AJKD
Original Investigation

Measuring GFR: A Systematic Review

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Background: No comprehensive systematic review of the accuracy of glomerular filtration rate (GFR) measurement methods using renal inulin clearance as reference has been published.

Study Design: Systematic review with meta-analysis of cross-sectional diagnostic studies.

Setting & Population: Published original studies and systematic reviews in any population.

Selection Criteria for Studies: Index and reference measurements conducted within 48 hours; at least 15 participants studied; GFR markers measured in plasma or urine; plasma clearance calculation algorithm verified in another study; tubular secretion of creatinine had not been blocked by medicines.

Index Tests: Endogenous creatinine clearance; renal or plasma clearance of chromium 51−labeled ethylenediaminetetraacetic acid (^{51}Cr-EDTA), diethylenetriaminepentaacetic acid (DTPA), iohexol, and iothalamate; and plasma clearance of inulin.

Reference Test: Renal inulin clearance measured under continuous inulin infusion and urine collection.

Results: Mean bias $< 10\%$, median bias $< 5\%$, the proportion of errors in the index measurements that did not exceed 30% (P_{30}) $\geq 80\%$, and $P_{10} \geq 50\%$ were set as requirements for sufficient accuracy. Based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, the quality of evidence across studies was rated for each index method. Renal clearance of iothalamate measured GFR with sufficient accuracy (strong evidence). Renal and plasma clearance of ^{51}Cr-EDTA and plasma clearance of iohexol were sufficiently accurate to measure GFR (moderately strong evidence). Renal clearance of DTPA, renal clearance of iohexol, and plasma clearance of inulin had sufficient accuracy (limited evidence). Endogenous creatinine clearance was an inaccurate method (strong evidence), as was plasma clearance of DTPA (limited evidence). The evidence to determine the accuracy of plasma iothalamate clearance was insufficient. With the exception of plasma clearance of inulin, only renal clearance methods had $P_{30} > 90\%$.

Limitations: The included studies were few and most were old and small, which may limit generalizability. Requirements for sufficient accuracy may depend on clinical setting.

Conclusions: At least moderately strong evidence suggests that renal clearance of ^{51}Cr-EDTA or iothalamate and plasma clearance of ^{51}Cr-EDTA or iohexol are sufficiently accurate methods to measure GFR.

Am J Kidney Dis. 64(3):411-424. © *2014 by the National Kidney Foundation, Inc.*

INDEX WORDS: Glomerular filtration rate (GFR); glomerular filtration rate (GFR) measurement; renal function; clearance marker; accuracy.

Direct measurement of glomerular filtration rate (GFR) is impossible because the filtration process simultaneously takes place in millions of glomeruli and filtrate composition and volume change when passing through the kidney. Instead, methods that record the clearance of exogenous substances that are eliminated by filtration only and neither secreted nor reabsorbed in the kidney are used. Classic inulin clearance during continuous inulin infusion and urine collection is considered the gold-standard method for measuring GFR.[1] However, it is a cumbersome method and lately, inulin also has become expensive. Therefore, in clinical practice and research, other clearance markers and methods are being used. These include renal (marker concentration measurements in urine and plasma) and plasma (marker concentration measurements in plasma only) clearance of chromium 51−labeled ethylenediaminetetraacetic acid

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**A list of the members of the Swedish Council on Health Technology Assessment (Swedish abbreviation, SBU) GFR Review Group appears in the Acknowledgements.*

Received November 9, 2013. Accepted in revised form April 4, 2014. Originally published online May 17, 2014.

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0272-6386/$36.00
http://dx.doi.org/10.1053/j.ajkd.2014.04.010

(^{51}Cr-EDTA), diethylenetriaminepentaacetic acid (DTPA), iohexol, and iothalamate. The choice of the marker depends on availability and tradition.

The accuracy of the methods to measure GFR is of critical importance. In clinical practice, accurate dosing of several medicines, such as cytostatics, is guided by measured GFR. Also, verifying normal kidney function in potential kidney donors relies on accurate GFR measurement. GFR estimating equations depend on the performance of the GFR measurement methods used as reference.

A narrative review of the performance of GFR measurement methods recently has been published.[2] To our knowledge, no comprehensive systematic review of the accuracy of GFR measurement methods using renal inulin clearance as the reference method has been published.

The aim of the present systematic review was to assess the accuracy of measuring GFR with endogenous creatinine clearance; renal and plasma clearance of ^{51}Cr-EDTA, DTPA, iohexol, and iothalamate; and plasma clearance of inulin. Renal inulin clearance was used as reference. The present study is based on extended analyses of results recently published in Swedish as part of a systematic review of methods to estimate GFR.[3]

METHODS

Search Strategy

The search strategy was adapted from the PICO process (population [adults, children, elderly, and different patient groups], index test [endogenous creatinine clearance; renal and plasma clearance of ^{51}Cr-EDTA, DTPA, iohexol, and iothalamate; and plasma clearance of inulin], control/reference test [renal inulin clearance], and outcome [bias, precision, and accuracy]). Librarians conducted the literature search in PubMed, Cochrane Library, EMBASE, CINAHL (Cumulative Index to Nursing and Allied Heath Literature). No earliest time limit was set. The main search was conducted July 12, 2011, and an update search, March 11, 2013. Further publications identified from reference lists and known publications were included. The literature search phrases are available in Item S1 (provided as online supplementary material).

Study Inclusion Criteria

The abstracts were evaluated by 2 independent reviewers and full-text articles were ordered if one or both reviewers regarded the publication as potentially relevant. Original studies and systematic reviews written in English or the Scandinavian languages were considered.

Study inclusion criteria were as follows: (1) the study compared endogenous creatinine clearance; renal or plasma clearance of ^{51}Cr-EDTA, DTPA, iohexol, or iothalamate; or plasma clearance of inulin to renal inulin clearance measured under continuous inulin infusion and urine collection; (2) index and reference measurements were conducted within 48 hours; (3) a minimum of 15 participants were studied (a minimum of 20 participants was required in studies with endogenous creatinine clearance as index test); (4) the GFR markers were measured in plasma or urine; (5) the plasma clearance calculation algorithm had been verified in another study; and (6) tubular secretion of creatinine had not been blocked by medicines.

The list of excluded articles is available online.[4]

Assessment of Study Quality

Two reviewers independently assessed the quality of included studies. The reviewers were selected to avoid potential conflict of interest due to authorship. For original studies, the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool was used.[5] However, due to the nature of the research question, this tool was found insufficient and study quality assessment criteria therefore were modified. Criteria for high study quality were: (1) adequate description of index and reference method, (2) at least 2 of the 3 outcome measures (bias, precision, and accuracy) reported or raw data provided, (3) adequate sampling time in case plasma clearance was used as index method, (4) adequate urine collection (bladder catheterization or hydration), and (5) at least 40 participants studied. Studies that only fulfilled criteria 1, 3, and 4 and reported one outcome measure or presented raw data were labeled as moderate-quality studies. Studies that did not fulfil the criteria for moderate or high study quality were considered low-quality studies and were not tabulated if studies of high or moderate quality were available. Systematic reviews were assessed according to AMSTAR (a Measurement Tool to Assess Systematic Reviews) criteria.[6]

Data Extraction for Meta-analysis

Reported outcome measures varied across studies. However, several studies reported raw data, and the majority included a scatter plot of the index-reference method relationship. In order to extract comparable data, we used raw data when available in the study or obtained from the authors. When raw data were not available, data were extracted from enlargements of index-reference method scatter plots by measuring the distance of individual data points to the x- and y-axes. No software program was used to extract data from scatterplots; this extraction was done manually. The accuracy of extracted data was confirmed by calculating regression parameters and correlation coefficients and comparing these with published ones. The data extraction process was repeated if the difference was more than marginal. In this manner, data from all except 2 studies could be obtained.[7,8] In scatterplots, GFR measurements presented in milliliters per minute per 1.73 m^2 and in milliliters per minute were both accepted. Data extraction for the index method endogenous creatinine clearance was not considered meaningful because consistent results were reported in a large number of studies.

Statistical Methods

Statistical analyses were conducted in IBM SPSS Statistics, version 20. For all index methods except endogenous creatinine clearance (discussed next), percentage of error was calculated for each measurement as the difference between the index and reference measurements in percent of the reference measurement. Bias was summarized as both the mean and median of these percentage errors. Accuracy encompasses both bias and precision and was expressed as P_{30} and P_{10}, that is, the proportion of errors in the index measurements that did not exceed 30% and 10%.[9] These calculations were done for each study separately together with asymptotic (mean bias), nonparametric (median bias), or exact (P_{10}, P_{30}) confidence intervals (CIs) and were based on the number of measurements in each study.

Bland-Altman diagrams were used to visualize bias and accuracy of each index method (with the exception of endogenous creatinine clearance). In these diagrams, the reference method (rather than the mean of the 2 methods) was depicted on the x-axis, an approach that is appropriate when 1 of the 2 methods is considered more accurate.[10]

Information was available for the number of measurements and number of participants in each study, but it was not possible to link individual measurements to individual participants. To compensate

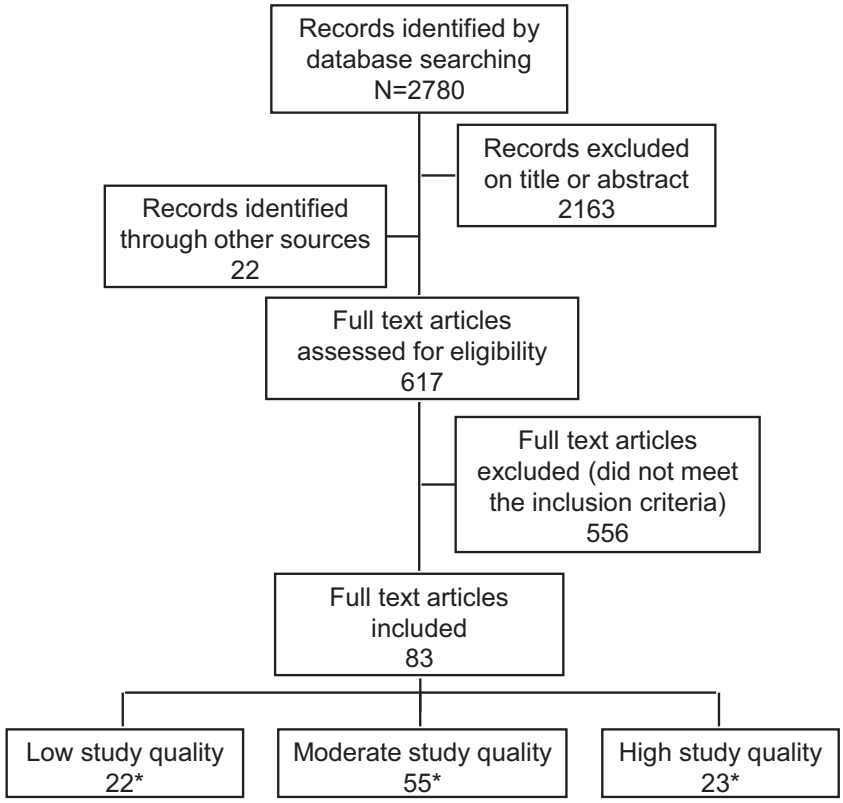

Figure 1. Flow of articles through review. *The number of study quality assessments exceeds the number of included articles because several included articles studied multiple glomerular filtration rate measurement methods and therefore were quality assessed for each method separately. Modified with permission of the Swedish Council on Health Technology Assessment.[3]

for this, the meta-analysis based on individual measurement data (pooled analysis) used statistical weights based on the number of participants in each study. In studies in which the number of measurements, *m,* exceeded the number of participants, *n,* each measurement received the weight *n/m*. Measurements in studies with equal or fewer identified measurements than participants received the weight 1. In that way, 2 studies with equal numbers of participants contributed equally to the results regardless of the number of measurements for each participant.

Any GFR expressed in milliliters per minute was converted to milliliters per minute per 1.73 m^2 assuming a body surface area of 1.73 m^2. This conversion does not affect bias and accuracy measures expressed in percent. However, the Bland-Altman diagrams and modeling at different GFR levels that are described next may have been affected to some extent.

Median bias was calculated directly (using the weights described previously) for each index method. Mean bias, P_{30}, and P_{10} were obtained from generalized linear mixed models using the normal distribution (mean percentage difference) or Poisson distribution (P_{30}, P_{10}; log-transformed outcome; and robust variance estimation). These generalized linear mixed models are specified in Item S2. To adjust for the differences in GFR levels across studies, the models were fitted with adjustment for the reference GFR level of each measurement. All estimates from both unadjusted and adjusted generalized linear mixed models were obtained as marginal means. From the adjusted models, estimates of mean bias, P_{30}, and P_{10} were obtained at the reference GFR of 60 mL/min/1.73 m^2. Differences in bias and accuracy at various GFR levels were studied further by fitting the adjusted models separately for reference GFR < 60 and >60 mL/min/1.73 m^2. In these models, mean bias, P_{30}, and P_{10} were evaluated at 30 and 90 mL/min/1.73 m^2. To minimize the influence of outlying observations on the estimated bias, mean percentage differences $> 100\%$ were set to 100%.

The meta-analysis for endogenous creatinine clearance was based on published data for mean bias (milliliters per minute or milliliters per minute per 1.73 m^2), standard deviation, and number of participants (or standard error) for each study. Mean bias was calculated with the inverse of the standard error in each study (published or calculated by us) used as weights and expressed in percent of the overall mean reference GFR.

Criteria for Sufficient Accuracy

The GFR measurement methods with extracted data available were considered to have sufficient accuracy when all the following criteria were met: (1) median bias (direct calculation) did not exceed 5% (when index method differed significantly from the reference method), (2) mean bias (in the unadjusted generalized linear mixed model) did not exceed 10%, (3) at least 80% of index measurements were within $\pm 30\%$ of reference measurements, and (4) at least 50% were within $\pm 10\%$ (ie, $P_{30} \geq 80\%$ and $P_{10} \geq 50\%$) in the unadjusted generalized linear mixed models. Endogenous creatinine clearance was evaluated based on mean bias ($<10\%$).

Strength of Evidence Across Studies

Adopted from the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, a 4-graded scale was used to rate the strength of evidence in the estimated accuracy for each index method.[11] The ratings reflect the extent of our confidence that the estimates are correct: strong scientific evidence (⊕⊕⊕⊕), moderately strong scientific evidence (⊕⊕⊕◯), limited scientific evidence (⊕⊕◯◯) and insufficient scientific evidence (⊕◯◯◯). The following reasons were used to downgrade evidence strength: study limitations (risk of bias due to shortcomings in individual studies, −1), inconsistency of results (inconsistency in study outcomes that cannot be explained by differences in study design, −1), indirectness of evidence (limited generalizability, −1), imprecision (N $<$ 100 in meta-analysis, −1; P_{30} lower 95% CI $\leq$ 80%, P_{10} lower 95% CI $\leq$ 50%, or mean

Table 1. Bias and Accuracy of Index Methods Compared to Reference Method When Measuring Glomerular Filtration Rate

	No. of Pts/ Studies	Median Bias[a] (95% CI)	Mean Bias (95 % CI)	P_{30} (95% CI)	P_{10} (95% CI)	Sufficient Accuracy	Scientific Evidence	Comments[b]
Criteria for sufficient precision		≤±5%	≤±10%	≥80%	≥50%			
Index method								
DTPA								
Renal clearance	126/5	−2 (−4 to 2)	−1 (−6 to 5)	87 (81 to 93)	53 (45 to 62)	Yes	⊕⊕◯◯	Inconsistency, −1; imprecision, −1
Plasma clearance	89/2	20 (18 to 35)	13 (5 to 22)	56 (47 to 68)	19 (13 to 29)	No	⊕⊕◯◯	Study limitations −1; imprecision −1
^{51}Cr-EDTA								
Renal clearance	198/9	−5 (−7 to −3)	−2 (−8 to 4)	95 (92 to 98)	56 (50 to 64)	Yes	⊕⊕⊕◯	Imprecision, −1
Plasma clearance	126/5	3 (−1 to 8)	8 (1 to 15)	86 (80 to 92)	50 (42 to 59)	Yes	⊕⊕⊕◯	Imprecision, −1
Iohexol								
Renal clearance	47/2	−7 (−10 to 0)	−7 (−16 to 2)	100[c]	53 (41 to 70)	Yes	⊕⊕◯◯	Imprecision, −2
Plasma clearance	172/5	3 (0 to 6)	2 (−4 to 9)	86 (81 to 91)	50 (43 to 58)	Yes	⊕⊕⊕◯	Imprecision, −1
Iothalamate								
Renal clearance	548/13	−1 (−2 to 0)	6 (1 to 11)	97 (95 to 98)	66 (62 to 70)	Yes	⊕⊕⊕⊕	
Plasma clearance	61/1	9 (0 to 15)	11 (−6 to 29)	82 (73 to 92)	33 (23 to 47)	—	⊕◯◯◯	Study limitations, −1; imprecision, −2
Inulin								
Plasma clearance	39/2	2 (−3 to 6)	1 (−9 to 11)	100[c]	72 (59 to 87)	Yes	⊕⊕◯◯	Imprecision, −1; indirectness, −1

Note: Modified with permission of the Swedish Council on Health Technology Assessment.[3] Accuracy and bias expressed as percentage. Renal inulin clearance served as reference method. Mean bias, P_{10}, and P_{30} were estimated using generalized linear mixed models based on normal distribution (mean bias) or Poisson distribution (P_{10}, P_{30}; log-transformed outcome and robust variance estimation), with a random intercept for each study and a fixed effect for each index method ("unadjusted model results"; see Statistical Methods section). All analyses were weighed with respect to number of participants in each study. Estimates were obtained as marginal means.

Abbreviations and definitions: ⊕⊕⊕⊕, strong evidence; ⊕⊕⊕◯, moderately strong evidence; ⊕⊕◯◯, limited evidence; ⊕◯◯◯, insufficient evidence; ^{51}Cr-EDTA, chromium 51−labeled ethylenediaminetetraacetic acid; DTPA, diethylenetriaminepentaacetic acid; CI, confidence interval; Imprecision, $N < 100$ in meta-analysis (−1), P_{30} lower 95% CI ≤ 80%, P_{10} lower 95% CI ≤ 50%, or median bias 95% CI ≥ ±5% (−1); Inconsistency, inconsistency in study outcomes that cannot be explained by differences in study design (−1); Indirectness, limited generalizability (−1); P_{10}, percentage of measurements by index method that differed no more than 10% from reference method; P_{30}, percentage of measurements by index method that differed no more than 30% from reference method; pts, patients; Study limitations, risk of bias due to shortcomings in individual studies (−1).

[a]Median bias was calculated directly (using the weights) for each index method together with nonparametric CIs.

[b]Strength of scientific evidence.

[c]The generalized linear mixed model does not yield valid estimates of confidence limits when estimated proportion (eg, P_{30}) is 100%.

Table 2. Endogenous Creatinine Clearance as Index Test, Mean Bias When Measuring Glomerular Filtration Rate

	No. of Pts/Studies	Mean Renal Inulin Clearance[a]	Mean Bias (mL/min)[a]	Mean Bias (%)	Sufficient Accuracy	Scientific Evidence
Index method: endogenous creatinine clearance	2,021/23	56	14 (13-14) [0.74-48]	25	No	⊕⊕⊕⊕

Note: Modified with permission of the Swedish Council on Health Technology Assessment.[3] Mean bias is accuracy compared to renal inulin clearance, which served as reference method, given as mean (95% confidence interval) [range].

Definition: ⊕⊕⊕⊕, strong evidence.

Abbreviation: pts, patients.

[a]Unit of measurement varied between mL/min and mL/min/1.73 m^2 across studies.

bias 95% CI $\geq \pm 5\%$, −1), and publication bias (relation between study size and study outcome indicated by funnel plots, −1).

RESULTS

Study Overview

The literature search flow is shown in Fig 1. Population characteristics at study level and individual study quality assessments are available online.[3] The assessment of the performance of index methods was based on meta-analysis results for bias, P_{30}, and P_{10} and is presented in Table 1. The assessment of the accuracy of the index method endogenous creatinine clearance was based on mean bias and is presented in Table 2.

Index Methods

DTPA Clearance

Six studies, including 226 measurements for 174 participants, compared DTPA clearance to the reference method (Table 3).[12-17] One study presented data for both renal and plasma DTPA clearance.[16] Individual differences with P_{30} and P_{10} limits are presented as a Bland-Altman plot (Fig 2A). Renal DTPA clearance (137 measurements, 126 participants) demonstrated sufficient accuracy to measure GFR (limited evidence). Plasma DTPA clearance (89 measurements, 89 participants) had insufficient accuracy to measure GFR (limited evidence; Table 1).

^{51}Cr-EDTA Clearance

Fourteen studies, including 469 measurements for 324 participants, compared ^{51}Cr-EDTA clearance to the reference method.[7,18-30] Renal clearance was measured in 9 studies (339 measurements, 198 participants), and plasma clearance, in 5 studies (130 measurements, 126 participants; Table 4). Individual differences with P_{30} and P_{10} limits are presented as a Bland-Altman plot (Fig 2B). Both renal and plasma clearances of ^{51}Cr-EDTA fulfilled the requirements for accurate GFR measurement (moderately strong evidence; Table 1).

Iohexol Clearance

Five studies, including 219 measurements for 219 participants, compared iohexol clearance to renal inulin clearance (Table 5).[13,31-34] Individual differences with P_{30} and P_{10} limits are presented as a Bland-Altman plot (Fig 2C). Renal clearance of iohexol (47 measurements, 47 participants) was within the limits of sufficient accuracy to measure GFR (limited evidence; Table 1). Plasma clearance of iohexol (172 measurements, 172 participants) also was sufficiently accurate (moderately strong evidence; Table 1).

Table 3. Accuracy and Bias of DTPA Clearance

Study	Method	No. of Measurements/Pts	GFR Interval (mL/min/1.73 m^2)	Median Bias (95% CI)	P_{30} (95% CI)	P_{10} (95% CI)
Lewis et al[13] (1989)	R	28/28	15-120	−3 (−15 to 5)	79 (63 to 94)	39 (21 to 57)
Perrone et al[14] (1990)	R	14[a]/14	5-130	5 (−11 to 15)	86 (57 to 98)	43 (17 to 69)
Petri et al[15] (1988)	R	36/25	23-123[b]	−7 (−11 to −3)	100 (90 to 100)	64 (48 to 80)
Shemesh et al[16] (1985)	R	41/41	10-135	0 (−5 to 7)	90 (81 to 99)	71 (57 to 85)
Wharton et al[17] (1992)	R	18/18	2-69[b]	8 (−19 to 37)	67 (45 to 88)	22 (3 to 41)
Dai et al[12] (2011)	P	47/47	5-129	25 (17 to 39)	60 (46 to 74)	23 (11 to 36)
Shemesh et al[16] (1985)	P	42/42	10-135	14 (−2 to 34)	52 (37 to 67)	14 (4 to 25)

Note: Modified with permission of the Swedish Council on Health Technology Assessment.[3] Accuracy and bias expressed as percentage; GFR interval, as mL/min/1.73 m^2 unless otherwise indicated.

Abbreviations and definitions: DTPA, diethylenetriaminepentaacetic acid; CI, confidence interval; GFR, glomerular filtration rate; P, plasma clearance; P_{10} and P_{30}, see Table 1; pts, patients; R, renal clearance.

[a]The study includes 17 participants, of whom 14 could be identified for the meta-analysis.

[b]In mL/min; GFR expressed in mL/min was converted to mL/min/1.73 m^2 assuming body surface area of 1.73 m^2.

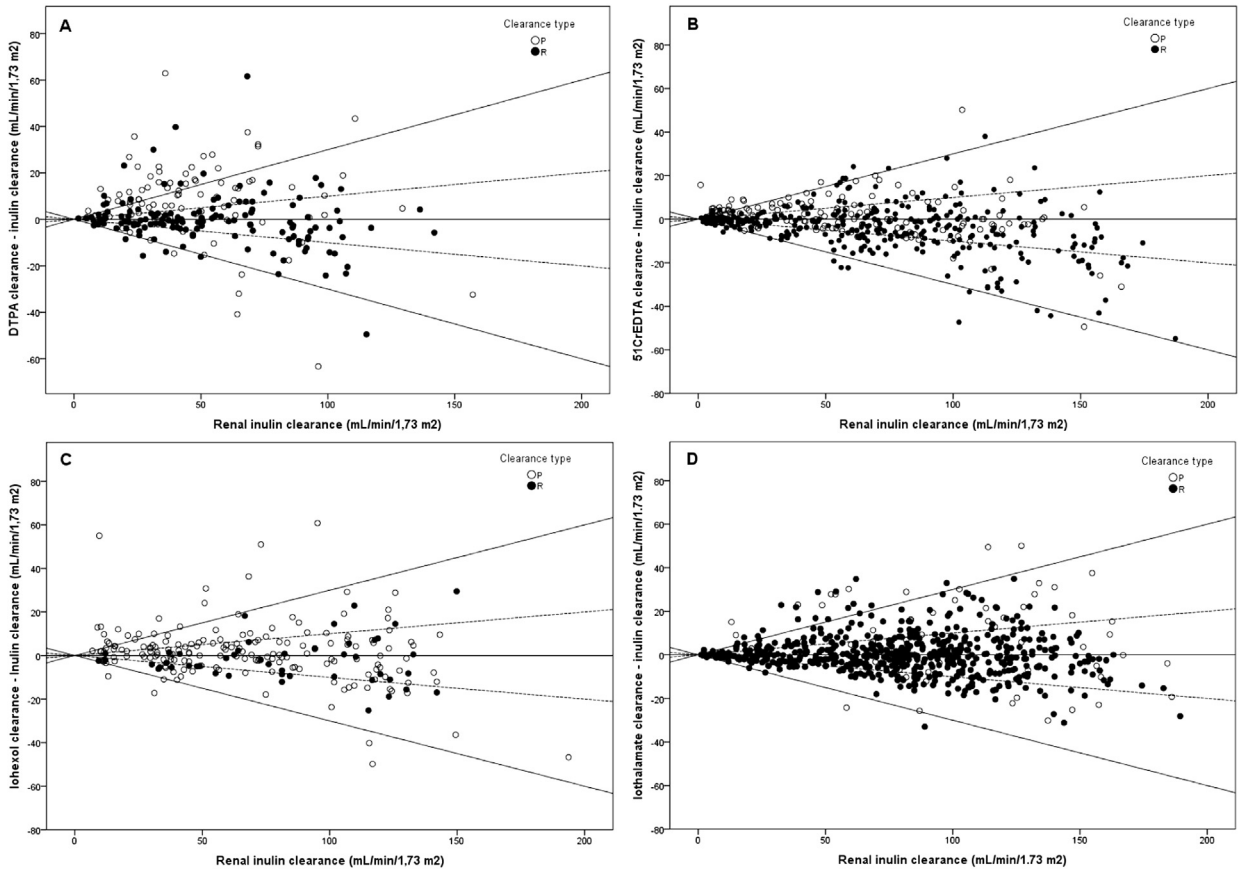

Figure 2. Differences between glomerular filtration rate (GFR) measured with (A) diethylenetriaminepentaacetic acid (DTPA), (B) chromium 51−labeled ethylenediaminetetraacetic acid (^{51}Cr-EDTA), (C) iohexol, or (D) iothlamate and renal inulin clearance in relation to renal inulin clearance (P, plasma clearance, R, renal clearance). The proportion of errors in the index measurements that did not exceed 30% (P_{30}) limits (solid lines) and P_{10} limits (dashed lines) are shown. GFR expressed in mL/min was converted to mL/min/1.73 m^2 assuming a body surface area of 1.73 m^2. Modified with permission of the Swedish Council on Health Technology Assessment.[3]

Table 4. Accuracy and Bias of ^{51}Cr-EDTA Clearance

Study	Method	No. of Measurements/Pts	GFR Interval	Median Bias (95% CI)	P_{30} (95% CI)	P_{10} (95% CI)
Chantler et al[19] (1969)	R	25/21	10-130[a]	−2 (−7 to 3)	96 (80 to 100)	76 (59 to 93)
Favre & Wing[21] (1968)	R	20/20	2-147[a]	3 (1 to 9)	100 (83 to 100)	65 (44 to 86)
Gibb et al[22] (1989)	R	22/22	80-200	−4 (−10 to 0)	100 (85 to 100)	59 (39 to 80)
Hagstam et al[23] (1974)	R	29/16	30-120	−7 (−9 to −1)	97 (82 to 100)	72 (56 to 89)
Heath et al[24] (1968)	R	39/39	0-220[a]	−21 (−25 to −15)	85 (73 to 96)	10 (1 to 20)
Jagenburg et al[25] (1978)	R	33/17	2-12[a]	1 (−2 to 4)	97 (84 to 100)	73 (58 to 88)
Lavender et al[26] (1969)	R	88/28	1-157[a]	−3 (−6 to 0)	92 (86 to 98)	64 (54 to 74)
Monteiro et al[30] (1970)	R	20/20	35-166	−6 (−14 to 4)	100 (83 to 100)	60 (39 to 81)
Stamp et al[29] (1994)	R	63/15	17-180[a]	−5 (−8 to −1)	84 (75 to 93)	44 (32 to 57)
Bröchner-Mortensen et al[18] (1969)	P	17/17	10-130[a]	1 (−10 to 15)	100 (80 to 100)	53 (29 to 77)
Ditzel et al[20] (1972)	P	20/20	6-166[a]	0 (−5 to 14)	85 (62 to 97)	65 (44 to 86)
Hagstam et al[23] (1974)	P	30/30	8-160	−2 (−7 to 6)	93 (86 to 99)	71 (55 to 88)
Manz et al[27] (1977)	P	19/15	0.9-18	33 (14 to 58)	42 (20 to 64)	13 (−2 to 27)
Medeiros et al[28] (2009)	P	44/44	12-78	5 (−1 to 16)	93 (82 to 99)	57 (43 to 72)

Note: Modified with permission of the Swedish Council on Health Technology Assessment.[3] Accuracy and bias expressed as percentage; GFR interval, as mL/min/1.73 m^2 unless otherwise indicated.

Abbreviations and definitions: ^{51}Cr-EDTA, chromium 51−labeled ethylenediaminetetraacetic acid; CI, confidence interval; GFR, glomerular filtration rate; P, plasma clearance; P_{10} and P_{30}, see Table 1; pts, patients; R, renal clearance.

[a]In mL/min. GFR expressed in mL/min was converted to mL/min/1.73 m^2 assuming body surface area of 1.73 m^2.

Table 5. Accuracy and Bias of Iohexol Clearance

Study	Method	No. of Measurements/Pts	GFR Interval	Median Bias (95% CI)	P_{30} (95% CI)	P_{10} (95% CI)
Brown & O'Reilly[32] (1991)	R	27/27	8-85	−10 (−14 to 0)	100 (87 to 100)	48 (29 to 67)
Sterner et al[34] (2008)	R	20/20	94-150	0 (−10 to 6)	100 (83 to 100)	60 (39 to 81)
Berg et al[31] (2011)	P	60/60	5-200	5 (−2 to 12)	84 (74 to 93)	43 (30 to 55)
Brown & O'Reilly[32] (1991)	P	27/27	8-85	6 (1 to 9)	93 (76 to 99)	70 (53 to 88)
Gaspari et al[33] (1995)	P	38/38	6-160	5 (−2 to 10)	92 (79 to 98)	53 (37 to 69)
Lewis et al[13] (1989)	P	28/28	9-117	−2 (−18 to 12)	68 (51 to 85)	32 (15 to 49)
Sterner et al[34] (2008)	P	19/19	94-150	−3 (−10 to 4)	100 (82 to 100)	68 (48 to 89)

Note: Modified with permission of the Swedish Council on Health Technology Assessment.[3] Accuracy and bias expressed as percentage; GFR interval, as mL/min/1.73 m^2.

Abbreviations and definitions: CI, confidence interval; GFR, glomerular filtration rate; P, plasma clearance; P_{10} and P_{30}, see Table 1; pts, patients; R, renal clearance.

Iothalamate Clearance

Fourteen studies including 662 measurements for 609 participants used iothalamate clearance as the index method (Table 6).[14,15,35-46] Individual differences with P_{30} and P_{10} limits are presented as a Bland-Altman plot (Fig 2D). Renal iothalamate clearance (601 measurements, 548 participants) was within the limits of sufficient accuracy to measure GFR (strong evidence; Table 1). The scientific evidence to assess the accuracy of plasma iothalamate clearance (61 measurements, 61 participants) was insufficient because only one low-quality study was identified.

Plasma Inulin Clearance

Three studies comparing plasma and renal inulin clearances were identified.[34,47,48] One of the identified studies investigated preterm infants and reported GFR per kilogram of body weight and therefore could not be included in the pooled analysis.[48] The 2 included studies did not report observations below GFR of 60 mL/min/1.73 m^2 (Table 7). Individual differences with P_{30} and P_{10} limits are presented as Bland-Altman plots (Fig 3). Plasma clearance of inulin was within the limits of sufficient accuracy to measure GFR (limited evidence; Table 1).

Endogenous Creatinine Clearance

In total, 52 original studies and one systematic review used endogenous creatinine clearance as the index method.[8,15,16,21-23,26,31,43,45,48-90] Sixteen studies including the systematic review were of high quality and in all these, endogenous creatinine clearance overestimated renal inulin clearance.[16,23,31,43,45,49-51,53,55,57,58,60,63,65,88] Mean bias

Table 6. Accuracy and Bias of Iothalamate Clearance

Study	Method	No. of Measurements/Pts	GFR Interval	Median Bias (95% CI)	P_{30} (95% CI)	P_{10} (95% CI)
Anderson et al[35] (1968)	R	18/18	3-139[a]	−1 (−12 to 13)	89 (65 to 99)	39 (16 to 61)
Cangiano et al[36] (1971)	R	49/18	0-160[a]	7 (4 to 10)	96 (86 to 100)	61 (48 to 75)
Elwood & Sigman[37] (1967)	R	26/21	16-136[a]	0 (−3 to 2)	100 (87 to 100)	100 (87 to 100)
Israelit et al[38] (1973)	R	22/22	6-125[a]	−2 (−11 to 11)	91 (71 to 99)	45 (25 to 66)
Maher et al[39] (1971)	R	194/194	2-153	−6 (−7 to −4)	99 (96 to 100)	68 (61 to 75)
Maher & Tauxe[40] (1969)	R	24/15	30-118	−11 (−14 to −5)	100 (86 to 100)	46 (26 to 66)
Mogensen[41] (1971)	R	57/57	64-187	−1 (−4 to 0)	100 (94 to 100)	91 (84 to 99)
Ott[42] (1975)	R	79/79	5-155[a]	2 (0 to 5)	99 (93 to 100)	68 (58 to 79)
Perrone et al[14] (1990)	R	17/17	5-50, 80-130	7 (−7 to 18)	88 (64 to 99)	41 (18 to 65)
Petri et al[15] (1988)	R	25/25	20-120[a]	13 (9 to 17)	88 (69 to 97)	36 (17 to 55)
Rosenbaum et al[43] (1979)	R	23/23	35-146[a]	21 (14 to 29)	74 (56 to 92)	17 (2 to 33)
Sigman et al[44] (1966)	R	24/16	2-167[a]	0 (−1 to 4)	100 (86 to 100)	92 (73 to 99)
Skov[45] (1979)	R	43/43	1.6-25	−4 (−7 to 1)	100 (92 to 100)	67 (53 to 81)
Silkalns et al[46,b] (1973)	P	61/61	10-190	9 (0 to 15)	82 (72 to 92)	33 (21 to 45)

Note: Modified with permission of the Swedish Council on Health Technology Assessment.[3] Accuracy and bias expressed as percentage; GFR interval, as mL/min/1.73 m^2 unless otherwise indicated.

Abbreviations and definitions: CI, confidence interval; GFR, glomerular filtration rate; P, plasma clearance; P_{10} and P_{30}, see Table 1; pts, patients; R, renal clearance.

[a]In mL/min. GFR expressed in mL/min was converted to mL/min/1.73 m^2 assuming body surface area of 1.73 m^2.

[b]Low study quality.

Table 7. Accuracy and Bias of Plasma Clearance of Inulin

Study	No. of Measurements/Pts	GFR Interval	Median Bias (95% CI)	P_{30} (95% CI)	P_{10} (95% CI)
Müller-Suur et al[47] (1983)	20/20	60-150	−1 (−7 to 5)	100 (83 to 100)	70 (50 to 90)
Sterner et al[34] (2008)	19/19	94-150	4 (−3 to 9)	100 (82 to 100)	74 (54 to 93)

Note: Modified with permission of the Swedish Council on Health Technology Assessment.[3] Accuracy and bias expressed as percentage; GFR interval, as mL/min/1.73 m^2.

Abbreviations and definitions: CI, confidence interval; GFR, glomerular filtration rate; P_{10} and P_{30}, see Table 1; pts, patients.

was reported in 23 original studies investigating 2,021 participants (Fig 4).[15,16,21,22,31,43,45,50-65] The meta-analysis based on these 23 studies demonstrated that endogenous creatinine clearance overestimated GFR and did not meet the accuracy requirements (strong evidence; Table 2). Relative overestimation was higher at low GFRs (Fig 5).

Adjusted Model Results and Bias at Different GFR Levels

Using generalized linear mixed models with adjustment for differences in GFR levels across studies, estimates of mean bias, P_{30}, and P_{10} were obtained for the index methods at GFR of 60 mL/min/1.73 m^2 (Table 8). The performance of plasma clearance of iothalamate appeared substantially worse after adjusting because this method has been studied in a setting with high mean GFRs. No important change in performance was noted for any of the other index methods. Plasma inulin clearance could not be evaluated because no data were available at GFR $\leq$ 60 mL/min/1.73 m^2.

Model-based estimates at different GFRs (30, 60, and 90 mL/min/1.73 m^2) revealed that renal clearance of iothalamate and renal clearance of ^{51}Cr-EDTA had a constant mean bias (in percent) across levels of GFR, whereas the other methods demonstrated more marked bias at lower GFRs (Table 9). The plasma clearance methods tended to overestimate renal clearance of inulin at lower GFRs. The statistical uncertainty in these results was considerable, illustrated by the wide CIs in estimates of mean bias.

Impact of Data Extraction

To analyze whether the use of manually extracted data had lead to underestimation of accuracy, 2 methods, renal clearance of iothalamate and plasma clearance of iohexol, both with a reasonable amount of raw data available, were assessed. No substantial increase in P_{10} was noted when only available raw data were used. For renal clearance of iothalamate, P_{10} assessed at GFR of 60 mL/min/1.73 m^2 increased from 62% to 66% (95% CI, 58%-75%; raw data available for 121 of 548 participants). For plasma clearance of iohexol, P_{10} assessed at GFR of 60 mL/min/1.73 m^2 decreased from 47% to 37% (95% CI, 28%-48%; raw data available for 107 of 172 participants).

Additional Search

The updated literature search in PubMed identified one relevant study of moderate quality with endogenous creatinine clearance as index method. Because no

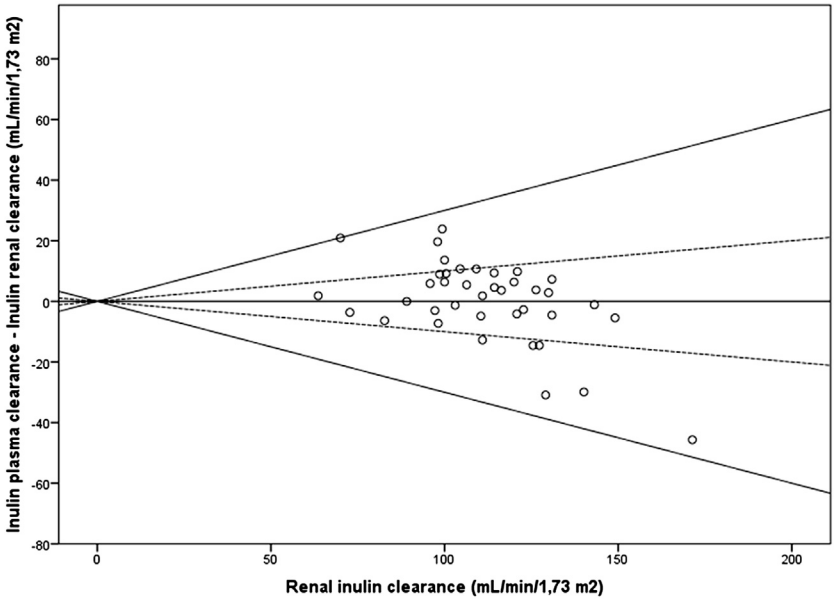

Figure 3. Differences between glomerular filtration rate measured with plasma and renal inulin clearance in relation to renal inulin clearance. The proportion of errors in the index measurements that did not exceed 30% (P_{30}) limits (solid lines) and P_{10} limits (dashed lines) are shown. Modified with permission of the Swedish Council on Health Technology Assessment.[3]

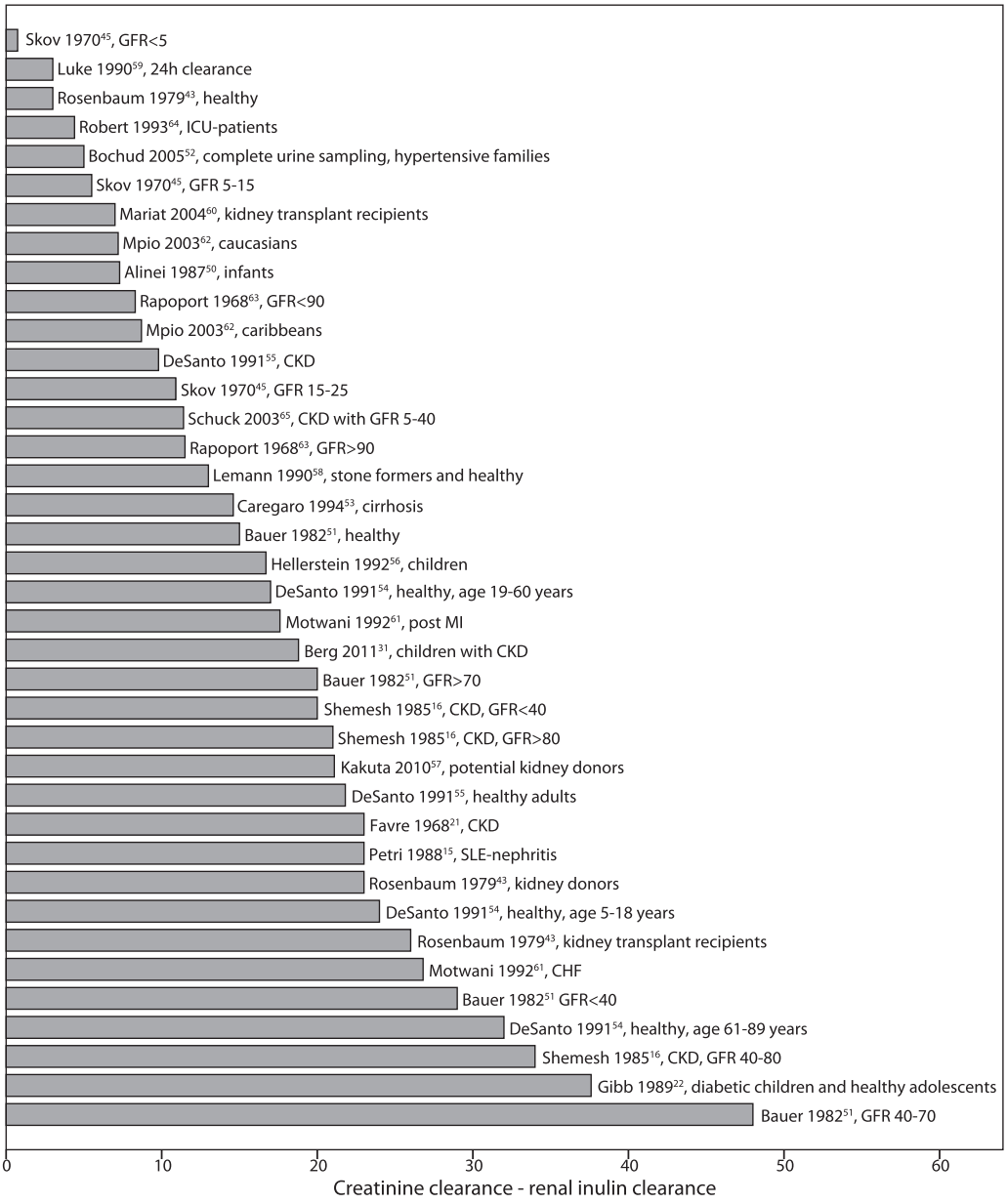

Figure 4. Difference between endogenous creatinine clearance and renal inulin clearance in the 23 studies reporting mean bias. Units are mL/min and mL/min/1.73 m^2. Subgroup results for glomerular filtration rate (GFR) intervals or specific patient groups are presented as separate bars. Abbreviations: CHF, congestive heart failure; CKD, chronic kidney disease; ICU, intensive care unit; MI, myocardial infarction; SLE, systemic lupus erythematosus. Modified with permission of the Swedish Council on Health Technology Assessment.[3]

mean bias was reported, the study was not included in the meta-analysis.[91] One study with plasma DTPA as the index test also was identified, but was not included due to low study quality.[92]

DISCUSSION

This systematic review has confirmed that several alternatives to renal inulin clearance exist when a measured GFR is required. The empirical evidence is strong for the renal clearance of iothalamate and moderately strong for renal and plasma clearance of ^{51}Cr-EDTA and plasma clearance of iohexol. The scientific evidence to suggest that renal clearance of iohexol and plasma clearance of inulin can substitute for renal inulin clearance is limited. Similarly, limited evidence suggests that plasma clearance of DTPA is an inaccurate method and there is insufficient evidence to draw conclusions about the utility of plasma clearance of iothalamate. Strong scientific evidence suggests that endogenous creatinine clearance is an inaccurate method.

To our knowledge, this is the first comprehensive systematic review investigating the accuracy of GFR measurement methods commonly used in clinical

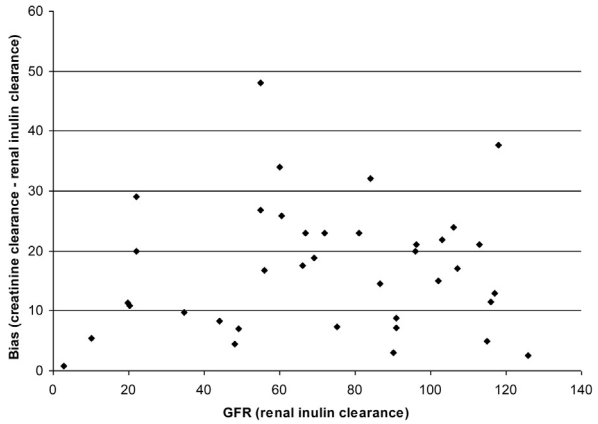

Figure 5. Difference between endogenous creatinine clearance and renal inulin clearance in relation to renal inulin clearance in the 23 studies reporting mean bias. Subgroup results for glomerular filtration rate (GFR) intervals or specific patient groups are presented as separate points. Modified with permission of the Swedish Council on Health Technology Assessment.[3]

practice and research. The development of these methods spans over a period of several decades, and earlier methods often have served as reference for the latter. To compare the methods, a common reference is required, and renal inulin clearance, due to its universal recognition, was a natural choice. However, the requirement of direct comparison to this reference resulted in fewer identified studies for the more recently introduced methods because these seldom have been evaluated against renal inulin clearance.

Studies in many cases were old and used statistical methods that were highly variable. Many older studies provide no or only limited information for accuracy. In order to obtain comparable information across studies, a meta-analysis of original data was undertaken. When raw data were not reported, data were extracted manually and the quality of extracted data was assessed. However, the data extraction process may still have introduced some error. For endogenous creatinine clearance, for which the number of published studies and investigated participants was large, a pooled analysis was not considered meaningful and instead a meta-analysis based on published results was conducted. Endogenous creatinine clearance consistently overestimated GFR and demonstrated relatively higher overestimation at low GFRs.

We could identify only one systematic review in which renal inulin clearance was used as reference method.[49] In that review, Proulx at al[49] studied the accuracy of endogenous creatinine clearance and found that the method is inaccurate and considerably overestimates GFR in patients with liver cirrhosis. This agrees with the conclusion of the present systematic review, which was not limited to a specific patient group. Considering that overestimation of GFR when measuring creatinine clearance was described already in 1935, the popularity of the method remains a mystery.[93,94]

Our criterion for sufficient accuracy of $P_{30} > 80\%$ is only slightly more strict than the requirement of 75% set for GFR estimating equations and is considered sufficient for good clinical decision making.[95] However, our P_{10} criterion of >50% is strict and not met by the best available GFR estimating equations.[96] If $P_{30} > 90\%$ was applied, all renal clearance methods with the exception of DTPA would fulfil the requirement,

Table 8. Adjusted Model-Based Estimates of Mean Bias and Accuracy

Marker	Method	N[a]	GFR	Mean Bias (95% CI)	P_{30} (95% CI)	P_{10} (95% CI)
DTPA	R	126	51 ± 32	0 (−5 to 5)	88 (83 to 94)	54 (46 to 63)
	P	89	48 ± 28	10 (3 to 18)	60 (50 to 71)	21 (13 to 31)
^{51}Cr-EDTA	R	198	70 ± 48	−4 (−10 to 1)	95 (92 to 98)	57 (50 to 64)
	P	126	60 ± 40	10 (3 to 16)	85 (79 to 91)	47 (39 to 56)
Iohexol	R	47	81 ± 38	−11 (−20 to −2)	100[b]	50 (36 to 70)
	P	172	66 ± 40	4 (−2 to 10)	84 (78 to 90)	47 (40 to 55)
Iothalamate	R	548	74 ± 41	6 (1 to 10)	96 (94 to 98)	62 (58 to 67)
	P	61	105 ± 42	23 (7 to 39)	61 (47 to 80)	19 (10 to 38)

Note: Estimates of mean bias (mean percentage difference) and accuracy evaluated at GFR of 60 mL/min/1.73 m^2 for index methods in relation to renal inulin clearance. A generalized linear mixed model, using the normal distribution (bias) or Poisson distribution (P_{10}, P_{30}; log-transformed outcome and robust variance estimation), with a random intercept for each study and fixed effects for each index method, GFR and the interaction GFR*index method was used. All analyses were weighted with respect to the number of participants in each study. Estimates were obtained as marginal means obtained at GFR of 60 mL/min/1.73 m^2. Accuracy and bias expressed as percentage. GFR expressed in mL/min was converted to mL/min/1.73 m^2 assuming body surface area of 1.73 m^2; values given as mean ± standard deviation.

Abbreviations and definitions: ^{51}Cr-EDTA, chromium 51−labeled ethylenediaminetetraacetic acid; DPTA, diethylenetriaminepentaacetic acid; CI, confidence interval; GFR, glomerular filtration rate; P, plasma clearance; P_{10} and P_{30}, see Table 1; R, renal clearance.

[a]Number of participants in meta-analysis.

[b]Generalized linear mixed model does not yield valid estimates of confidence limits when estimated proportion (eg, P_{30}) is 100%.

Table 9. Adjusted Model-Based Estimates of Mean Bias

Marker	Method	N[a]	GFR = 30	GFR = 60	GFR = 90
DTPA	R	80/46	4 (−3 to 12)	0 (−5 to 5)	−2 (−8 to 4)
	P	63/26	30 (19 to 40)	10 (3 to 18)	−8 (−17 to 1)
^{51}Cr-EDTA	R	88/110	−4 (−12 to 4)	−4 (−10 to 1)	−5 (−11 to 2)
	P	67/59	16 (7 to 25)	10 (3 to 16)	2 (−5 to 10)
Iohexol	R	15/32	−18 (−34 to −1)	−11 (−20 to −2)	−2 (−11 to 6)
	P	85/87	10 (2 to 19)	4 (−2 to 10)	0 (−6 to 7)
Iothalamate	R	194/354	7 (1 to 13)	6 (1 to 10)	5 (0 to 10)
	P	10/51	50 (27 to 73)	23 (7 to 39)	7 (−10 to 23)
Inulin	P	0/39	—[b]	—[b]	6 (−4 to 16)

Note: Estimates of mean bias—mean percentage difference (95% confidence interval)—evaluated at different GFR levels for index methods in relation to renal inulin clearance. A generalized linear mixed model using the normal distribution with a random intercept for each study and fixed effects for each index method, GFR and the interaction GFR*index method was used. All analyses were weighed with respect to the number of participants in each study. Estimates were obtained as marginal means. Bias expressed as percentage. GFR expressed in mL/min was converted to mL/min/1.73 m^2 assuming body surface area of 1.73 m^2. Results at GFR 30/90 mL/min/1.73 m^2 were evaluated using only data <60/>60 mL/min/1.73 m^2.

Abbreviations: ^{51}Cr-EDTA, chromium 51−labeled ethylenediaminetetraacetic acid; DTPA, diethylenetriaminepentaacetic acid; GFR, glomerular filtration rate; P, plasma clearance; R, renal clearance.

[a]Number of participants with GFR < 60 and >60 mL/min/1.73 m^2, respectively, in meta-analysis.

[b]No data available for GFR ≤ 60 mL/min/1.73 m^2.

whereas most plasma clearance methods would not. This may be due to design limitations in some plasma clearance studies, such as overlooking the need for late samples in the setting of low GFR or suboptimal accounting for the distribution phase in area calculations. Also, imprecision in reference method assay and errors in urine sampling cannot be overlooked when defining accuracy requirements.[97] In addition, biological variation in GFR is present when investigations are performed on separate days.

The present systematic review did not investigate the suitability of GFR markers, but the suitability of GFR measurement methods using these markers. For example, overestimation of GFR by plasma clearances but not renal clearances of DTPA and iothalamate may indicate a significant extrarenal route of marker elimination. However, for both markers, plasma sampling was performed in a time frame in which remaining distribution appears likely and overestimation thus may have been due to study design rather than marker properties. Unfortunately, the low number of studies using plasma clearance measurements did not allow us to investigate optimal sampling procedures at different GFRs.

Bias at different GFRs was modeled. A general pattern was that plasma clearance methods overestimated renal inulin clearance at lower GFRs. We speculate that plasma sampling in the period of ongoing marker distribution may have contributed. In contrast, renal clearance of ^{51}Cr-EDTA and iothalamate demonstrated fixed bias across GFRs. However, it is important to recognize that many studies were small and the statistical uncertainty in results across GFRs therefore was substantial.

For renal iothalamate clearance, the only method with a considerable number of studies of varying size, a funnel plot did not indicate publication bias (data not shown). Limiting inclusion to studies published in English or the Scandinavian languages may have introduced bias. The extent and effect of language bias in systematic reviews has been studied previously but yielded conflicting results.[98]

Today, the evidence regarding the accuracy of renal and plasma clearance of DTPA, renal clearance of iohexol, plasma clearance of iothalamate, and plasma clearance of inulin is limited or insufficient. In plasma clearance studies, optimal sampling time at different GFRs needs to be investigated further. Furthermore, the accuracy of plasma clearance methods in patients with low GFRs or abnormal distribution volumes warrants further investigation.

In the absence of access to renal inulin clearance measurements, accurate methods to measure GFR are renal clearance of ^{51}Cr-EDTA, renal clearance of iothalamate, plasma clearance of ^{51}Cr-EDTA, and plasma clearance of iohexol. For the measurement of GFR, endogenous creatinine clearance is an inaccurate method. The conclusions are supported by moderately strong to strong scientific evidence.

ACKNOWLEDGEMENTS

Members of the SBU GFR Review Group are as follows: Carl-Gustaf Elinder (chair), Maria Ahlberg, Susanne Vilhelmsdotter Allander, Anders Alvestrand, Charlotte Asker-Hagelberg, Max Bell, Ulla Berg, Jonas Björk, Agneta Brolund, Sten-Erik Bäck, Thomas Davidson, Nasim Farrokhnia, Anders Grubb, Anders Larsson, Lars-Åke Marké, Ingegerd Mejaré, Patrik Midlöv, Magnus Nord, Anders Norlund, Ulf Nyman, Karin Rydin, Per Sjöström, Inga Soveri, Gunnar Sterner, Maria Svensson, and Sara

Wickström; Adjunct member: Gunnar Nordin; External review board: Peter Bárány, Lars Bernfort, Monica Edholm, Ola Samuelsson, Ellen Vinge, and Carl-Johan Östergren.

Except for Dr Elinder, who revised the manuscript, all authors conducted the study, interpreted the data, drafted the manuscript, and gave final approval to the submitted version. Dr Björk analyzed the data. All members of the SBU GFR Review Group designed the study. The authors thank David Traneus for data extraction.

Support: None.

Financial Disclosure: Drs Soveri, Berg, Björk, Grubb, and Bäck report personal fees from the Swedish Council on Health Technology Assessment during the conduct of the study. The other authors declare that they have no relevant financial interests.

SUPPLEMENTARY MATERIAL

Item S1: Literature search phrases.

Item S2: Generalized linear mixed models.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.04.010) is available at www.ajkd.org

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