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ARTICLE

Estimation of glomerular filtration rate for drug dosing in patients with very high or low body mass index

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Abstract

An accurate estimated glomerular filtration rate (eGFR) is essential in drug dosing. This study demonstrates the limitations of indexed (ml/min/1.73 m^2) and de-indexed (ml/min) eGFR based drug dosing in patients with obesity or underweight. This systematic study aimed to determine the most appropriate approach to estimate the GFR for standardized eGFR based drug dosing in these patients. (Raw) data of 12 studies were selected to investigate the accuracy and bias of both the indexed and de-indexed estimations of the Modification of Diet in Renal Disease (MDRD) study equation and the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), and of the Cockcroft–Gault (CG) in patients with obesity or underweight. Accuracy was calculated as the proportion of eGFR values within 30% of the measured GFR (P30) using an inert tracer (e.g., iohexol, inulin, ^{51}Cr-EDTA, or iothalamate clearance). An accuracy of at least 80% was considered acceptable. GFR values estimated with the CG, MDRD, and CKD-EPI differ significantly within a patient with obesity or underweight regardless of whether it is indexed or de-indexed. All studies, with two exceptions, show that all three equations are inaccurate for patients with underweight or class II obesity (P30: 55%–94%). De-indexing eGFR improves not or modestly the accuracy, and mostly remains below the 80% (P30: 62%–100%). CG was highly inaccurate in obese and underweight patients (P30: 7%–82%). Although these results show that CG is obsolete, the accuracy of MDRD and CKD-EPI is low in patients with obesity or underweight and de-indexing is not the solution. Better education and more accurate methods for appropriate drug dosing (e.g., measured GFR with inert tracer, therapeutic drug monitoring, or 24-h creatinine clearance) are recommended.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THIS TOPIC?

An accurate estimation of glomerular filtration rate (eGFR) is essential for drug dosing. Studies on the impact of indexing or de-indexing the eGFR for drug dosing

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in a population with obesity or underweight has been studied insufficiently. More insight in estimating GFR for this population will increase safe and effective drug prescribing.

WHAT QUESTIONS DID THIS STUDY ADDRESS?

What is the most appropriate approach in estimating GFR for standardized eGFR based drug dosing in patients with obesity or underweight?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The Cockcroft–Gault and both the indexed and de-indexed Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration have a low accuracy and high bias in estimating GFR in patients with obesity or underweight.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

More reliable methods, such as measuring GFR with an exogenous tracer (e.g., iohexol or iothalamate), therapeutic drug monitoring, or 24-h creatinine clearance should be considered when body mass index (BMI) is >35 or <18.5 kg/m^2 and the eGFR is at a critical point for dosing drugs with a drug with a narrow therapeutic window. Prescribers and pharmacists should be aware of the impact of a strongly deviating BMI on eGFR. Dedicated pharmacokinetic (PK) studies should include and evaluate new biomarkers, such as cystatin C when estimating the eGFR-PK effect in obesity and cachexia.

INTRODUCTION

Individualized drug dosing is essential for renally excreted drugs in patients with chronic kidney disease (CKD) to prevent toxicity while maintaining efficacy. Therefore, it is of vital importance to accurately assess the glomerular filtration rate (GFR) when prescribing drugs that are primarily eliminated by glomerular filtration. The gold standard method is to determine the average GFR over a period of time (mostly between 5 and 8 h) with a measurement using an inert tracer (e.g., iohexol or iothalamate).[1] However, this measurement is invasive, time-consuming, and expensive. Therefore, clinicians mostly either estimate the GFR (eGFR) or estimate 24-h urinary creatinine clearance based on serum creatinine. The most commonly used equation to estimate the creatinine clearance is the Cockcroft–Gault (CG), whereas the Modification of Diet in Renal Disease (MDRD) Study equation and Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) are the most commonly used equations to estimate GFR.[2–4]

As stated by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Kidney Disease Improving Global Outcome (KDIGO), drug dosing should be based on the absolute GFR of the patient (expressed in ml/min) because this reflects the true renal elimination capacity for a defined patient.[5–7] Recent reviews describe the controversies with regard to GFR estimation in clinical studies and clinical setting, according to the FDA and EMA.[8,9] Even though these reviews and guidelines recommend against using the CG equation for evaluating GFR for drug dosing recommendations, most clinical drug research applies the CG, an equation that expresses the estimated creatinine clearance in ml/min. Consequently, national formularies in the United Kingdom, Australia, the United States, and the Netherlands use the estimated creatinine clearances for their drug dosing recommendations. On the other hand, in clinical practice, the MDRD and CKD-EPI are most commonly used. Both equations express the eGFR in ml/min indexed for a normalized body surface area (BSA) of 1.73 m^2 which enables one to compare renal function between individuals with different body composition. Physicians and pharmacists often use this indexed eGFR for drug dosing. In patients with a strongly deviating body mass index (BMI), indexed eGFR may not reflect the true renal elimination capacity. We experienced this in two patients with class II obesity and underweight using apixaban, which is a direct oral anticoagulant (DOAC) that is ~30% renally excreted and has a small therapeutic window. DOAC therapy thus needs dosage adjustment in patient with a GFR below 30 ml/min according to the summary of product characteristics.

Patient 1 was a 48-year-old woman with a history of complicated diabetes mellitus type 2, hypertension, hyperlipidemia, nephrotic syndrome, ischemic

cardiomyopathy, and obesity (BMI of 36.6 kg/m^2 and BSA of 2.3 m^2). She was admitted to the hospital because of dyspnea, fever, and chest pains caused by a subsegmental pulmonary embolism with pulmonary infarction and pleuritis. The physician started treatment with apixaban 10 mg twice daily for 7 days, followed by 5 mg twice daily. The hospital pharmacist was directly alerted by the advanced clinical decision support system showing that the patient had an eGFR of 28 ml/min/1.73 m^2 (creatinine: 181 µmol/L), which, according to the Dutch clinical support system, means that the dose of the apixaban should be adjusted.

Patient 2 was a 97-year-old woman with a history of migraine, atrial fibrillation, iron deficiency anemia, underweight (BMI of 17.1 kg/m^2 and BSA of 1.2 m^2) and eGFR of 60 ml/min/1.73m^2 (creatinine: 72 µmol/L). She was admitted to the hospital because of fever and dyspnea, what was explained by a pulmonary embolism. Subsequently, she was treated with apixaban 10 mg twice daily for 7 days, followed by 5 mg twice daily. The hospital pharmacist was directly alerted by the advanced clinical decision support system because, based on her age and weight, the dose of the apixaban should be adjusted, and the pharmacist noticed the potential unreliability of eGFR (Table 1).

As mentioned above, for drug dosing current standards recommend using the absolute GFR expressed in ml/min to reflect the true, individual, renal elimination capacity. In our hospital, the electronic health record reports eGFR indexed for a normalized BSA of 1.73 m^2. In patients within the normal BSA range, indexed eGFR is most of the times comparable with eGFR expressed in ml/min. However, in patients with abnormal BSA, this may not be the case. Therefore, for such patients, some experts recommend calculating eGFR in ml/min by multiplying the current indexed estimated GFR by the true BSA of the patient, and then dividing it by 1.73 (eGFR*BSA/1.73).[3] Table 1 shows the GFR estimates per equation in the two presented case studies. As can be seen, the values differ significantly. These values coincide with different dosing regimens, raising the question of which approach is most appropriate to use. The aim of this study was to identify the most appropriate approach in estimating GFR for standardized eGFR based drug dosing in patients with obesity or underweight.

TABLE 1 Patient characteristics of the two cases

	Case 1 (obese)	Case 2 (underweight)
Age, years	48	97
Gender	Female	Female
Ethnicity	White	White
Weight, kg	111	37
Length, m	1.74	1.47
BMI, kg/m^2	36.7	17.1
BSA, m^2	2.3	1.2
Creatinine, µmol/L	181	72
CG, ml/min	59.2	23.2
eGFR CKD-EPI, ml/min/1.73 m^2	28.1	60.7
eGFR CKD-EPI de-indexed, ml/min	37.6	43.6
eGFR MDRD, ml/min/1.73 m^2	25.9	65.0
eGFR MDRD de-indexed, ml/min	34.4	45.1

Abbreviations: BMI, body mass index; BSA, body surface area via Dubois method: $0.007184 \times \text{height}^{0.725} \times \text{weight}^{0.425}$; CG, Cockcroft–Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

CKD-EPI: $141 \times \min(\text{SCr}/\kappa, 1)^{\alpha} \times \max(\text{SCr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}}$ (Female: Male × 1.018; Black people: × 1.159).

MDRD: $175 \times (\text{SCr}/88.4)^{-1.154} \times \text{age}^{0.203}$ (Female: Male × 0.742; Back people: × 1.212).

Cockcroft–gault: ([140 – age] × weight (kg)] / (SCr × 0.81) (Female: Male × 0.85).

SCr = serum creatinine in µmol/L; Age in years; κ is 61.9 for females and 79.6 for males; α is −0.329 for females and −0.411 for males; min is minimum of SCr/κ of 1; max is maximum of Scr/κ of 1.

METHODS

Study search

A systematic search was performed in the databases: OVID MEDLINE, Embase.com, Clarivate Analytics/ Web of Science Core Collection, and the Wiley/Cochrane Library. The timeframe within the databases was from inception to February 9, 2022, and conducted by authors E.M.D. and G.L.B. The search included keywords and free text terms for (synonyms of) "glomerular filtration rate" combined with (synonyms of) "non-indexed GFR estimations" combined with (synonyms of) "indexed GFR estimations" combined with (synonyms of) "measured GFR" combined with (synonyms of) "obesity" or "underweight." A full overview of the search terms per database can be found in Appendix S1. No limitations on date or language were applied in the search. Studies with patients under 18 years of age were excluded.

Study selection

Two researchers (authors E.M.D. and I.B.) independently selected eligible studies based on prespecified criteria

using the online software Rayyan (Rayyan Systems Inc., Boston, MA). If there was no agreement after discussion, a third party was consulted (author M.vA.). Studies were found to be eligible when all GFR estimates were compared with measured GFR (mGFR). The mGFR had to be expressed in ml/min as this reflects the true renal elimination capacity of an individual needed for drug dosing.[5–7] Studies using solely the Jaffé method for creatinine determination or 24-h urine creatinine clearance were excluded. If the accuracy and bias for both the (de-)indexed CKD-EPI and MDRD were not available, raw data were requested to perform the analysis.

Statistics

Accuracy was calculated as the proportion of eGFR values within plus and minus 30% of measured GFR in ml/min (P30) stratified by BMI group and per study. Absolute bias of eGFR was defined as the mean or median difference between the eGFR and mGFR (eGFR–mGFR) and was presented per BMI group and per study. As in other studies, P30 of 80% was considered acceptable.[3,4] Analysis was performed in Microsoft Excel 2016 (Microsoft, Redmond, WA).

Risk of bias in the literature search was independently assessed by two authors (E.M.D. and I.B.) using the Quality Assessment of Diagnostic Accuracy Studies-Comparative (QUADAS-C) tool and was discussed until agreement was reached. The QUADAS-C is a risk-of-bias judgment tool focusing on four domains: (1) patient selection, (2) index test, (3) reference standard, and (4) flow and timing.[10] For each domain, prespecified signaling questions for potential bias (e.g., "Could the selection of patients have introduced bias?" or "Did all patients receive the same reference standard?") have to be scored as "yes," "no," or "unclear." In case one of the questions was scored with "yes"' or "unclear," concerns regarding applicability of the study had to be judged as "low," "high," or "unclear."

RESULTS

A total of 151 studies were retrieved from the initial search and four were added by the investigators' knowledge. Of those, 113 were excluded after screening titles and abstracts. The remaining 42 articles were examined by reading the full text. Figure 1 provides a detailed overview of the selection process. In total, two studies were eligible for inclusion, and 20 for requesting raw data. Of these, we

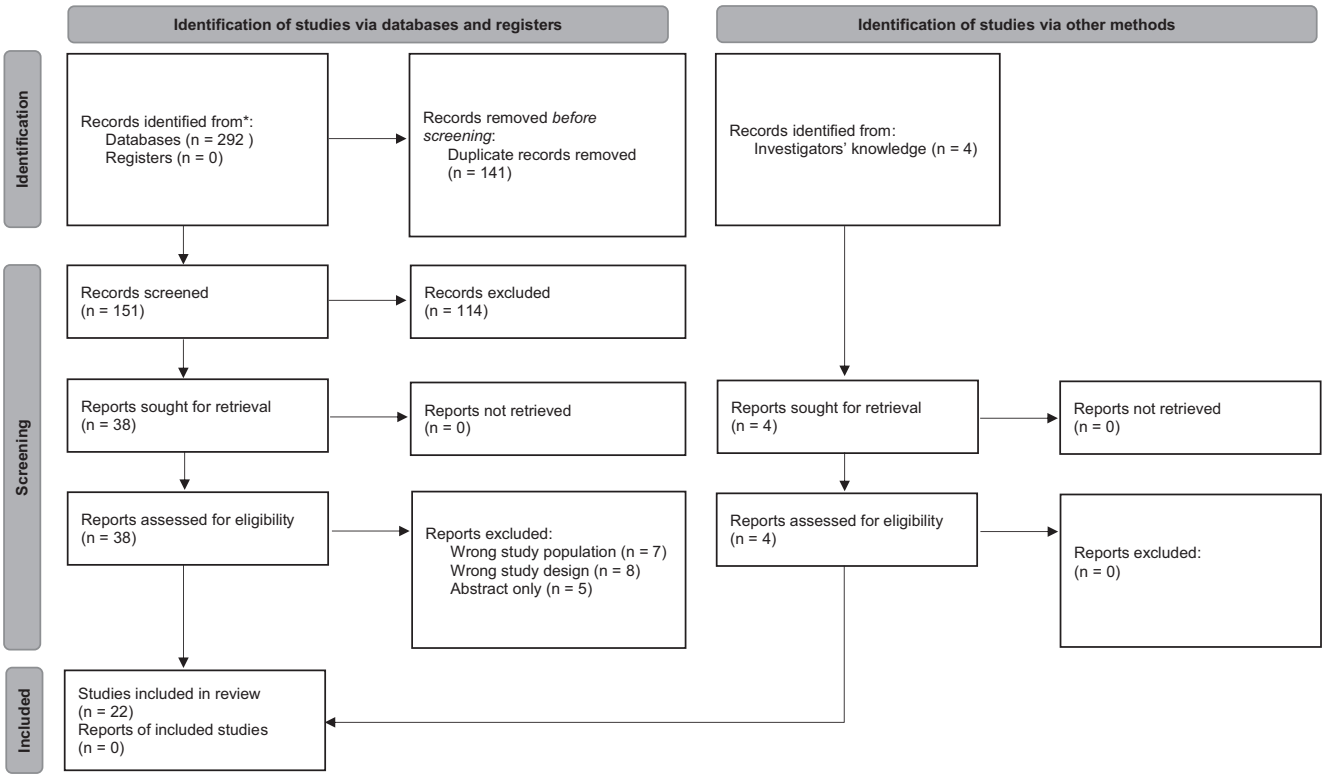

FIGURE 1 PRISMA diagram. *OVID MEDLINE, Embase.com, Clarivate Analytics/Web of Science Core Collection and the Wiley/Cochrane Library.

received raw data from eight (40%) studies. For two studies (10%), we did not receive raw data, but the available data were sufficient to use for one part of the study. Of the remaining 10 (50%) studies we did not receive a response, or were informed that raw data was no longer available. This resulted in 12 studies for which (raw) data was available for the analyses (Table 2).[11–22] The results including the re-analyses are shown in Table 3.

In general, the risk of bias and concerns regarding applicability was scored as low in all included studies (Appendix S2). The risk of bias was scored high for the domain "patient selection" if the study was retrospective or included patients with high muscle mass. The risk of bias was scored high for the domain "index test" when serum creatinine levels were analyzed with the nonstandardized Jaffé method, potentially limiting applicability.

The results of our analyses confirm the low accuracy of the CG in all patients and shows that the accuracy decreases as the BMI of the patient rises (range: 11%–82%). Moreover, the GFR estimated by the CG shows large bias up to 108 ml/min, specifically in obese or underweight patients (range 7.9–108.6 ml/min), versus patients with a non-deviating BMI (range −1.7–23.3 ml/min).[11,12,14–16,18,22] Indexed MDRD and CKD-EPI show, with the exception in the study by Martus et al. and the study by Lemoine et al.,[15,16] a low accuracy and/or high bias (range mean P30 CKD-EPI: 42%–84%, MDRD: 55%–81%; range mean bias CKD-EPI: −56.0–7.7 ml/min, MDRD: −29.6–7.4 ml/min).

In 10 studies, we examined the differences in accuracy and bias of indexed and de-indexed MDRD and CKD-EPI compared with mGFR in obese or underweight patients (Figures 2 and 3, and Table 3). With the exception of the studies by Lemoine et al. and in some BMI subgroups, the studies show similar or modestly improved accuracy and bias for both the de-indexed CKD-EPI and de-indexed MDRD. However, except for the studies by Chang et al. and by Martus et al., and in some BMI subgroups, the accuracy in all studies was below the predefined acceptable percentage of at least 80% (Figures 2 and 3, and Table 3).

DISCUSSION

Estimating GFR with the CKD-EPI, MDRD or CG gives significantly different estimations within one patient with underweight or obesity. Our study shows that all three estimations have low accuracy in these patients. Moreover, data including in the present systematic study show that de-indexing the CKD-EPI and MDRD, a suggested approach by some experts, does not increase accuracy to the acceptable level of >80% that has been found in normal weighted people (CDK-EPI 84.1% and MDRD 80.6%).[4]

Deviations in BMI can be a result of various causes (excessive fat mass, cachexia, edema, increasing muscle mass, amputations, etc.), each of which require a different interpretation and approach when estimating GFR. To our knowledge, this is the first systematic study investigating the effect of underweight and obesity on eGFR based drug dosing and how it is done in clinical practice. As presented in our cases, it is important that prescribers and pharmacists be aware of the limitations of the CKD-EPI and MDRD when estimating GFR in obese and underweight patients, and specifically the influence of (de-)indexing. A study in Australia suggests that there is a lack of awareness among physicians. Only 62% of physicians were aware that BSA is part of the unit used to describe eGFR.[23] We suggest that by adding BMI to medical reports and advanced clinical decision support systems awareness could be improved. Moreover, when eGFR is around a critical point for drug dosing (e.g., 30 or 50 ml/min) and the BMI is strongly deviated (below 18.5 kg/m^2 or above 35 kg/m^2), we recommend in a clinically stable, steady-state situation using a more accurate method (e.g., measuring GFR with an exogenous tracer, iohexol or iothalamate), therapeutic drug monitoring, or 24-h creatinine clearance (with possible errors in urine collecting and overestimation as limitations in mind).[1] The second is specifically recommended for drugs with a small therapeutic window. In our DOAC cases, we can rely on either a pharmacokinetic target (drug concentration) or pharmacodynamic target (anti-Xa level), which is a topic for further research.

To determine the critical point, the patient's weight and height should be reported accurately in electronic health records. This requires relatively small effort and has other potential benefits for the patient. BMI is commonly used as a marker of disease risk, and weight and height are used to determine other clinical measures, such as ideal body weight.

Several limitations must be kept in mind when interpreting the results of this study. First, we did not receive all requested raw data. Second, in our post hoc analysis, we compared values using two different units (ml/min vs. ml/min/1.73m^2). Although this comparison is not acceptable from a mathematical standpoint, it does reflect clinical practice where physicians and pharmacists use the eGFR expressed in ml/min/1.73m^2 for drug dosing, which in fact should be based on the individual kidney function expressed in ml/min. Third, we did not account for other factors (confounders) that might influence the accuracy of the GFR estimates, such as age and diabetes, like in our cases, and the inferiority of the MDRD in patients with a normal-high kidney function. Fourth, we used the same acceptable accuracy of 80% as in other studies. However, this may be inappropriately large for drugs with a (very)

TABLE 2 Study characteristics

Studies	Number of participants	Mean BMI (kg/m^2)	Mean BSA (m^2)	Age (years, SD)	Gender (female, %)	Ethnicity (African)	Method mGFR	Method creatinine	Used equation(s)	Mean creatinine (μmol/L)
Bouquegneau et al. (2016)[11]	366	36.0	2.16	55 ± 14	181 (51)	50 (14%)	^{51}Cr-EDTA clearance	IDMS	CG, CKD-EPI, MDRD	151.5
Friedman et al. (2014)[12]	36	46.0	2.33	50 ± 11	28 (78)	34 (94%) White 2 (6%) other	Iohexol clearance	IDMS	CG, CKD-EPI, MDRD	71.6
Guebre-Egziabher et al. (2019)[13]	598	39.6	2.09	58 ± 12	284 (47)	Unknown	Inulin or iohexol clearance	Kinetic, colorimetric and compensated Jaffe technique, and IDMS	CKD-EPI, MDRD	106.1 (median)
Lemoine et al. (2014)[14]	209	34.8	2.01	57 ± 13	90 (43)	Unknown	Inulin clearance	IDMS	CG, CKD-EPI, MDRD	126
Lemoine et al. (2016)[15]	166	36.7	2.04	58 ± 14	94 (56)	Unknown	Inulin or iohexol clearance	IDMS	CG, CKD-EPI, MDRD	199
Martus et al. (2014)[16]	570	28.0	1.85	79 (range 70–96)	244 (43)	Unknown	Iohexol clearance	IDMS	CG, CKD-EPI, MDRD	87.5
Cirillo et al. (2005)[17]	393	27.9	1.79	46 ± 14	168 (43)	100% white	Inulin clearance	Kinetic alkaline picrate assay	CG, CKD-EPI, MDRD	88.4
Chang et al. (2020)[18]	44	48.2	2.36	Unknown	Unknown	Unknown	Iohexol clearance	IDMS	CG, CKD-EPI, MDRD	75.1
López-Martínez et al. (2020)[19]	944	30.8	2.06	58 ± 14	287 (30)	Unknown	Iohexol clearance	IDMS	CKD-EPI, MDRD	122.0 (median)
Chew-Harris et al. (2015)[20]	78	34.1	2.08	40 ± 14	Unknown	Unknown	^{99m}Tc-DTPA	IDMS	CKD-EPI	81.4
Nyman et al.[21]	850	25.0	1.88	60 (median, range 26–85)	376 (44)	Unknown	Iohexol clearance	IDMS	CKD-EPI, MDRD	107
Delanaye et al. (2021)[22]	4328	25.5	1.82	71 (median, 2.5–97.5 percentile 19-89)	2052 (47)	Unknown	Iohexol, inulin, ^{51}Cr-EDTA or iothalamate clearance	IDMS and Jaffe method	CKD-EPI, MDRD	143.2

Abbreviations: ^{51}Cr-EDTA, ^{51}Chromium Ethylenediaminetetraacetic acid; ^{99m}Tc-DTPA, ^{99m}Technetium-diethylenepentaacetic acid; BMI, body mass index; BSA, body surface area; CG, Cockcroft–Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; IDMS, isotope dilution mass spectrometry traceable reference measurement procedure; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate.

TABLE 3 Bias and accuracy of (de-)indexed equations to estimate GFR

Studies	BMI categories	Number of GFR measurements	Accuracy P30 (% of subjects within 30% mGFR)[b]			Bias in ml/min/1.73m^2 or ml/min		
			Indexed/de-indexed[c] CKD-EPI	Indexed/de-indexed MDRD	CG	Indexed/de-indexed CKD-EPI	Indexed/de-indexed MDRD	CG
Bouquegneau et al. (2016)[a11]	Total	366	72/76	70/80	57	−10/6.2 (mean)	−13/2.8 (mean)	25.0 (mean)
	BMI 30–<35	217	73/82	71/86	71	−10/1.8	−12.5/−1.2	13.2
	BMI ≥35–<40	76	68/71	68/74	51	−8.1/7.9	−11.3/3.9	25.9
	BMI ≥40	73	70/63	66/71	22	−12.2/17	−14.8/13.6	58.7
Friedman et al. (2014)[a12]	Total	36	67/64	64/72	17	−23.7/8.2 (mean)	−29.6/0.2 (mean)	99.0 (mean)
	BMI 33–<40	7	86/71	71/71	29	−7.4/13.4	−16.5/2.4	59.1
	BMI ≥40	29	55/62	62/72	14	−27.6/6.9	−32.8/−0.3	108.6
Guebre-Egziabher et al. (2019)[a13]	Total	706	75/78	73/74	Not reported	10.18/9.0 (median)	10.3/9.8 (median)	Not reported
	BMI 35–<40	465	74/84	73/77		9.5/8.8	10.2/10.0	
	BMI ≥40	241	75/73	74/69		10.7/9.5	10.5/10.0	
Lemoine et al. (2014)[a14]	Total	209	77/71	78/76	31	0.3/9.9 (mean)	−2.5/6.6 (mean)	26
	BMI 30–35	134	79/72	82/76	34	2.4/11.5	−1/7	25
	BMI 35–40	54	76/67	76/74	30	−3/7	−4/6	27
	BMI ≥40	21	65/75	60/80	15	−6/6	−8/3	32
Lemoine et al. (2016)[a15]	Total	166	84/75	81/70	37	−1/7 (mean)	−1.14/11 (mean)	31
	BMI 30–35	73	83/77	79/74	49	−1.5/7	0.81/10	24
	BMI 35–40	51	78/72	75/67	43	−7/4.8	−4.2/8	26
	BMI ≥40	42	93/76	94/67	7	−4.6/10.4	−0.75/15	51
Martus et al. (2014)[a16]	Total	570	81/80	77/72	88	3.9/8.7 (mean)	6.1/11.2 (mean)	3.1
	BMI <25	149	63/75	57/65	92	11.4/10.6	14.3/13.5	−1.7
	BMI 25–30	261	86/81	82/74	92	4.1/8.9	6.3/11.4	1.7
	BMI 30–35	130	93/82	91/76	82	6.4/15.4	8.0/17.3	7.9
	BMI ≥35	30	73/80	77/78	67	3.3/18.2	5.3/20.8	17.5
Cirillo et al. (2005)[a17]	Total	393	76/73	73/71	55	7.7/11.0 (mean)	7.4/10.7 (mean)	27.3
	BMI <18.5	3	67/100	67/100	33	2.8/−11.1	−3.0/−16.2	−26.1
	BMI 18.5–25	177	71/68	66/66	64	15.5/12.8	15.0/12.4	19.1
	BMI 25–30	121	79/76	77/74	62	6.1/9.7	6.2/9.8	23.3
	BMI 30–35	33	67/79	76/64	39	1.6/9.9	4.2/12.8	34.6

TABLE 3 (Contiuned)

Studies	BMI categories	Number of GFR measurements	Accuracy P30 (% of subjects within 30% mGFR)[b]			Bias in ml/min/1.73m^2 or ml/min		
			Indexed/de-indexed[c] CKD-EPI	Indexed/de-indexed MDRD	CG	Indexed/de-indexed CKD-EPI	Indexed/de-indexed MDRD	CG
	BMI 35–40	31	90/94	84/90	36	−10.5/1.5	−12.2/−0.2	36.9
	BMI ≥40	28	93/64	89/75	11	−6.9/19.9	−9.6/16.5	83.3
Chang et al. (2020)[a18]	Total	82	65/84	55/83	20	−25.4/3.7 (median)	−31.2/−2.2 (median)	68.3
López-Martínez et al. (2020)[19]	Total	944	79/79	79/79	Not reported	Not reported		Not reported
Chew-Harris et al. (2015)[20]	Total	78	42/74	Not reported	Not reported	−56/−30 (mean)	Not reported	Not reported
Nyman et al. (2011)[21]	Total	850	80/NA	80/NA	Not reported	2.3/NA (median)	1.2/NA (median)	Not reported
	BMI <20	75	65/NA	64/NA		21.5/NA	15.4/NA	
	BMI ≥20 to <25	318	82/NA	82/NA		7.3/NA	4.0/NA	
	BMI ≥25 to <30	307	81/NA	81/NA		3.6/NA	1.9/NA	
	BMI ≥30	150	77/NA	81/NA		1.9/NA	−0.1/NA	
Delanaye et al. (2021)[22]	Total	4328	NA/65	NA/67	59	NA/4.4 (median)	NA/3.9 (median)	6.1 (median)
	BMI <18.5	262	NA/37	NA/49	59	NA/15.8	NA/11.2	7.5
	BMI 18.5–25	1713	NA/63	NA/66	66	NA/5.6	NA/4.6	3.9
	BMI 25–30	1415	NA/70	NA/71	62	NA/3.0	NA/3.0	5.2
	BMI 30–35	643	NA/69	NA/69	50	NA/2.5	NA/2.7	8.5
	BMI 35–40	203	NA/68	NA/69	34	NA/3.7	NA/3.4	15.4
	BMI ≥40	92	NA/67	NA/70	27	NA/0.1	NA/−0.5	17.2

Note: Indexed: ml/min/1.73m^2; De-indexed: ml/min.

Abbreviations: BMI, body mass index; CG, Cockcroft–Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

[a]The results of this study include new data based on post-hoc analysis.

[b]Accuracy was calculated as the proportion of estimated GFR values within 30% of the measured GFR (P30). An accuracy of ≥80% was considered acceptable.

[c]De-indexation was performed by multiplying the current indexed estimated GFR by the true BSA of the patient, and then divide it by 1.73.

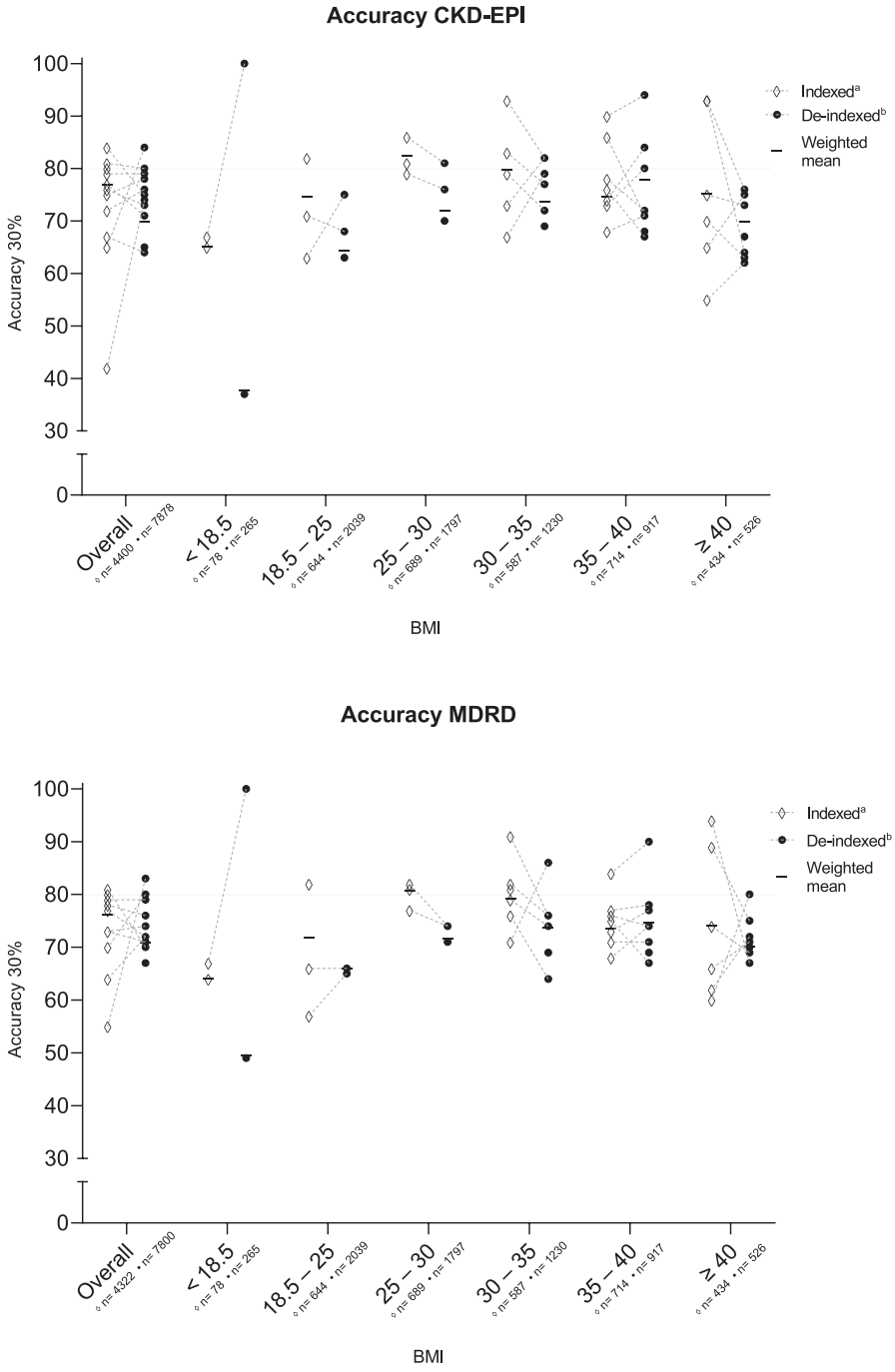

FIGURE 2 Accuracy of (de-) indexed equations to estimate GFR. Per subgroup, each datapoint represents a study. Accuracy 30%: the proportion of eGFR values within plus and minus 30% of measured GFR in ml/min. Weighed mean: the sum of each study mean multiplied by sample size, divided by the sum of all sample sizes. [a]ml/min/1.73m^2. [b]ml/min. BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

narrow therapeutic window because dose adjustments for these types of drugs may have large clinical implications.

In the future, the use of cystatin C with or without serum creatinine might be another solution. Cystatin C can also be used as biomarker to estimate GFR. Cystatin C is a protein produced by all nucleated human cells, and is therefore less influenced by muscle mass.[24] In current practice, the use of cystatin C is recommended by the KDIGO only as a confirmatory test in evaluating the GFR when the use of creatinine is thought to be imprecise.[25] A recent meta-analysis showed that, in a general population, the CKD-EPI equation based on cystatin C was less biased and using the combination of cystatin C and creatinine yielded the highest accuracy (mean bias difference of 4.84 ml/min/1.73 m^2, mean P30 difference of 7.50% compared to the CKD-EPI equation using only creatinine).[26] Two studies in obese populations showed that the combined CKD-EPI equation was more accurate (P30: 83% vs. 76% and 80% vs. 58%), and less biased (2.4 vs. 5.9 and 1.6 vs. −18.2 ml/min/1.73 m^2) than the creatinine-based CKD-EPI.[12,15] The same seems to be true for patients with a low body mass index.[27] The studies suggest that cystatin C and creatinine-based eGFR is superior for drug dosing in patients with strongly deviating BMI, but further

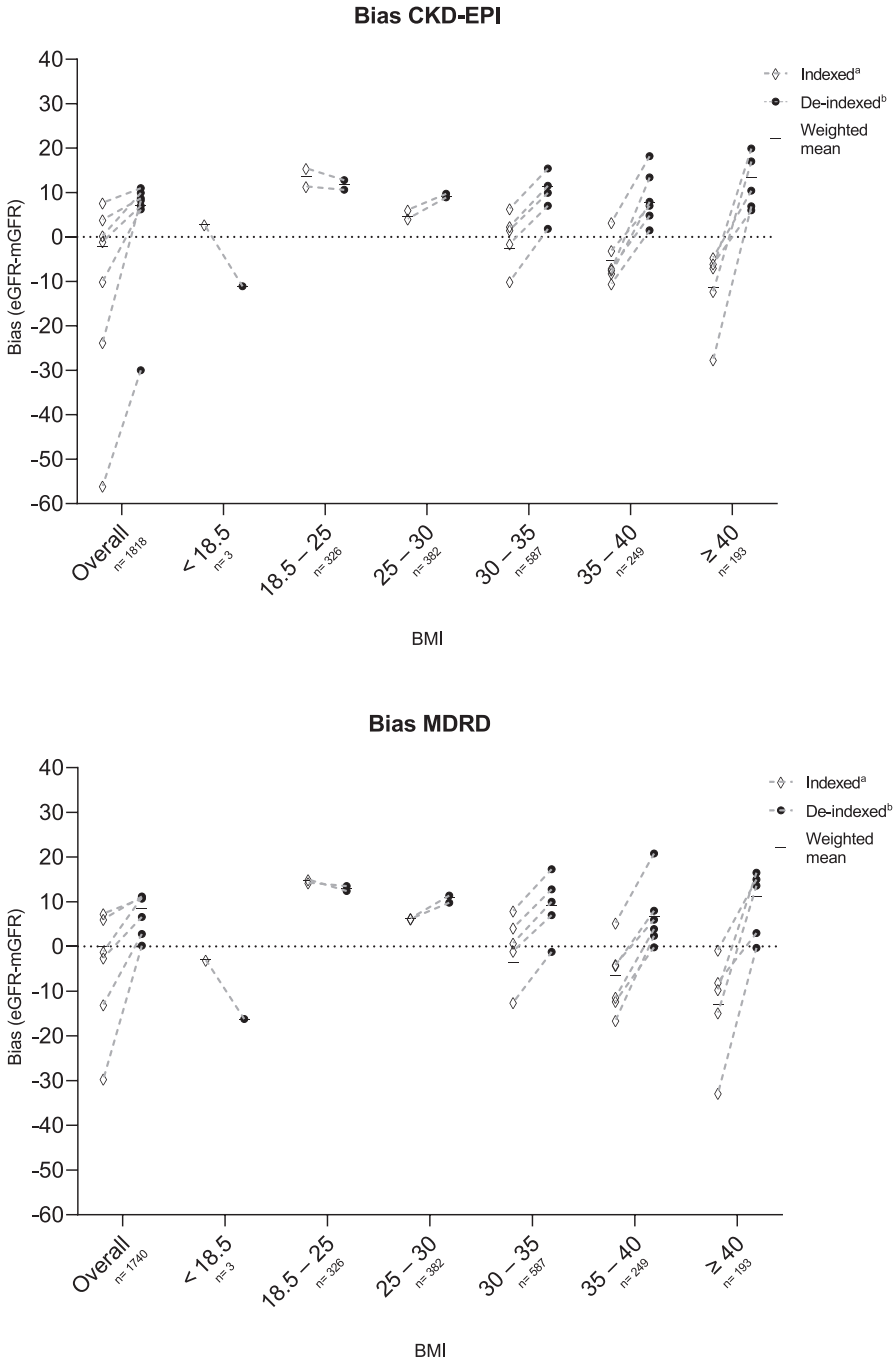

FIGURE 3 Bias of (de-)indexed equations to estimate GFR. Per subgroup, each datapoint represents a study. Only studies with a bias expressed as a mean value are included. Bias: mean difference between the eGFR and mGFR (eGFR – mGFR). Weighed mean: the sum of each study mean multiplied by sample size, divided by the sum of all sample sizes. For a full overview, see Table 3. [a]ml/min/1.73m^2. [b]ml/min. BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate.

(pharmacokinetic) studies including various renally excreted drugs are needed prior to recommending it as the standard method.

CONCLUSION

In conclusion, to safely and effectively dose drugs that are renally excreted in patients with CKD, it is of vital importance to know the patient's true renal clearance. This report shows the limitations of estimating GFR in an obese or underweight population with the CG, MDRD, or CKD-EPI equations. Furthermore, we show that de-indexing eGFR (multiplying by individual BSA/1.73) has the same low accuracy, and thus also may lead to inappropriate dose adjustments. Estimating GFR using serum cystatin C with or without creatinine is promising, but dedicated pharmacokinetic research using this estimate in obese and underweight patients should be performed. In the meantime, drug dosing could be improved by including the individual BMI in medical reports and advanced clinical decision support systems. In the case of obesity or underweight, it is recommended that drug dosing, especially for drugs with a small therapeutic window, should be based on a more reliable approach fitting the patient (e.g., mGFR with an exogenous tracer, iohexol or

iothalamate), therapeutic drug monitoring, or 24-h creatinine clearance.

AUTHOR CONTRIBUTIONS

E.M.D. and I.B. wrote the manuscript. E.M.D., P.B., M.Av.A., A.N., E.S. and I.B. designed the research; E.M.D., P.B., M.Av.A., A.N., E.S., G.L.B., A.N.F., A.B., S.L., N.E., M.C., and I.B. performed the research. E.M.D., A.N.F., A.B., S.L., N.E., M.C., and I.B. analyzed the data.

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CONFLICT OF INTEREST

A.N.F. is on the scientific advisory committee of GI Dynamics and Gila Therapeutics and is a scientific consultant for Goldfinch Bio and Astra Zeneca. All other authors declared no competing interests for this work.

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SUPPORTING INFORMATION

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

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