proposed by Fleming [10] in which the coefficient for the equation was proposed as 0.17. Pottel and Gheysens compared the Fleming and CKiD-MACS

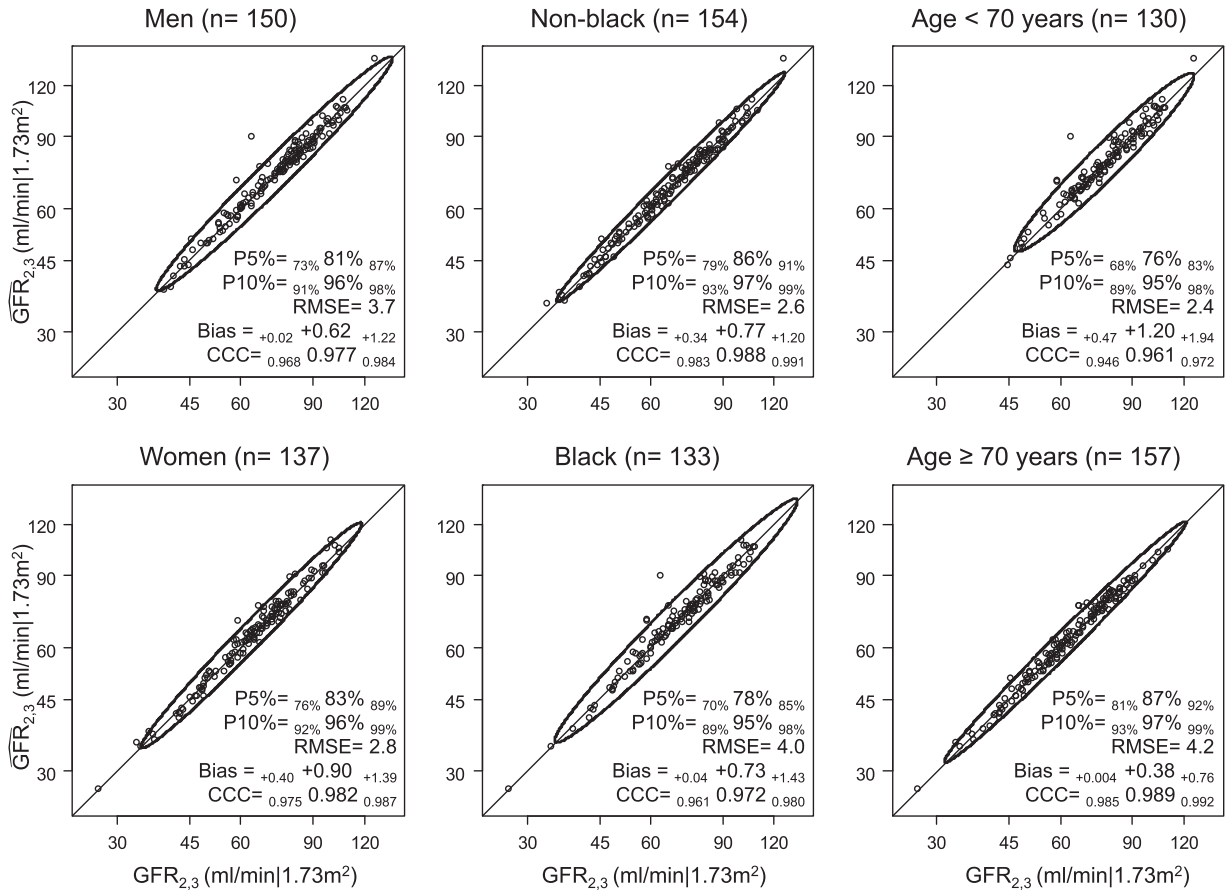

FIGURE 1: Agreement plots comparing $\widehat{GFR}_{2,3}$ (y-axis) to observed $GFR_{2,3}$ (x-axis) by sex, race and age categories. $\widehat{GFR}_{2,3}$ is based on the calibrated CKiD-MACS equation. Ellipsoids depict the 95% confidence region from a bivariate normal distribution. P5% and P10% is the proportion of $\widehat{GFR}_{2,3}$ within 5% and 10% of $GFR_{2,3}$, respectively. RMSE units are mL/min/1.73 m^2. Bias is the average difference between $\widehat{GFR}_{2,3}$ and $GFR_{2,3}$ in mL/min/1.73 m^2 (where $GFR_{2,3}$ denotes GFR calculated from all measurements in both compartments and $\widehat{GFR}_{2,3}$ denotes GFR calculated from measurements in the slow compartment only; see Materials and methods section for explanation of nomenclature). CCC refers to the concordance correlation coefficient. Subscript values represent the 95% CIs for the concordance correlation coefficient and mean bias ($_{\text{Lower confidence limit}}$ Estimate $_{\text{Upper confidence limit}}$).

equations and found that the latter had preferred properties in a large dataset [11]. Practically, the equations yield similar results, particularly in normal and low kidney function, but we note the convergence of similarities suggests that these equations capture the same physiologic principles of the distribution of plasma clearance of a marker within the first (fast) compartment. The original BM equation was derived as a simple solution and based on a linear regression model with no intercept and was based on 74 adult patients using [^{51}Cr]EDTA clearance. Fleming derived the proposed equation primarily based on physiologic principles, data from 10 subjects with evaluation in 200 clinical studies. In contrast, the CKiD-MACS equation was developed and validated from 1041 subjects contributing 1347 iohexol GFR studies based on a series of regression models, and identified that the fast area is dependent on BSA alone. We further note that the slowGFR (i.e. $GFR_{0,3}$ in this example) is indexed to BSA as previously described [1]. Since the fast area is dependent on BSA and the imputation of the missing fast area from a slow compartment only, GFR to derive $\widehat{GFR}_{2,3}$ requires that slowGFR be indexed to BSA when using the equation.

The diverse population of older adults with low–normal kidney function in the MESA-Kidney study provided a crucial population that was not represented in the original proposed equation. However, not all groups across the age and GFR spectrum were represented here; in particular, women aged 18–50 years with low and normal GFR remain unstudied, and no participants had hyperfiltration. Despite this limitation, the consistency of results in the three diverse cohorts indicates that this equation will likely perform well in other populations. In addition, we note that in the original development of the equation, men with hyperfiltration were included from the MACS cohort [1, 12].

The calibrated CKiD-MACS equation to compute GFR from two-compartment plasma clearance of iohexol from measurements from the slow compartment only was accurate in a completely disparate population of elderly individuals with low–normal GFR, and the results validate this simpler method for GFR measurement.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

ACKNOWLEDGEMENTS

The authors thank the other investigators, the staff and participants in the MESA Study for valuable contributions. A full list of participating MESA investigators and institutions can be found at www.mesa-nhlbi.org.

FUNDING

Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (NIH). This publication was made possible by the Johns Hopkins Institute for Clinical and Translational Research, which is funded in part by grant UL1 TR 001079 from the National Center for Advancing Translational Sciences, a component of the NIH, and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the Johns Hopkins Institute for Clinical and Translational Research, National Center for Advancing Translational Sciences or NIH. This research was also supported by grant R01DK087961 from the NIH; contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung and Blood Institute; and grants UL1-TR-000040 and UL1-TR-001079 from the National Center for Research Resources. The funders of this study had no role in the study design; collection, analysis and interpretation of the data; writing of the report; or the decision to submit the report for publication. Efforts for D.K.N. and A.M. were supported by grant U24-DK-66116.

AUTHORS' CONTRIBUTIONS

L.A.I., M.G.S., A.S.L. and T.S. contributed to the research idea and study design; L.A.I., A.S.L. and T.S. were responsible for acquisition of data; D.K.N., T.S. and A.M. were responsible for statistical analysis and interpretation; D.K.N. was involved in drafting of manuscript; L.A.I., A.S.L., M.G.S., T.S. and A.M. were responsible for critical revision of manuscript for important intellectual content. All authors approved the final version of this manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

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