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Creatinine-based equations for the adjustment of drug dosage in an obese population

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- For the purpose of chronic kidney disease follow-up, the CG equation is no longer recommended and GFR should be estimated using the creatinine-derived MDRD or CKD EPI equations and expressed in ml min^{-1} 1.73 m^{-2}. We have recently shown that both equations perform similarly in a population of obese patients. For the specific issue of drug dose adaptation, thresholds of GFR are given in ml min^{-1}, and most authors recommend using the CG equation, although others recommend using the MDRD or CKD-EPI equation with de-indexation of the GFR result. Very few data are available, especially in obese patients, to recommend which is the best strategy.

AIM

For drug dosing adaptation, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend using estimated glomerular filtration rate (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, after 'de-indexation' by body surface area (BSA). In pharmacology, the Cockcroft–Gault (CG) equation is still recommended to adapt drug dosage. In the context of obesity, adjusted ideal body weight (AIBW) is sometimes preferred to actual body weight (ABW) for the CG equation. The aim of the present study was to compare the performance of the different GFR-estimating equations, non-indexed or de-indexed by BSA for the purpose of drug-dosage adaptation in obese patients.

METHODS

We analysed data from patients with a body mass index (BMI) higher than 30 kg m^{-2} who underwent a GFR measurement. eGFR was calculated using the CKD-EPI and Modification of Diet in Renal Disease (MDRD) equations, de-indexed by BSA, and the CG equation, using either ABW, AIBW or lean body weight (LBW) for the weight variable and compared with measured GFR, expressed in ml min^{-1}.

RESULTS

In our population of obese patients, use of the AIBW instead of the ABW in the CG equation, markedly improved the overall accuracy of this equation [57% for CG_{ABW} and 79% for CG_{AIBW} ($P < 0.05$)]. For high BMI (over 40 kg m^{-2}), the accuracy of the CG equations is no different when using LBW than when using AIBW. The MDRD and CKD-EPI equations de-indexed by the BSA also performed well, with an overall higher accuracy for the MDRD de-indexed equation [(80% and 76%, respectively ($P < 0.05$)].

WHAT THIS STUDY ADDS

- In obese patients, the most accurate equation to estimate absolute GFR (in ml min^{-1}, measured using the plasma clearance of ^{51}Cr-ethylene diamine tetraacetic acid (EDTA)) is the de-indexed MDRD equation. While the CG equation with ABW displays a poor performance in obese patients, the CG equation using AIBW has markedly improved accuracy *vs.* the measured GFR (in ml min^{-1}), and also appears to be suitable for the purpose of drug dose adaptation.

CONCLUSIONS

The de-indexed MDRD equation appeared to be the most suitable for estimating the non-indexed GFR for the purpose of drug dosage adaptation in obese patients.

Introduction

Obesity has become one of the most important public health problems all over the world [1]. The World Health Organization (WHO) recommends using the body mass index (BMI) as the standard measure of overweight and obesity. Adults with a BMI between 25 kg m^{-2} and 30 kg m^{-2} are considered overweight; those with a BMI $\geq$ 30 kg m^{-2} are considered to be obese [2]. The prevalence of obesity is increasing and was recently reported as having reached 25% of the population in Europe [3]. Alongside this, there is also an increasing prevalence of the co-morbidities associated with this condition, such as diabetes, hypertension, dyslipidaemia, cardiovascular disease, osteoarthritis and cancers [4]. Most of these comorbidities can alter renal function.

Obesity is a significant risk factor for chronic kidney disease (CKD), independent of other known risk factors, and is also a risk factor for the progression of kidney disease [5–7]. A raised BMI is associated with an increased risk of end-stage renal disease (ESRD) [5, 7, 8]. The association of obesity with the rate of progression of CKD is assumed to be related to many different factors, including, among others, hyperfiltration, glomerular hypertension and over-activation of the renin–angiotensin system (RAS) [9]. Drug dosage adaptation raises a number of pharmacokinetic issues in obese patients, including variations in the volume of distribution of drugs, but also difficulties in assessing renal function accurately [10]. Estimating glomerular filtration rate (GFR) in the obese population is, indeed, challenging, and creatinine-based equations are less accurate in this specific population as they have not been developed specifically for an obese population [11, 12].

The Kidney Disease: Improving Global Outcome (KDIGO) guidelines for the definition and classification of CKD clearly state that the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation should be used preferentially for GFR estimation [13]. The added value of the CKD-EPI equation over the prior Modification of Diet in Renal Disease (MDRD) study equation has, however, been challenged in the literature [14], including in studies about obese patients [11, 12]. In fact, we have already demonstrated the good performance of the creatinine-based equations in comparison with a measured GFR (mGFR) indexed by body surface area (BSA) in an obese population [11]. Beyond this debate, there is a clear consensus in the nephrology community to promote the MDRD or the CKD-EPI equation over the Cockcroft–Gault (CG) equation [15, 16]. In the context of pharmacology and for the issue of drug adjustment, the evidence is, however, not as clear. Until 2008, the CG equation was still the only equation recommended by the Food and Drug Administration (FDA) for the determination of dose adjustments studies for a new drug [17]. Since 2008, the FDA has accepted the use of the MDRD equation in dose adjustment studies and leaves the door open to other formulae, such as the CKD-EPI equation, that would prove their superiority for estimating GFR in the future. The European Medicines Agency (EMA) and the KDIGO guidelines are in accord on this issue [18, 19]. However, there are no clear data to enable a choice to be made between MDRD or CKD-EPI on the one hand, and the CG equation on the other, in the field of drug dosage adjustment in obese patients with normal or impaired renal function.

There is another issue, which is particularly relevant for obese patients in the context of GFR and renal dose adaptation. Indeed, when drug dosing is considered, the KDIGO, FDA and EMA recommend using a value for estimated GFR (eGFR) which is not adjusted to the BSA [13, 18, 20]. Hence, the formulae providing a BSA-adjusted GFR (ml min^{-1} 1.73 m^{-2}) must be 'de-indexed' to give the absolute GFR value, in ml min^{-1}, for each

individual. This de-indexation obviously has very little impact in the general population as the mean BSA is close to 1.73 m^2. By contrast, the impact is highly relevant in obese patients [21].

We have already studied the performance of the BSA-indexed creatinine-based equations (CKD-EPI and MDRD) in our population of obese patients but in the context of drug dosing adaptation, it seemed crucial to evaluate the performance of these equations de-indexed by BSA but also of the CG equation, and for the latter to determine which variable should be used for weight. Therefore, we tested the performance of two creatinine-based equations de-indexed by BSA [using the actual body weight (ABW)]: $CKD\text{-}EPI_{de\text{-}indexed}$ and $MDRD_{de\text{-}indexed}$, and the performance of the CG equation using either ABW (CG_{ABW}), lean body weight (LBW; CG_{LBW}) or adjusted ideal body weight (AIBW; CG_{AIBW}), all expressed in ml min^{-1}, in comparison with a mGFR not indexed to BSA (also expressed in ml min^{-1}). All patients were classified according to the five KDIGO stages. Lastly, we evaluated the consequence of the equation used in the case of dose adaptation of metformin.

Population and methods

The studied population was the same as that from a previous study [11]. Eligible patients were ≥18 years and had a BMI over 30 kg m^{-2}. Patients treated with glucocorticoids, cimetidine or trimethoprim were excluded. In the non-CKD but obese population, the indication for GFR measurement was an imminent living kidney transplant or patients being about to start a weight-loss diet. In obese CKD patients, GFR was measured in the context of CKD follow-up, and not because of obesity. Each local review board approved the study, and informed consent was obtained from all patients in accordance with the local review board of each of the participating institutions.

GFR was measured by the plasma clearance of ^{51}Cr-ethylene diamine tetraacetic acid (EDTA), using the single-injection method with two samples at 120 min and 240 min and the Bröchner–Mortensen correction. BSA was calculated using the equation developed by Gehan and George [22], Mosteller [23], Du bois and Du bois [24] and Livingston and Lee [25]. The results are shown for the Gehan–George equation, which has been validated in a larger number of patients and seems to be the most appropriate equation, from a methodological point of view [26]. However, using other equations yielded very similar BSA results (see Supplementary Table S1). Serum creatinine (Scr) was sampled on the same day as GFR determination and measured using the isotope dilution mass spectrometry (IDMS)-traceable compensated Jaffé method [27]. eGFR was calculated using the CKD-EPI [28], MDRD study [29] and CG equations, as indicated below. The CKD-EPI and MDRD de-indexed values were computed by multiplying eGFR by BSA calculated using ABW, and then dividing this intermediate result by 1.73 m^2 in each patient, as recommended by the KDIGO.

CG equation (calculating eGFR in ml min^{-1}):
- {[140 – age (years)]/[72 × SCr (mg dl^{-1})} × Weight [ABW (kg)] × (0.85 in females)
- The CG equation can also use the AIBW:
  - AIBW was calculated as follows:
    - Ideal weight + {0.4 *[ABW (kg) – ideal weight]} [30]
    - Ideal weight = [height (cm) – 152.4] *0.9 + 45.5 + 4.5 (in males) [31]
- The CG equation can also use the LBW:
  - LBW was calculated as follow:
    - LBW (kg) male = (9270 * ABW)/(6680 + 216 * BMI)
    - LBW (kg) female = (9270 * ABW)/(8780 + 244 * BMI)

MDRD equation (calculating eGFR in ml min^{-1} 1.73m^{-2})
- 175 × [SCr (mg $d1^{-1}$)]$^{-1.154}$ × [age (years)]$^{-0.203}$ × (0.742 in females) × (1.21 in black individuals)
- $MDRD_{de\text{-}indexed}$ in ml min^{-1} = (eGFR in ml min^{-1} 1.73m^{-2} × BSA) 1.73 m^{-2}

CKD-EPI (calculating eGFR in ml min^{-1} 1.73m^{-2}):
- k1 × (SCr/k2)$^{-\alpha}$ × 0993^{age}
- SCr: in mg dl^{-1}
- k1 = 141, 143, 163 and 166 for white men and women and black men and women, respectively
- k2 = 0.7 and 0.9 for women and men, respectively
- α =1.209, 1.209, 0.411 and 0.329 for men with SCr > 0.9 mg dl^{-1}, women with SCr > 0.7 mg dl^{-1}, men with SCr ≤ 0.9 mg dl^{-1}, and women with SCr ≤ 0.7 mg dl^{-1}, respectively
- $CKD\text{-}EPI_{de\text{-}indexed}$ in ml min^{-1} = (eGFR in ml min^{-1} 1.73 m^{-2} × BSA)/1.73 m^2

Patients were classified in CKD stages, as defined by the KDIGO [13], with each equation. Subgroups were defined according to non-indexed values of mGFR – namely, absolute mGFR (in ml min^{-1}). We added the 'hyperfiltration' stage, which is not included in the KDIGO guidelines, to this classification. This disorder is seen more frequently in obese and diabetic patients than in healthy individuals [32], and is characterized by an eGFR over 130 ml min^{-1} 1.73 m^{-2} [33]. Finally, we took a practical example of adaptation of drug dosage with the different equations, using metformin. As recommended by the KDIGO [13], metformin may be continued in patients with a GFR > 45 ml min^{-1}; its use should be reduced in those with a GFR between 30 ml min^{-1} and 45 ml min^{-1}; and it should be discontinued in patients with a

GFR < 30 ml min^{-1}. In our population of obese patients, we predicted the percentage of patients in each category according to the equation used, and the consequences in terms of drug prescription.

Descriptive statistics for studied variables are presented as: mean with standard deviation (SD) for normally distributed variables, and median with range for non-normally distributed variables. The agreement between GFR estimated by the different equations and mGFR was evaluated using the concordance correlation coefficient (rho_c), which measures both precision and accuracy, to determine how far the difference between the observed data deviates from the line of perfect concordance. The commonly adopted classification for rho_c can be described as follows: rho_c < 0 = poor, 0–0.2 = slight, 0.21–0.4 = fair, 0.41–0.6 = moderate, 0.61–0.8 = substantial and 0.81–1 = almost perfect agreement. The performances of GFR estimates were assessed using the following parameters: bias (absolute and relative) expressed the systematic deviation from the mGFR and was calculated as the mean difference between eGFR and mGFR.

The precision of the estimates was determined as the SD of the mean difference between eGFR and mGFR. These parameters are represented in Bland–Altman graphs.

Accuracy was calculated as the percentage of eGFR values within 30% of mGFR.

Comparison of bias, precision and accuracy was performed using Student's *t*-test, the *F*-test and McNemar's paired test, respectively. Analysis was performed using IBM SPSS Statistics for Mac (Version 22.0. Armonk, NY, USA: IBM Corp.).

Results

Performances of equations for estimating absolute mGFR

The population included 366 patients (185 women). The characteristics of the population are shown in Table 1. The mean age was 55 ± 14 years and mean BMI 36 ± 7 kg m^{-2}. The mean mGFR was 71 ± 35 ml min^{-1}. The mean eGFR by CG_{ABW} and CG_{AIBW} were 96 ± 64 and 72 ± 44 ml min^{-1}, respectively. The mean eGFR was 77 ± 44 ml min^{-1} and 73 ± 43 ml min^{-1} for $MDRD_{de\text{-}indexed}$ and $CKD\text{-}EPI_{de\text{-}indexed}$, respectively.

A significant concordance was found between mGFR and CG_{ABW} (rho_c = 0.6253), CG_{AIBW} (0.8544), $CKD\text{-}EPI_{de\text{-}indexed}$ (0.8685) and $MDRD_{de\text{-}indexed}$ (0.8728) equations. These coefficients did not differ significantly, except for the correlation between CG_{ABW} and mGFR, which was significantly lower ($P < 0.05$).

In the whole population, the bias and precision for the CG_{ABW} and CG_{AIBW} equations were +25 ± 39.8 ml min^{-1} and +1.6 ± 21.4 ml min^{-1}, respectively ($P < 0.05$). For the $CKD\text{-}EPI_{de\text{-}indexed}$ and the $MDRD_{de\text{-}indexed}$ equations, the biases were +6.2 ± 19.7 ml min^{-1} and +2.8 ± 19.5 ml min^{-1}, respectively. The bias of $MDRD_{de\text{-}indexed}$ was better than for the other equations, except the CG_{AIBW} equation. The accuracy within 30% was 56.8% and 79% for the CG_{ABW} and CG_{AIBW} equations, respectively ($P < 0.05$). For the $CKD\text{-}EPI_{de\text{-}indexed}$ and the $MDRD_{de\text{-}indexed}$ equations, the accuracy within 30% was 75.7% and 80.3%, respectively ($P < 0.05$) (Table 2). The accuracy for the CG_{AIBW} equation was no different from that of the $MDRD_{de\text{-}indexed}$ equation, but statistically better than the $CKD\text{-}EPI_{de\text{-}indexed}$ equation.

Using AIBW in the CG equation significantly improved the performance, especially in terms of bias compared with using ABW in this equation, and this was true at every GFR level (Table 2). Using LBW in the CG equation did not improve its performance compared with using AIBW in this equation. In fact, the bias and the accuracy were worse than those obtained using the AIBW in the CG equation, in all GFR subgroups (see Supplementary Table S2).

The $MDRD_{de\text{-}indexed}$ equation outperformed the $CKD\text{-}EPI_{de\text{-}indexed}$ equation in the overall population in terms of bias and accuracy. The accuracy (within 30%) of the CG_{AIBW} and $MDRD_{de\text{-}indexed}$ equations was similar.

The Bland–Altman analysis for the CG_{ABW}, CG_{AIBW}, $MDRD_{de\text{-}indexed}$ and $CKD\text{-}EPI_{de\text{-}indexed}$ equations are represented in Figure 1.

The cut-off of 30 ml min^{-1} for GFR is particularly relevant in pharmacology. It is usually the value below which drugs eliminated by the kidney need a dose adaptation or are contraindicated. In patients with an mGFR below 30 ml min^{-1}, all the equations slightly underestimated mGFR, except for the CG_{ABW} equation, which strongly overestimated mGFR.

At stage 3b (see Table 2), the $MDRD_{de\text{-}indexed}$ and $CKD\text{-}EPI_{de\text{-}indexed}$ equations performed similarly. These equations had a better bias than the CG_{AIBW} equation but a similar accuracy. Once again, the CG_{ABW} equation had the poorest performance.

At stage 3a (see Table 2), the $CKD\text{-}EPI_{de\text{-}indexed}$ equation had a slightly better bias (−1.4 ± 9.4 ml min^{-1}) than the $MDRD_{de\text{-}indexed}$ equation (−2.9 ± 8.4 ml min^{-1}) ($P < 0.05$) but the accuracy was no different (91.8% and 95.9% for $CKD\text{-}EPI_{de\text{-}indexed}$ and $MDRD_{de\text{-}indexed}$, respectively; $P = 0.89$). In this subgroup, the performances (both bias and accuracy) were better for the $CKD\text{-}EPI_{de\text{-}indexed}$ than for both the CG_{ABW} and CG_{AIBW} equations. The performance of the CG_{AIBW} equation was the same as that of the $MDRD_{de\text{-}indexed}$ and better than that of the CG_{ABW} equation in term of bias ($P < 0.001$). In terms of accuracy, there were statistical differences between the $MDRD_{de\text{-}indexed}$ and CG_{AIBW}, but not between the CG_{ABW} and CG_{AIBW} equations.

At high GFR values (mGFR >60 ml min^{-1}), the performances of both the CG_{AIBW} and $MDRD_{de\text{-}indexed}$ equations were slightly better than the $CKD\text{-}EPI_{de\text{-}indexed}$ equation.

Table 1
Characteristics of the population

Main characteristics	
Age (years)	55 ± 14 [18–86]
Gender (female)	185 (51%)
Weight (kg)	100 ± 22 [67–258]
Height (cm)	166 ± 10 [144–193]
Ethnicity (African)	50 (14%)
BMI (kg m^{-2})	36 ± 7 [30–77]
• 30–35 kg m^{-2}	217 (59%)
• 35–40 kg m^{-2}	76 (21%)
• > 40 kg m^{-2}	73 (20%)
BSA [Gehan–George equation (m^2)]	2.16 ± 0.26 [1.67–3.7]
Creatinine (mg l^{-1})	16 ± 11 [5–74]
eGFR:	
• CG_{ABW} (ml min^{-1})	96 ± 64 [10–610]
• CG_{AIBW} (ml min^{-1})	72 ± 44 [9–354]
• CKD-$EPI_{de\text{-}indexed}$ (ml min^{-1})	77 ± 44 [9–283]
• $MDRD_{de\text{-}indexed}$ (ml min^{-1})	73 ± 43 [10–306]
Measured GFR (ml min^{-1})	71 ± 35 [11–169]
CKD stages:	
1. GFR ≥ 90 ml min^{-1}	110 (30%)
2. GFR 60–89 ml min^{-1}	100 (27%)
3. GFR 30–59 ml min^{-1}	107 (29%)
3a. GFR 45–59 ml min^{-1}	49 (13%)
3b. GFR 30–44 ml min^{-1}	58 (16%)
4. GFR 15–29 ml min^{-1}	44 (12%)
5. GFR < 15 ml min^{-1}	5 (1%)
Hyperfiltration (GFR ≥ 130 ml min^{-1})	19 (5%)

Mean (standard deviation) for continuous variables; *n* (%) for categorical variables. Values between square brackets are the minimum and maximum values. ABW, actual body weight; AIBW, adjusted ideal body weight; BMI, body mass index; BSA, body surface area; CG, Cockcroft–Gault; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated GFR; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

However, the CG_{ABW} equation performed poorly compared with the other three equations.

Difference in staging according to the KDIGO classification using the different equations

Table 3 illustrates the percentage of patients in the different CKD stages, according to the KDIGO classification and depending on the type of equation used. For each stage, the percentage of patients with an eGFR over or under the mGFR is also shown. We therefore evaluated the proportion of patients at risk of an over- or underdose of a drug. For instance, 54.5%, 75%, 65.9% and 72.7% of patients were classified as CKD stage 4 (see Table 3) using the CG_{ABW}, CG_{AIBW}, CKD-$EPI_{de\text{-}indexed}$ and $MDRD_{de\text{-}indexed}$ equations, respectively ($P < 0.05$ between CG_{ABW} and CG_{AIBW}). The eGFR will overestimate the mGFR in 45.5%, 18.2%, 11.4% and 13.6% of patients, respectively, with the CG_{ABW}, CG_{AIBW}, CKD-$EPI_{de\text{-}indexed}$ and $MDRD_{de\text{-}indexed}$ equations ($P < 0.05$ between CG and the other three equations).

Table 4 presents the performance of the eGFR equations according to the mGFR level when metformin is used. With the CG_{AIBW}, CKD-$EPI_{de\text{-}indexed}$ and $MDRD_{de\text{-}indexed}$ equations, patients with an mGFR below 30 ml min^{-1} were correctly classified in 81.6%, 87.8% and 85.7% of the cases, respectively. By contrast, a correct staging occurred only in 57.1% of patients if the CG_{ABW} equation was used ($P < 0.05$).

All the equations gave an overestimation of the mGFR for the highest level of GFR (>60 ml min^{-1}), therefore overestimating the percentage of patients with hyperfiltration. In our study, the eGFR equations detected hyperfiltration in 90 (24.6%), 36 (9.8%), 50 (13.7%) and 31 (8.5%) patients when using the CG_{ABW}, CG_{AIBW}, CKD-$EPI_{de\text{-}indexed}$ and $MDRD_{de\text{-}indexed}$ equation, respectively. Using this subgroup of the population, 28 (31.1%), 21 (58.3%), 26 (52%) and 22 (71%) patients were misclassified as 'hyperfiltering', having an actual mGFR below 130 ml min^{-1} (Table 5).

Discussion

In our cohort of obese patients, the CG_{ABW} equation, which yields a GFR result non-indexed by BSA, although is still recommended by the FDA and the EMA for drug dosage adaptation, is imprecise and biased, and overestimates mGFR in all CKD subgroups. It is therefore not the most appropriate equation for estimating the GFR in order to adapt the drug dosage to renal function in obese subjects. However, using the AIBW instead of the ABW in the CG equation markedly improved the performances of this equation, to a greater extent than did the use of LBW. For the other, creatinine-based equations de-indexed by BSA, the $MDRD_{de\text{-}indexed}$ outperformed the CKD-$EPI_{de\text{-}indexed}$ equation in terms of bias and accuracy in the whole obese population (Table 2).

Estimating renal function is a key step for the individual adaptation of the dosage of drugs eliminated by the kidney. This is especially important when choosing a maintenance dose for drugs with a narrow therapeutic window, such as antibiotics (e.g. gentamicin) or newer oral anticoagulants [34]. Whereas overestimating renal function may lead to the administration of inappropriately large doses and possible toxicity, underestimating renal function (which may especially occur in obese patients with hyperfiltration) may lead to subtherapeutic dosing, treatment failures and prolonged illness.

The CG equation has been used for several decades and is still part of the guidance from the FDA and the EMA in pharmacokinetic studies in the setting of renal impairment [18, 20, 35]. Its accuracy for estimating GFR is, however, not optimal in obese patients, as expected by the bias induced by the ABW in the equation [16, 36–39].

Table 2

Performances of the CG_{ABW}, CG_{AIBW}, $MDRD_{de\text{-}indexed}$ and $CKD\text{-}EPI_{de\text{-}indexed}$ equations at the different levels of mGFR

	Mean mGFR (ml min^{-1})	Mean eGFR (ml min^{-1})	Mean bias (ml min^{-1})	Relative bias (%)	Accuracy (within 30%)
Total (*n* = 366)					
$MDRD_{de\text{-}indexed}$	71 ± 35	73 ± 43	2.8 ± 19.5*‡	2.5 ± 28.7*‡	80.3%*
$CKD\text{-}EPI_{de\text{-}indexed}$	71 ± 35	77 ± 44	6.2 ± 19.7†‡	6.4 ± 30†‡	75.7%†‡
CG_{ABW}	71 ± 35	96 ± 64	25 ± 39.8*†‡	32.9 ± 43.4*†‡	56.8%*†‡
CG_{AIBW}	71 ± 35	72 ± 44	1.6 ± 21.4*†	0.8 ± 28.1*†	79%
mGFR <30 ml min^{-1} (*n* = 49)					
$MDRD_{de\text{-}indexed}$	23 ± 5	21 ± 9	−1.4 ± 8.4‡	−3 ± 49.1	67.3%
$CKD\text{-}EPI_{de\text{-}indexed}$	23 ± 5	21 ± 10	−1.3 ± 8.9‡	−2.9 ± 49	61.2%
CG_{ABW}	23 ± 5	30 ± 12	7.4 ± 11.6*†‡	37.5 ± 62.7*†‡	63.3%
CG_{AIBW}	23 ± 5	22 ± 9	−0.1 ± 8*†	2.8 ± 42.7*†	65.3%
mGFR 30–44 ml min^{-1} (*n* = 58)					
$MDRD_{de\text{-}indexed}$	37 ± 5	38 ± 11	0.1 ± 9.9‡	−0.1 ± 27.2‡	84.5%
$CKD\text{-}EPI_{de\text{-}indexed}$	37 ± 5	38 ± 12	0.4 ± 10.4‡	0.8 ± 28.5‡	77.6%
CG_{ABW}	37 ± 5	47 ± 13	9.2 ± 12.1*†‡	24.5 ± 33.4*†‡	62.1%*†‡
CG_{AIBW}	37 ± 5	36 ± 10	−1.5 ± 8.6*†	−4.1 ± 23.5*†	87.9%
mGFR 45–59 ml min^{-1} (*n* = 49)					
$MDRD_{de\text{-}indexed}$	53 ± 4	50 ± 9	−2.9 ± 8.4*	−5.5 ± 15.9*	95.9%‡
$CKD\text{-}EPI_{de\text{-}indexed}$	53 ± 4	52 ± 10	−1.4 ± 9.4‡†	−2.6 ± 17.8†‡	91.8%‡
CG_{ABW}	53 ± 4	64 ± 19	10.8 ± 18.2*†‡	20.2 ± 33.9*†‡	67.3%*†
CG_{AIBW}	53 ± 4	49 ± 12	−4.1 ± 11.3*	−7.7 ± 21.1*	77.6%*†
mGFR <60 ml min^{-1} (*n* = 156)					
$MDRD_{de\text{-}indexed}$	38 ± 13	36 ± 15	−1.3 ± 9*	−2.7 ± 33.2*	82.7%*
$CKD\text{-}EPI_{de\text{-}indexed}$	38 ± 13	37 ± 16	−0.7 ± 9.6†‡	−1 .4 ± 33.8†‡	76.9%†
CG_{ABW}	38 ± 13	47 ± 20	9.1 ± 14.1*†‡	27.2 ± 45.1*†‡	64.1%*†‡
CG_{AIBW}	38 ± 13	36 ± 15	−1.9 ± 9.4*	−3.1 ± 30.4*	77.6%
mGFR >60 ml min^{-1} (*n* = 210)					
$MDRD_{de\text{-}indexed}$	95 ± 24	101 ± 35	5.9 ± 24.1†‡	6.3 ± 24.2*‡	78.6%
$CKD\text{-}EPI_{de\text{-}indexed}$	95 ± 24	106 ± 35	11.3 ± 23.4†‡	12.2 ± 25.4†‡	74.8%‡
CG_{ABW}	95 ± 24	132 ± 61	36.8 ± 47.9*†‡	37.1 ± 41.7*†‡	51.4%*†‡
CG_{AIBW}	95 ± 24	99 ± 39	4.2 ± 26.9*†	3.6 ± 26*†	80%*
mGFR 60–89 ml min^{-1} (*n* = 100)					
$MDRD_{de\text{-}indexed}$	74 ± 8	80 ± 22	5.7 ± 18.8*‡	7.4 ± 25.6*‡	74%*
$CKD\text{-}EPI_{de\text{-}indexed}$	74 ± 8	85 ± 25	10.5 ± 22†‡	13.7 ± 29.9†‡	67%†‡
CG_{ABW}	74 ± 8	99 ± 34	25.3 ± 30.6*†‡	33.6 ± 40.9*†‡	52%*†‡
CG_{AIBW}	74 ± 8	76 ± 23	2 ± 20.3*†	2.2 ± 27.3*†	77%*
mGFR 90–119 ml min^{-1} (*n* = 73)					
$MDRD_{de\text{-}indexed}$	103 ± 9	108 ± 25	4.7 ± 23.1*	4.5 ± 21.2*	86.3%
$CKD\text{-}EPI_{de\text{-}indexed}$	103 ± 9	115 ± 23	11.7 ± 20.9†‡	11.4 ± 20†‡	82.2%
CG_{ABW}	103 ± 9	141 ± 40	37.9 ± 37.5*†‡	36.4 ± 34.8*‡†	53.4%*†‡
CG_{AIBW}	103 ± 9	106 ± 24	2.6 ± 22.1*	2.3 ± 21*	89%
mGFR ≥130 ml min^{-1} (*n* = 19)					
$MDRD_{de\text{-}indexed}$	144 ± 10	146 ± 47	1.7 ± 43.5	0.8 ± 27.8	84.2%
$CKD\text{-}EPI_{de\text{-}indexed}$	144 ± 10	151 ± 38	7 ± 34.6	4.6 ± 22.2	89.5%
CG_{ABW}	144 ± 10	209 ± 107	64.1 ± 102.3*†‡	42.8 ± 62.3*†‡	57.9%*
CG_{AIBW}	144 ± 10	152 ± 56	7.4 ± 52.5	4.6 ± 33	78.9%

*$P < 0.05$ compared with the CKD-EPIde-indexed equation. †$P < 0.05$ compared with the MDRDde-indexed equation. ‡$P < 0.05$ compared with the CGAIBW equation. ABW, actual body weight; AIBW, adjusted ideal body weight; CG, Cockcroft–Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated GFR; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured GFR.

Pharmacologists justify the use of the CG equation by different arguments. First of all, this formula has been used in most studies for the adaptation of drug dosages [40]. Secondly, the weight variable is present in the CG equation. This can be an advantage at the pharmacokinetic level because weight is a (rough) estimate of the drug distribution volume, which is necessarily involved in pharmacokinetic studies [41]. This could explain why the CG equation gives

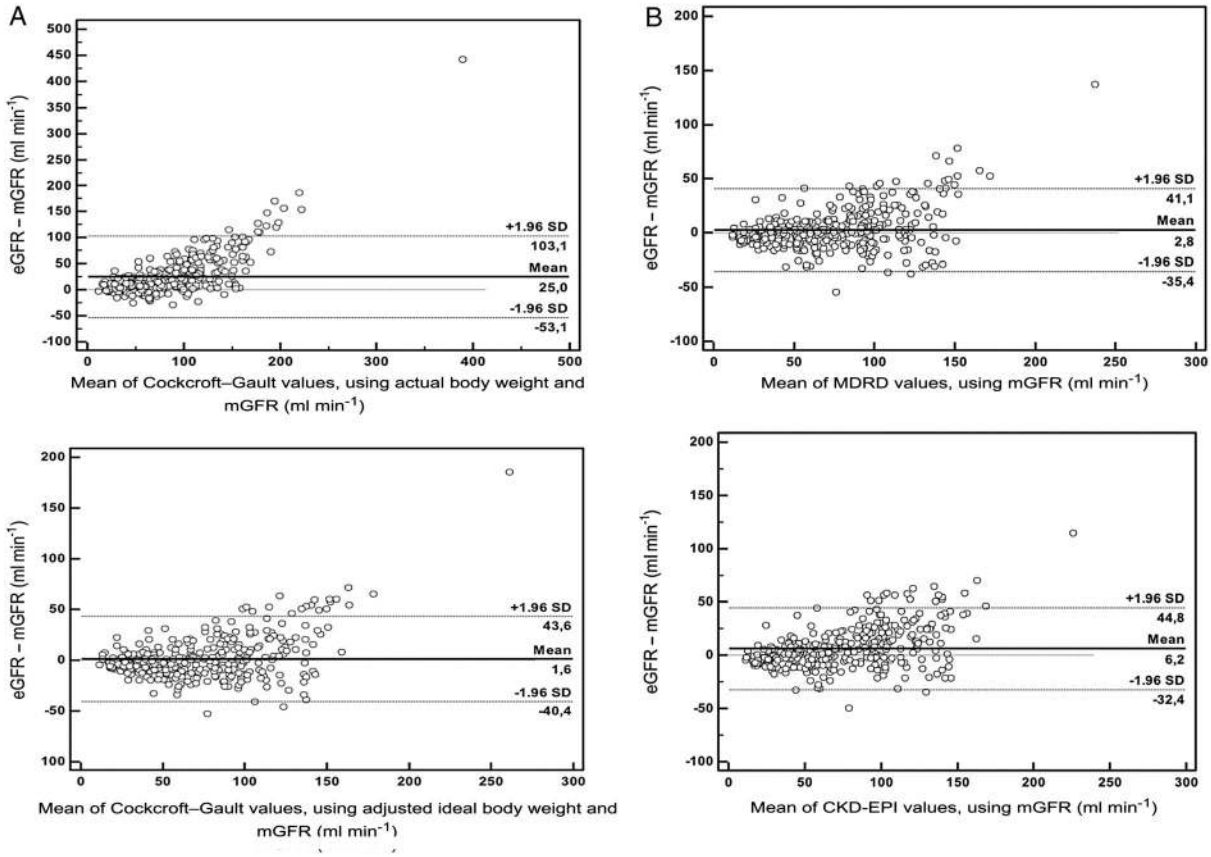

Figure 1

(A) Bland–Altman analysis for the CGABW (upper panel) and CGAIBW (lower panel) compared to mGFR. (B) Bland–Altman analysis for the MDRDde-indexed (upper panel) and CKD-EPIde-indexed (lower panel) equations compared to measured GFR. ABW, actual body weight; AIBW, adjusted ideal body weight; CG, Cockcroft–Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated GFR; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured GFR; SD, standard deviation

better results in some pharmacokinetic studies and is still preferred by some authors [42]. In our population of obese patients, as previously reported by other authors [43, 44], the CG equation overestimated mGFR in all ranges of GFR, with poor performances in terms of bias and accuracy. In fact, the CG equation has been shown to overestimate GFR in a population of 279 obese patients in which GFR was simultaneously assessed by ^{51}Cr-EDTA renal clearance [15]. Similar findings were found by Verhave *et al.* using technetium-labelled diethylenetriamine pentaacetate (^{99}mTc- DTPA) [45]. This overestimation by the CG formula could lead to the administration of inappropriate doses of drugs, and could also allow some patients to receive a drug which is contraindicated below a specific threshold. In fact, as showed in Table 4, there are significantly fewer patients classified as having an eGFR below 30 ml min^{-1} using the CG equation (57.1%) compared with the other equations (81.6%, 87.8% and 85.7% for the CG_{AIBW}, CKD-$EPI_{de\text{-}indexed}$ and $MDRD_{de\text{-}indexed}$ equations, respectively). Therefore, a higher proportion of patients will be classified with an eGFR over 30 ml min^{-1} (42.9% for the CG equation compared with 18.4%, 12.2% and 14.4% for the CG_{AIBW}, CKD-$EPI_{de\text{-}indexed}$ and $MDRD_{de\text{-}indexed}$ equations, respectively) and could receive a drug which is normally contraindicated below this level. A similar mistake will occur for a GFR between 30 ml min^{-1} and 45 ml min^{-1}.

Although the weight variable in the CG equation explains, at least in part, the continued interest in this formula by pharmacologists, this variable can also be a source of confusion. Indeed, there is no clear consensus regarding which weight is to be used in the CG equation: ABW, ideal body weight (IBW), AIBW or LBW [19]. Many data have shown significant discrepancies in terms of dosage adjustment, depending on whether one or the other weight is used, especially when obese or anorexic populations are considered [36, 40, 41, 46–51].

The choice of the weight variable in the CG equation is much debated and neither the FDA nor the KDIGO has issued clear recommendations on the topic. Cockcroft and Gault themselves recommended using IBW or LBW instead of ABW in patients with pronounced obesity or volume overload [52]. Conversely, other authors recommend adjusting doses on the basis of ABW [53], arguing that drug clearance increases in proportion to ABW, which has been demonstrated to be wrong [54]. The

Table 3

Percentage of patients in the different CKD subgroups, depending on the type of equations used and misclassification associated (eGFR higher or lower than the mGFR)

CKD stage	Number of patients classified by mGFR (%)§	Number of patients classified by the CG_{ABW} equation in the different mGFR stages (%)¶	Number of patients classified by the CG_{AIBW} equation in the different mGFR stages (%)¶	Number of patients classified by the CKD-$EPI_{de\text{-}indexed}$ equation in the different mGFR stages (%)¶	Number of patients classified by the $MDRD_{de\text{-}indexed}$ equation in the different mGFR stages (%)¶
		mGFR relative to eGFR [*n* patients (%)]¶			
Stage 5	5 (1.4%)	1 (20%)	2 (40%)	3 (60%)	4 (80%)
				eGFR > mGFR	
		4 (80%)	3 (60%)	2 (40%)	1 (20%)
Stage 4	44 (12%)	24‡ (54.5%)	33 (75%)	29 (65.9%)	32 (72.7%)
				eGFR > mGFR	
		20*†‡ (45.5%)	8 (18.2%)	5 (11.4%)	6 (13.6%)
Stage 3b	58 (15.8%)	24 (41.4%)	29 (50%)	28 (48.3%)	26 (44.8%)
				eGFR > mGFR	
		30*†‡ (51.7%)	10 (17.2%)	13 (22.4%)	15 (25.9%)
Stage 3a	49 (13.4%)	22‡ (44.9%)	16† (32.7%)	24 (49%)	29‡ (59.2%)
				eGFR < mGFR	
		5*†‡ (10.2%)	23*† (46.9%)	14‡ (28.6%)	12‡ (24.5%)
Stage 2	100 (27.3%)	39 (39%)	45 (45%)	43 (43%)	46 (46%)
				eGFR < mGFR	
		9*†‡ (9%)	29*† (29%)	15‡ (15%)	20‡ (20%)
Stage 1	110 (30.1%)	109†‡ (99.1%)	88* (80%)	104†‡ (94.5%)	93* (84.5%)
				eGFR < mGFR	
		1†‡ (0.9%)	22* (20%)	6†‡ (5.5%)	17* (15.5%)

*$P < 0.05$ compared with the CKD-$EPI_{de\text{-}indexed}$ equation. †$P < 0.05$ compared with the $MDRD_{de\text{-}indexed}$ equation. ‡$P < 0.05$ compared with the CG_{AIBW} equation. §Percentage of total population. ¶Percentage of subgroup population. ABW, actual body weight; AIBW, adjusted ideal body weight; CG, Cockcroft–Gault; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated GFR; GFR, glomerular filtration rate mGFR, measured GFR; MDRD, Modification of Diet in Renal Disease.

use of AIBW has been advocated by some authors [36, 54, 55]. In the present study, we confirm that using AIBW instead of ABW greatly improves the performance of the CG equation in all GFR subgroups. The accuracy of the CG_{AIBW} equation in the whole population was even slightly better than that of the CKD-$EPI_{de\text{-}indexed}$ equation, but not better than that of the $MDRD_{de\text{-}indexed}$ equation. Finally, some authors have favoured the use of LBW in the CG equation [56–58]. However, in our cohort, using LBW instead of AIBW in the CG equation did not improve the performance of the equation, with worse bias and accuracy (see Supplementary Table S2). Park *et al.* [47] have shown that the use of AIBW is not adequate for all BMI values. These authors have, in fact, shown that AIBW might be adequate in patients with a BMI between 30 kg m^{-2} and 40 kg m^{-2}, but inferior in patients with a BMI over 40 kg m^{-2}. However, in our analysis, for the patients with a high BMI, the accuracy of the CG equation was not better when using LBW than when using AIBW (see Supplementary Table S3).

In our obese population, the creatinine-based equations and the CG_{AIBW} equation had good concordance with mGFR, and were statistically better than the CG_{ABW} equation in terms of bias and accuracy. These formulae are thus helpful for obtaining an accurate estimate of the GFR in stages where adaptation of drug dosage is crucial (GFR < 60 ml min^{-1}). In the specific range of 30–45 ml min^{-1}, both equations ($MDRD_{de\text{-}indexed}$ and CKD-$EPI_{de\text{-}indexed}$) performed better than the CG_{ABW} and CG_{AIBW} equations in terms of bias (even if the accuracies were similar). Below 30 ml min^{-1}, the CG_{AIBW}, $MDRD_{de\text{-}indexed}$ and CKD-$EPI_{de\text{-}indexed}$ equations underestimated mGFR, which is relatively safe for the adaptation of drug dosage. In fact, if the drug is contraindicated below 30 ml min^{-1}, using these equations allowed the exclusion of virtually all the patients with an mGFR below this level, as a result of the specificity of these equations (Table 3).

When mGFR is considered in obese patients, one important issue is the question of BSA indexation. BSA indexation is recommended in clinical nephrology, even though this approach has been largely criticized. In a previous work, we studied the performance of indexed equations in obese patients. Because non-indexed GFR is recommended in the pharmacology context, in the present study, we investigated de-indexed and non-indexed equations. To sum up, the use of non-indexed mGFR in the context of drug dosing adjustment seems to be intuitively correct; by contrast, the de-indexation of eGFR is not carried out frequently. However, de-indexation is crucial because the performance of the CKD-EPI equation (in ml min^{-1} 1.73 m^{-2})

Table 4

Percentage of patients in the different groups for the dose adaptation of metformin, depending on the type of equation used and the associated misclassification

	Number of patients classified by the CG_{ABW} equation in the different mGFR stages (%)¶	Number of patients classified by the CG_{AIBW} equation in the different mGFR stages (%)¶	Number of patients classified by the $CKD\text{-}EPI_{de\text{-}indexed}$ equation in the different mGFR stages (%)¶	Number of patients classified by the $MDRD_{de\text{-}indexed}$ equation in the different mGFR stages (%)¶
mGFR stage *n* patients (%)§	**eGFR regarding the cut-off of mGFR n patients (%)**			
< 30 ml min^{-1} 49 patients (13.4%): metformin contraindicated	28*† (57.1%)	40 (81.6%)	43 (87.8%)	42 (85.7%)
	eGFR > mGFR: patients receiving the drug while they should not			
	21*† (42.9%)	9 (18.4%)	6 (12.2%)	7 (14.3%)
30–44 ml min^{-1} 58 patients (15.9%): Dose of metformin should be adjusted	24 (41.4%)	29 (50%)	28 (48.3%)	26 (44.8%)
	eGFR > mGFR: patients receiving the full dose of the drug while it should be adjusted			
	30*† (51.7%)	10 (17.2%)	13 (22.4%)	15 (25.9%)
≥ 45 ml min^{-1} 259 patients (70.8%): Normal dose of metformin	253*† (97.7%)	232* (89.6%)	240 (92.7%)	242 (93.4%)
	eGFR < mGFR: patients receiving a adjusted dose while they should receive the complete dose			
	6*† (2.3%)	27* (10.4%)	19 (7.3%)	17 (6.6%)

*$P < 0.05$ compared with the $CKD\text{-}EPI_{de\text{-}indexed}$ equation. †$P < 0.05$ compared with the $MDRD_{de\text{-}indexed}$ equation. ‡$P < 0.05$ compared with the CG_{AIBW} equation. §Percentage of total population. ¶Percentage of subgroup population. ABW, actual body weight; AIBW, adjusted ideal body weight; CG, Cockcroft–Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated GFR; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured GFR.

Table 5

Hyperfiltrating patients with estimated and measured GFR

mGFR *n* (%)†	Number of patients classified by the CG_{ABW} equation (%)†	Number of patients classified by the CG_{AIBW} equation (%)†	Number of patients classified by the $CKD\text{-}EPI_{de\text{-}indexed}$ equation (%)†	Number of patients classified by the $MDRD_{de\text{-}indexed}$ equation(%)†
≥ 130 ml min^{-1} 19 patients (5.2%)	90 patients (24.6%)	36 patients (9.8%)	50 patients (13.7%)	31 patients (8.5%)
	mGFR < eGFR ‡ *n* patients (%)			
	28 patients (31.1%)	21 patients (58.3%)	26 patients (52%)	22 patients (71%)

†Percentage of total population. ‡Percentage of subgroup population. ABW, actual body weight; AIBW, adjusted ideal body weight; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CG, Cockcroft–Gault; eGFR, estimated GFR; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured GFR.

compared with the non-indexed mGFR equations (ml min^{-1}) is significantly worse, and underestimates the mGFR more (data not shown). The same results have been demonstrated in a recent study by Chew-Harris *et al.* [59]. In this study, only 78 obese patients were included but the authors showed that the CKD-EPI without normalization (in ml min^{-1}) was superior to the CKD-EPI equation indexed (in ml min^{-1} 1.73 m^{-2}) in estimating the absolute clearance of ^{99}mTc-DTPA (in ml min^{-1}).

Numerous authors have also found that creatinine-based equations overestimate GFR in different types of population [12, 60–62], especially in obese patients with a high GFR (GFR > 60 ml min^{-1}) [43, 47]. Lemoine *et al.* [12] studied 209 obese patients, compared with a non-obese group of participants that underwent an evaluation of kidney function by a reference method. They clearly showed that the performance of the CKD-EPI equation was poorer in obese *vs.* non-obese subjects. Similarly to the present study, they show that CKD-EPI (indexed) overestimated indexed mGFR. This overestimation decreased when non-indexed mGFR was considered but their results with non-indexed mGFR were not comparable with ours as they did not de-index the CKD-EPI results.

Metformin is an effective drug for obese patients with type 2 diabetes [63], and, as recommended by KDIGO and other diabetes guidelines [64, 65], needs an adaptation of its dosage in case of kidney failure [13]. A good estimation of kidney function, especially in CKD stage 3b and 4, is thus crucial. When we considered the adjustment of drug dosage (threshold below 30 ml min^{-1}), our simulation showed that overestimation by the CG_{ABW} equation would lead to an over-prescription of the drug in 42.9% of patients in whom it is contraindicated. Using the CG_{AIBW}, $CKD\text{-}EPI_{de\text{-}indexed}$ and $MDRD_{de\text{-}indexed}$ equations, over-prescription would occur in only 18.4%, 12.2% and 14.3% of patients, respectively (Table 4). With a threshold between 30 ml min^{-1} and 45 ml min^{-1}, an inadequate drug dosage would be erroneously given to the patient in 51.7%, 17.2%, 22.4% and 25.9% of patients if the CG_{ABW}, CG_{AIBW}, $CKD\text{-}EPI_{de\text{-}indexed}$ and $MDRD_{de\text{-}indexed}$ equations were used, respectively.

The increase in the absolute GFR observed in obese patients with hyperfiltration may be responsible for an increase in the clearance of drugs, which could affect their efficacy. For instance, antibiotic drugs such as gentamicin [66] and vancomycin [67] could have their concentration reduced by this increased drug clearance, and ultimately have an impact on the efficiency of the drugs. The increased absolute clearances of cisplatin and paclitaxel were also noted in obese patients compared with lean individuals [68, 69]. In the subgroup of patients with an mGFR over 130 ml min^{-1}, the $MDRD_{de\text{-}indexed}$ and $CKD\text{-}EPI_{de\text{-}indexed}$ equations have the same performances and are significantly better than the CG equation with ABW, but not with AIBW. Accuracy is high, at around 78–89%. In a cohort of diabetic, overweight patients with hyperfiltration, Gaspari *et al.* [70] showed that the CG, CKD-EPI and MDRD equations indexed by BSA underestimated mGFR (assessed using iohexol clearance) and thus ignored the hyperfiltration state. The discrepancy with the present results can be explained by the excessive correction for BSA in overweight patients. In our population, using de-indexed GFR, we observed an overestimation of mGFR by all eGFR equations, but especially with the CG equation. In the present study, eGFR equations detected hyperfiltration in 24.6%, 9.8%, 13.7% and 8.5% of patients when using the CG_{ABW}, CG_{AIBW}, $CKD\text{-}EPI_{de\text{-}indexed}$ and $MDRD_{de\text{-}indexed}$ equations, respectively, although true hyperfiltration assessed by mGFR occurred in only 5.2% of our population.

The strengths of the present study include the fact that we measured GFR in a large sample of obese subjects, over a large range of GFRs, from two centres, using a reference method. In addition, we measured creatinine using a IDMS-traceable Jaffé method. Enzymatic methods would theoretically give even more precise results (which tend to become the reference standard) but these methods are more costly. Another strength of the present study is the fact that all the subjects included were obese, rather than just overweight.

There are also limitations to the present study. First, plasma clearances are less accurate than urinary clearances. However, measurement of plasma clearance is considered as a reference method, and several studies have illustrated its concordance with the urinary clearance of inulin [71]. Secondly, most of our subjects were Caucasian, and a study in obese patients from other ethnicities would be of interest. Thirdly, no elderly patients were included; we are aware that this section of the population is more at risk of GFR decline and therefore is more likely to need an adaptation of drug dosage. Furthermore, our population was not representative of the general obese population as CKD patients were obviously overrepresented. Fourthly, the consensus in favour of a drug dose adjustment based on non-indexed GFR has not been free from criticism. Indeed, this recommendation is based on theoretical arguments, and no studies to date have proved the superiority of one strategy over the other. Moreover, even if recommended by the FDA and EMA, de-indexation of the MDRD and CKD-EPI equations is mathematically questionable, especially for patients with a BSA beyond that observed in cohorts used to develop these equations, as it is the case in our work. Further studies might still be necessary. Fifthly, apart from the estimation of renal clearance, obese patients raise other important pharmacological issues, including a potentially increased volume of distribution of drugs. This will affect the selection of the loading dose, the elimination half-life and also the peak concentration of a drug after injection of a single dose. The present study was not designed to address these issues, and further dedicated studies would be required to address the pharmacokinetic and pharmacodynamic issues raised by the population of patients with high and very high body weight, which go beyond the sole question of GFR estimation. Finally, the present study lacked a paired non-obese population, which would be necessary to evaluate the specific impact of obesity on the intrinsic performance of each equation.

Conclusion

For several years, the CG equation has been the most commonly used method for estimating kidney function for drug dosing purposes. The widespread clinical use of MDRD and CKD-EPI-derived eGFR has facilitated the identification and classification of patients with CKD, and now provides clinicians with an alternative to the CG equation for drug dosing. Discrepancies between the CG equation and others equations are well known. This is especially relevant in obese patients as weight is an important variable of the CG equation (and is absent in both the MDRD and CKD-EPI equations).

We have demonstrated that the performance of the CG_{ABW} equation is poor in the obese population. The use of AIBW instead of ABW in the CG equation (non-indexed) drastically increases the performance compared with that of other eGFR equations, especially when deciding whether or not the drug should be stopped (GFR $<$ 30 ml min^{-1}). When adaptation of drug dosage needs to be carried out at GFR levels between 30 ml min^{-1} and 45 ml min^{-1}, the $MDRD_{de\text{-}indexed}$ and $CKD\text{-}EPI_{de\text{-}indexed}$ equations are reasonably equivalent, with good performance. Currently, the use of AIBW or other weight variables in the CG equation is still debated. Therefore, using creatinine-based equations such as MDRD and CKD-EPI de-indexed by BSA seems to be the easiest and most accurate way to estimate GFR and adapt the drug dosage for obese patients to individual renal function. For drugs with a tight therapeutic window, where a very precise GFR determination is

necessary, it may still be prudent to measure GFR using a reference method prior to administration of the medication.

Competing Interests

The authors of this manuscript have no conflicts of interest to disclose as described by the British Clinical Journal of Pharmacology. All authors have completed the Unified Competing Interest form and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1
Equations frequently used to estimate BSA and values from our cohort ($n = 366$). Accuracies for MDRD and CKD-EPI de-indexed with the different BSA estimations

Table S2
Performances of the CG_{ABW}, CG_{AIBW}, CG_{LBW} equations at the different levels of mGFR

Table S3
Performances of the $MDRD_{de\text{-}indexed}$, $CKD\text{-}EPI_{de\text{-}indexed}$, CG_{ABW}, CG_{AIBW}, CG_{LBW} equations at the different levels of BMI