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

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# Abstract

Background.

The prevalence of obesity is dramatically rising worldwide. For drug dosing adaptation, the KDIGO guidelines recommend using estimated glomerular filtration rate (eGFR), the CKD-EPI equation, which is not adjusted to the 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 our study was to evaluate to performances of creatinine-based GFR estimating equations in obese patients and their implication in terms of drug-dosage adjustment.

Methods.

We retrospectively analysed the data from patients with a body mass index (BMI) higher than 30 kg/m2 who underwent a GFR measurement with plasma clearance of 51Cr-EDTA in Paris or Liège Hospitals. eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification in Diet in Renal Disease (MDRD) equations, « de-indexed » by BSA (CKD-EPI deindexed and MDRD deindexed), and the CG equation (non-indexed by BSA), using either ABW or AIBW for the weight variable. The performances of each equation were evaluated by the bias, the precision and the accuracy 30%.

Results.

366 patients (185 women) were included in the study. Mean age was 55 ± 14 years and mean BMI was 36 ± 7 kg/m2. Mean mGFR was 71 ± 35 mL/min. In the global population, bias of CGABW and CGAIBW displayed a mean bias of + 25 ± 39.8 mL/min and + 1.6 ± 21.4 mL/min, respectively (p<0.05) and accuracy 30% of 57% and 79%, respectively (p<0.05). For the CKD-EPI deindexed and MDRD deindexed equations, the bias was + 6.2 ± 19.7 and 2.8 ± 19.5 mL/min respectively (p<0.05) and the accuracy 30% was 76% and 80% (p<0.05).

Conclusions.

In our population of obese patients, CG using the AIBW instead of the ABW in the CG equation, which is generally used for drug dosage, markedly improved the overall accuracy of this equation. The eGFR equations deindexed by the BSA (MDRD deindexed and CKD-EPI deindexed equations) have also good performances with an overall better performance for the MDRD deindexed equation. In conclusion, both de-indexed MDRD and the CG equation using AIBW appear suitable to estimated non-indexed GFR and hence to adequately adjust drug dosage in obese patients.

# Introduction

Obesity has become one of the most important public health problems all over the world (1). The World Health Organisation (WHO) recommends using body mass index (BMI) as the standard measure of overweight and obesity. Adults with a BMI between 25 and 30 kg/m2 are considered overweight; those with a BMI ≥ 30 kg/m2 are considered to be obese (2). The rate of obesity reaches 25% of the population in Europe (3). With the increasing prevalence of obesity, there is also an increasing prevalence of the co-morbidities associated with this condition, such as diabetes, hypertension, dyslipidaemia, cardiovascular disease (CVD), osteoarthritis and cancers (4). Most of these comorbidities may alter renal function.

Obesity is a significant risk factor for chronic kidney disease (CKD) independently of other known risk factors and also a risk factor of progression of kidney disease (5–7). Studies reported that an increased BMI was associated with an increased risk of end stage renal disease (ESRD) (5,7,8). The association of obesity with the rate of progression of chronic kidney disease (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). Estimating glomerular filtration rate (GFR) in the obese population is challenging and creatinine-based equations are less accurate in this specific population, as they have not been developed in an obese population specifically (10,11).

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 (12). The added value of the CKD-EPI equation over the prior “Modification in Diet in Renal Disease” (MDRD) study equation has, however, been challenged in the literature (13), including in studies about obese patients (10,11). In fact, we have already demonstrated the good performances of the creatinine-based equations indexed by the body surface area (BSA) in an obese population (10). 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 (14,15). In the context of pharmacology and “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 (16). Since 2008, the FDA has accepted the use of the MDRD equation in the dose adjustment studies and leaves the door open to other formulae that would prove their superiority in the future to estimate the GFR, such as the CKD-EPI equation. European Medecines Agency (EMA) and the KDIGO guidelines are on the same wavelength (17,18). However, there is no clear data to choose between MDRD and CKD-EPI, on one side, and the CG equation, on the other side, in the field of drug dosage adjustment in obese patients.

There is another specificity in the context of GFR and renal dose adaptation. Indeed, when drug dosing is considered, the KDIGO, FDA and EMA recommend using eGFR, which is not adjusted to the BSA (19,17,12). Hence formulae providing BSA-adjusted GFR (mL/min/1.73 m2) must be adapted to give the absolute GFR in mL/min for each individual. This “de-indexation” has obviously very little impact in the general population. On the contrary, the impact is highly relevant in obese patients (20). The use of the ABW in the computation of the BSA in obese patients leads to a decrease of its absolute value, and therefore decreases the impact on the “de-indexation” of eGFR.

We have already studied the performances of the creatinine-based equations (CKD-EPI and MDRD) in the obese population, but in the context of drug dosing adaptation, it seemed crucial to evaluate the performances of those equations de-indexed by the BSA and also the CG equation compared to a reference method of GFR. Therefore, we have tested and compared with a measured GFR (mGFR), the performances of two creatinine-based equations “de-indexed” by BSA (using the ABW): CKD-EPI deindexed and MDRD deindexed, expressed in mL/min. We have also evaluated the performances of the CG equation (non-indexed by BSA) with actual body weight (ABW) (CGABW) or with adjusted ideal body weight (AIBW) (CGAIBW), expressed in mL/min. All patients have been classified according to the five KDIGO stages and we have compared the concordance of the different equations for such a staging. Lastly, we have compared the results of the different equations to classify the patients according to the different GFR levels recommended by the KDIGO for adaptation of metformin (18).

# Population and Methods

The studied population is the same as we have already published in 2013. As a reminder, eligible patients were > 18 years and had a BMI > 30 kg/m2. Patients treated with steroids, cimetidine or trimethoprim were excluded. In the non-CKD obese population, indication for GFR measurement was before a potential living kidney donation or before a slimming diet. In CKD obese patients, GFR was measured in the context of CKD follow-up, and not because of obesity. GFR was measured by plasma clearance of 51Cr-EDTA: single-injection method with two samples at 120 and 240 min and Bröchner–Mortensen correction. BSA was calculated with the equation developed by Gehan and George (21). Serum creatinine was sampled the same day as GFR determination and measured using the IDMS-traceable compensated Jaffe method (22). The CG and eGFR were calculated with the CKD-EPI (23) and MDRD (24) study equations as follows. The CKD-EPI and MDRD « de-indexed » recommended by the KDIGO were computed by multiplying eGFR by each individual’s body surface area, using actual body weight, and by dividing this intermediate result by 1.73 m2.

* Cockcroft and Gault mL/min
  + [(140-age) / (72×SCr)]× Weight (kg) × (0.85 in females)
    - SCr = Serum Creatinine in mg/dL
    - Weight is the actual body weight (ABW)
  + Cockcroft and Gault is also computed with the adjusted ideal body weight (AIBW)
    - Adjusted Ideal Body Weight (AIBW) was calculated as follow:
      * Ideal Weight + (0.4 \*(ABW (kg) - Ideal Weight)) (25)
      * Ideal Weight = (Height (cm) - 152.4)\*0.9 + 45.5 + 4.5 (in males) (26)
* MDRD
  + eGFR in mL/min/1.73m2
  + 175 × (SCr (mg/dL)) −1.154 × (age (years)) −0.203 × (0.742 in females) x (1.21 in black)
  + MDRD deindexed in mL/min = (eGFR in mL/min/1.73m2 x BSA) / 1.73m2
* CKD-EPI
  + eGFR in mL/min/1.73m2
  + k1 × (SCr/k2) -α × 0,993 age
  + SCr: Serum creatinine in mg/dL
  + 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, women with SCr > 0.7 mg/dl, men with SCr ≤ 0.9 mg/dl, and women with SCr ≤ 0.7 mg/dl, respectively
  + CKD-EPI deindexed in mL/min = (eGFR in mL/min/1.73m2 x BSA) / 1.73m2

We have also considered the performances of the two equations to classify the patients in the stages of CKD, as defined by the KDIGO (12). The definition of the subgroups was set according to non-indexed values of mGFR. We added in this classification the “hyperfiltration” stage which is not included in the KDIGO guidelines. This status is more frequently seen in obese and diabetic patients (27), and is characterized as a eGFR over 130 mL/min/1.73m2 (28). Also, we took a practical example of adaptation of drug dosage using the metformin. As recommended by the KDIGO (12), it has to be continued in people with GFR > 45 mL/min, its use should be reviewed in those with GFR between 30 to 45 mL/min; and it should be discontinued in people with GFR < 30 mL/min. We have simulated the percentage of patients in each category according to the type of equations used, and the percentage of over- or underestimation using the different equations.

Descriptive statistics for studied variables are presented as: mean with standard deviation (SD) for normally distributed variables, median with range for non-normally distributed variables. The correlation between GFR estimated by the different equations and mGFR was done with the Pearson’s analysis. The performances of GFR estimates were assessed with 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.

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

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

Comparison of bias, precision and accuracy was performed using t-test, F-test and McNemar paired test, respectively. Analysis was performed using IBM SPSS Statistics for Mac (Version 22.0. Armonk, NY: IBM Corp.).

# Results

## Performances of equations to estimate mGFR

The population included 366 patients (185 women). The characteristics of the population are shown in table 1. Mean age was 55±14 years and mean BMI was 36±7 kg/m2. Mean mGFR was 71±35 mL/min. Mean eGFR by CGABW and CGAIBW were 96±64 and 72±44 mL/min, respectively. Mean eGFR was 77±44 mL/min and 73±43 mL/min for MDRDdeindexed and CKD-EPIdeindexed, respectively.

A significant correlation was found between mGFR and CGABW equation (*r* = 0.83), CGAIBW (*r* = 0.879), CKD-EPIdeindexed (*r* = 0.905), and MDRDdeindexed (*r* = 0.893). These correlations were almost similar, except for the correlation between CGABW and mGFR that was significantly lower (p<0.05).

In the whole population, the bias and precision for CGABW and CGAIBW equation were +25±39.8 mL/min and +1.6±21.4 mL/min, respectively (p < 0.05). For the CKD-EPIdeindexed and the MDRDdeindexed equations, the biases were +6.2±19.7mL/min and +2.8±19.5 mL/min, respectively. The bias of MDRD deindexed is better than other equations, except the CGAIBW equation. The accuracy within 30% was 56.8% and 79% for the CGABW and CGAIBW equation, respectively (p<0.05). For the CKD-EPIdeindexed and the MDRDdeindexed equations, accuracy 30% was 75.7% and 80.3%, respectively (p<0.05) (table 2). The accuracy for the CGAIBW was not different from the accuracy of the MDRDdeindexed, but statistically better than CKD-EPIdeindexed.

Using AIBW in the CG equation significantly improved the performances, especially in terms of bias compared to CG equation with ABW, and this was true at every GFR level (table 2).

The MDRDdeindexed equation outperformed the CKD-EPIdeindexed equation in the global population in terms of bias and accuracy. Accuracy within 30% of CGAIBW and MDRDdeindexed were similar.

Bland and Altman analysis for the CGABW, CGAIBW, MDRDdeindexed and CKD-EPIdeindexed are represented in Figures 1a and 1b.

The cut-off of 30 mL/min is particularly relevant in pharmacology. It is usually the value under which drugs eliminated by the kidneys need a dose adaptation (or are contra indicated). All the equations slightly underestimate the mGFR below 30mL/min, except CGABW, which strongly overestimates mGFR. At this level, the bias for CGAIBW is better than the bias for MDRDdeindexed and CKD-EPIdeindexed, which are not different from one another. The accuracies are, however, not statistically different (table 2).

At stage 3b (mGFR between 30-45 mL/min), MDRDdeindexed and CKD-EPIdeindexed have the same performances. These equations have a better bias than CGAIBW but the accuracy is similar. Once again, the CGABW equation has the worse performances.

At stage 3a, the CKD-EPIdeindexed has a slightly better bias (-1.4±9.4 mL/min) than MDRDdeindexed (-2.9±8.4 mL/min) (p<0.05), but accuracies are not different (91.8% and 95.9% for CKD-EPIdeindexed and MDRDdeindexed, respectively). In this subgroup, the performances (both bias and accuracy) are better for CKD-EPIdeindexed than for both CGABW and CGAIBW.CGAIBW performance is the same compared to MDRDdeindexed and better than CGABW in term of bias (p<0.001). In terms of accuracies, there were statistical differences between MDRDdeindexed and CGAIBW, but not between CGABW and CGAIBW.

In high GFR values (mGFR > 60 mL/min), performances of both the CGAIBW and MDRDdeindexed are globally slightly better than CKD-EPIdeindexed. The CGABW is, however, performing poorly compared to 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 equations used. For each stage, the percentage of patients with an eGFR over- or under the mGFR is also shown. Therefore, we evaluate the proportion of patients with a risk of over- or under- dosage of a drug. For instance, 54.5%, 75%, 65.9% or 72.7% of patients are classified as CKD stage 4 (mGFR between 15-30 mL/min) using CGABW, CGAIBW, CKD-EPIdeindexed and MDRDdeindexed respectively (p<0.05 between CGABW and CGAIBW). The eGFR will overestimate the mGFR in 45.5%, 18.2%, 11.4% and 13.6% of patients respectively with CGABW, CGAIBW, CKD-EPIdeindexed and MDRDdeindexed (p<0.05 between CG and the other three equations).

Table 4 represents the performances of eGFR equations according to the mGFR level when metformin is used. With CGAIBW, CKD-EPIdeindexed and MDRDdeindexed, patients with mGFR below 30 mL/min are correctly classified in 81.6%, 87.8%, and 85.7% of the cases, respectively. On the contrary, a correct staging occurs only in 57.1% of patients if CGABW is considered (p<0.05).

All the equations give an overestimation of the mGFR, for the high level of GFR (> 60mL/min), therefore overestimating the percentage of patients with a hyperfiltration status. In our study, the eGFR equations detect hyperfiltration status in 90 (24.6%), 36 (9.8%), 50 (13.7%) and 31 (8.5%) patients with CGABW, CGAIBW, CKD-EPIdeindexed and MDRDdeindexed, respectively. Using this sub-group of population 28 (31.1%), 21 (58.3%), 26 (52%) and 22 (71%) patients are misclassified as “hyperfiltrating”, having actually a mGFR below 130 mL/min (table 5).

# Discussion

In our obese cohort, CGABW equation, still recommended by the FDA and the EMA for drug dosage adaptation, is imprecise and biased, and overestimates the mGFR in all CKD groups. It is therefore not the most appropriate equation to use for this purpose in this group of patients. Using the AIBW instead of the ABW in the CG equation increases the performances of this equation. For the other creatinine-based equations, MDRDdeindexed outperforms the CKD-EPIdeindexed equation in terms of bias and accuracy in the whole obese population (table 2).

Estimating an individual’s renal function is a key step in the individualisation of the dosage of renal-cleared drugs. 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 (29). A correct assessment of the renal function is paramount in the group of obese individuals, who frequently need drug treatments for obesity-associated co-morbidities. Overestimated kidney function may lead to the administration of inappropriately large doses and possible toxicity, and conversely, underestimated kidney function (by the way of hyperfiltration) may lead to sub-therapeutic dosing, treatment failures, and prolonged illness.

The CG equation has been used for several decades and is still part of the guidance for the FDA and the EMA in pharmacokinetic studies regarding the setting of renal impairment (19,17,30). Its accuracy to estimate GFR is, however, not optimal in obese patients, as expected by the bias induced by the ABW in the equation (14,31–34). Pharmacologists justify the use of CG equation by different arguments. First of all, this formula was used in most studies for the adaptation of drugs dosage (35). Secondly, the weight is present in the CG equation. This can be an advantage at the pharmacokinetic level, because the weight is a (rough) estimate of the drug distribution volume, which is necessarily involved in the pharmacokinetics studies (36). This could explain why the CG gives better results in some pharmacokinetic studies and is still preferred by some authors (37). In our population of obese patients, as noticed by other authors (38,39), the CG equation overestimates the mGFR in all ranges of GFR, with poor performances in terms of bias and accuracies. Actually, the CG formula has been shown to overestimate GFR in a selected population of 279 obese patients where GFR was simultaneously assessed by 51Cr-EDTA renal clearance (15). Similar findings were found by Verhave *et al.* using 99mTc- DTPA (40). This overestimation by the CG formula could lead to the administration of inappropriate dose of drugs, and could also allow some patients to receive a drug, which is contra-indicated below a specific threshold. In fact, as showed in the table 4, there are significantly fewer patients classified below 30 mL/min with the CG equation (57.1%) compared to the other equations (81.6%, 87.8% and 85.7% for CGAIBW, CKD-EPIdeindexed and MDRDdeindexed respectively). Therefore a higher proportion of patients will be classified with an eGFR over 30 mL/min (42.9% for the CG equation compared to 18.4%, 12.2% and 14.4% for the CGAIBW, CKD-EPIdeindexed and MDRDdeindexed, respectively) and could receive a drug, which is normally contra-indicated below this level. The same reasoning is valid for drug adaptation required when GFR is between 30 and 45 mL/min.

If the weight in the CG equation explains, at least in part the continued interest for 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 lean body weight (LBW) (18). A lot of data has 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 (31,35,36,41–46).

The initial version of CG equation used ABW, but Cockcroft and Gault recommended using IBW or LBW in patients with pronounced obesity or volume overload (47). Use of ABW is not optimal in patients at the extremes of weight and may lead to the misclassification of kidney function and to inappropriate dose adjustment (48). Other authors suggest that clinicians may adjust doses on the basis of ABW (49). This approach assumes that drug clearance increases in proportion to ABW. However, drug clearance through the kidney is not proportional to ABW (50). Using AIBW has been advocated by some authors (31,50,51). We confirm that using AIBW instead of ABW greatly improves the performances of the CG equation over the different subgroups. The accuracy of the CGAIBW in the global population is even slightly better than the accuracy of the CKD-EPIdeindexed equation, but not better than the MDRDdeindexed equation. However, in clinical practice, we have doubt that AIBW is used, because its computation is much more complicated and the choice of the type of “weight” remains highly debated in the literature. Neither the FDA nor the KDIGO make a clear choice for the specific weight to use in this equation for the obese population. Some authors have favoured the LBW in CG equation (52,53). However, in our cohort, using the LBW instead of the AIBW in the CG equation does not improve the performances of the equation with worse bias and accuracies (data not shown). With those results, we confirmed data previously published (31,54). The adjustment of the CG equation by the AIBW, finally conducts to diminish the importance of the weight in the CG equation.

In our obese population, the creatinine-based equations and the CGAIBW equation have good concordance with mGFR, and are statistically better than the CGABW equation in terms of bias and accuracy. These formulae are thus helpful to accurately estimate the GFR in stages where adaptation of drug dosage is crucial (GFR < 60 mL/min). In the specific range of 30 to 45 mL/min, both equations (MDRDdeindexed and CKD-EPIdeindexed) have better performances than CGABW and CGAIBW equations in terms of bias (even if accuracies are similar). Below 30 mL/min, CGAIBW, MDRDdeindexed and CKD-EPIdeindexed underestimate the mGFR, which is relatively safe for the adaptation of drug dosage. Actually, if the drug is contra-indicated below 30 mL/min, using these equations allowed excluding roughly all the patients with an mGFR below this level thanks to the good specificity of these equations (table 3).

When mGFR is considered in obese patients, one important issue is the question of BSA indexation. In clinical nephrology, the BSA indexation is recommended even if this approach has been largely criticized. In a previous work, we studied the performances of indexed equation in obese patients. Because non-indexed GFR is recommended in the pharmacology context, we studied here non-indexed equations. Compared to our previous study, we found quite the same accuracies and bias in the different CKD stages (10). Indeed, in the previous study, we found that MDRD outperformed the CKD-EPI equation in terms of bias and accuracy, too (10). The only noticeable difference concerns the subgroup of stage 3a: although in non-indexed population the bias is better for CKD-EPIdeindexed with a negative bias, in the indexed population the bias is better for MDRD study equation with a positive bias. The same conclusions drawn in both articles are probably linked to the fact that we always compared all indexed values or all de-indexed values for the mGFR and the eGFR.

To sum up, use mGFR non-indexed in the context of drug dosing adjustment seems to be intuitively correct; contrariwise, the de-indexation of eGFR is not frequent. However, de-indexation is crucial, because the performances of the CKD-EPI equation (non de-indexed in mL/min/1.73m2) compared to non-indexed mGFR (mL/min) are significantly lower, and underestimate the mGFR, than the performances between CKD-EPIdeindexed and non-indexed mGFR (data not shown). The same results have been demonstrated in a recent study from Chew-Harris et *al.* (55). In this study, only 78 obese patients were included, but they showed that the CKD-EPI without normalisation (in mL/min) was superior to the CKD-EPI equation indexed (in mL/min/1.73m2) in estimating absolute clearance of Tc-DTPA (in mL/min).

Numerous authors have also found that creatinine-based equations overestimate GFR in different types of population (11,56–58), especially in obese patients with a high level of GFR (GFR > 60 mL/min) (38,42). Lemoine *et al.* (11) have studied 209 obese patients, compared to a non-obese group of participants that had an evaluation of kidney function by reference method. They clearly showed that performance of CKD-EPI equation is less in obese versus non-obese subjects. Like us, they show that CKD-EPI (indexed) globally overestimates indexed mGFR. This overestimation decreased when non-indexed mGFR is considered but their results with non-indexed mGFR are not comparable to ours as they do not de-indexed CKD-EPI results.

Metformin is an effective drug for obese patients with type 2 diabetes (59) and as recommended by KDIGO and other diabetes guidelines (60,61), needs an adaptation of its dosage in case of kidney failure (12). A good estimation of kidney function especially in CKD stage 3b and 4 is thus crucial. When we consider the adjustment of drug dosage (threshold below 30 mL/min), our simulation shows that overestimation by the CGABW equation would lead to an over-prescription of the contra-indicated drug in 42.9% of patients. Using CGAIBW, CKD-EPIdeindexed and MDRDdeindexed over-prescription would occur only in 18.4%, 12.2% and 14.3% of patients, respectively (table 4). With a threshold between 30-45 mL/min, an inadequate drug dosage would be erroneously given to the patient in 51.7%, 17.2%, 22.4% and 25.9% of patients if CGABW, CGAIBW, CKD-EPIdeindexed and MDRDdeindexed were used, respectively.

The increased absolute GFR observed in obese patients with a hyperfiltration status may be responsible for an increased drugs clearance, which could affect their efficacy. For instance, antibiotic drugs such as gentamicin (62) and vancomycin (63) could have their concentration reduced by this increased drug clearance, and in fine have an impact on the efficiency of the drugs. Increased absolute clearances of cisplatin and paclitaxel were also noted in obese patients compared to lean individuals (64,65). In the subgroup of our patients with an mGFR over 130 mL/min, the MDRDdeindexed and CKD-EPIdeindexed equations have the same performances and are significantly better than the CG equation with ABW, but not with AIBW. The accuracies reach a good value, around 78 to 89%. In a cohort of diabetic, overweight patients with a hyperfiltration status, Gaspari *et al.* (66) showed that CG, CKD-EPI and MDRD equations indexed by the BSA underestimated the mGFR (iohexol) and thus ignore the hyperfiltration status. Discrepancy with our own results is explained by the excess of correction induced by the BSA in overweight patients. In our population, using deindexed GFR, we observed an overestimation of mGFR by all eGFR equations but especially with the CG. In our study, eGFR equations detect hyperfiltration in 24.6%, 9.8%, 13.7% and 8.5% of patients when CGABW, CGAIBW, CKD-EPIdeindexed and MDRDdeindexed are considered, respectively, although true hyperfiltration by mGFR occurs in only 5.2% of the population.

The strengths of our study include that we measured GFR in a large sample of obese subjects from two centres with a reference method. Also, we measured creatinine with a Jaffe IDMS-traceable method. Enzymatic methods would theoritically give still better results in precision (and tend to become the reference) but this method remains more costly. Another strength of our study is the fact that subjects included are all obese, and not only overweight.

There are also limitations to this study. First, plasma clearances are less physiological than urinary clearances. However, this technique is considered as a reference and several studies have illustrated its concordances with urinary clearances of inulin (67). Second, most of our subjects were Caucasians and a study in obese patients from other ethnicities would be of interest. Third, there were no elderly patients; we also know that this part of the population is more at risk of GFR decline and therefore needs more frequently the adaptation of drug dosage. Furthermore, our population was not representative of the general obese population as CKD patients were obviously overrepresented. Fourth, the consensus in favour of a dose adjustment of drugs from non-indexed GFR brings are not free from criticisms. Indeed, this recommendation is based on theoretical arguments, almost logical, but 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, espeically for patients with BSA beyond the BSA observed in cohorts used to develop these equations, as it is the case in our work. Further studies could be still necessary. Finally, our study lacks a paired non-obese population, which would be necessary to evaluate the specific impact of obesity on the intrinsic performances of each equation.

# Conclusion

For several years, the CG equation has been the most commonly used method to estimate 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 CG and other equations could build up, and this is especially relevant in obese population, as weight is an important variable of the CG (and absent in both MDRD and CKD-EPI).

We demonstrate that the performance of the CGABW equation is low in the obese population. Using AIBW instead of ABW in the CG equation (no-indexed) increases drastically the performances compared to other eGFR equations, especially when deciding whether the drug should be stopped or not (GFR < 30 mL/min). When adaptation of drug dosage needs to be done at GFR levels between 30-45 mL/min, MDRDdeindexed and CKD-EPIdeindexed are quite equivalent, with good performances. Currently, the use of AIBW or other weights in the CG equation is still debated. Therefore, using the creatinine-based equations such as MDRD and CKD-EPI de-indexed by the BSA seems to be the easiest and more accurate way to adapt the drug dosage. For drugs with a tight therapeutic window, where a very precise GFR determination is necessary, it may be still prudent to measure the GFR with a reference method prior administration of the medication.

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# Tables and Figures

**Table 1.** Characteristics of the population

Mean (SD) for continuous variables, n (%) for categorical variables

|  |  |
| --- | --- |
| **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%) |
| **Body mass index (kg/m²)**   * **30-35 kg/m2** * **35-40 kg/m2** * **> 40 kg/m2** | 36 ± 7 [30-77]  217 (59%)  76 (21%)  73 (20%) |
| **BSA (Gehan and Georges formula m²)** | 2.16 ± 0.26 [1.67–3.7] |
| **Creatinine (mg/L)** | 16 ± 11 [5-74] |
| **Estimated GFR (eGFR):** |  |
| * **CG**ABW **(mL/min)** * **CGAIBW (mL/min)** * **CKD-EPI deindexed (mL/min)** * **MDRD deindexed (mL/min)** | 96 ± 64 [10-610]  72 ± 44 [9-354]  77 ± 44 [9-283]  73 ± 43 [10-306] |
| **Measured GFR (mL/min)** | 71 ± 35 [11-169] |
| **CKD stages**   1. **GFR ≥ 90 mL/min** 2. **GFR 60-89 mL/min** 3. **GFR 30-59 mL /min**   **3a. GFR 45-59mL/min**  **3b. GFR 30-44mL/min**   1. **GFR 15-29 mL /min** 2. **GFR < 15 mL/min**   **Hyperfiltration status (GFR ≥ 130 mL/min)** | 110 (30%)  100 (27%)  107 (29%)  49 (13%)  58 (16%)  44 (12%)  5 (1%)  19 (5%) |

BSA: Body Surface Area; GFR: Glomerular Filtration Rate; MDRD: Modification Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology; CG: Cockcroft & Gault; ABW: Actual Body Weight; AIBW: Adjusted Ideal Body Weight

**Table 2.** Performances of the CGABW, CGAIBW, MDRDdeindexed and CKD-EPIdeindexed equations regarding the different levels of mGFR

* \* If p < 0.05 regarding CKD-EPIdeindexed equation
* ¥ If p < 0.05 regarding MDRDdeindexed equation
* † If p < 0.05 regarding CGAIBW equation

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

mGFR: measured Glomerular Filtration Rate; eGFR: estimated Glomerular Filtration Rate; MDRD: Modification Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology; CG: Cockcroft & Gault; ABW: Actual Body Weight; AIBW: Adjusted Ideal Body Weight

**Table 3.** Percentage of patients in the different CKD groups depending on the type of equations used and misclassification associated (eGFR over or under mGFR)

* \* If p < 0.05 regarding CKD-EPIdeindexed equation
* ¥ If p < 0.05 regarding MDRDdeindexed equation
* † If p < 0.05 regarding CGAIBW equation

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **CKD stage** | **mGFR**  **n patients**  **(%) a** | **Classified by**  **CGABW in mGFR stage**  **n patients**  **(%) b** | **Classified by**  **CGAIBW in mGFR stage**  **n patients**  **(%) b** | **Classified by**  **CKD-EPI deindexed in mGFR stage**  **n patients**  **(%) b** | **Classified by**  **MDRD deindexed in mGFR stage**  **n patients**  **(%) b** |
| **mGFR regarding the eGFR**  **n patients**  **(%) b** | | | |
| *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%) |

mGFR: measured Glomerular Filtration Rate; MDRD: Modification Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology; CG: Cockcroft & Gault; ABW: Actual Body Weight; AIBW: Adjusted Ideal Body Weight

a percentage of total population

b percentage of subgroup population

**Table 4.** Percentage of patient in the different groups for the adaptation of metformin depending on the type of equations used and misclassification associated

* \* If p < 0.05 regarding CKD-EPI deindexed equation
* ¥ If p < 0.05 regarding MDRD deindexed equation
* † If p < 0.05 regarding CG AIBW equation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Classified by**  **CGABW in mGFR stage**  **n patients**  **(%) b** | **Classified by**  **CGAIBW in mGFR stage**  **n patients**  **(%) b** | **Classified by**  **CKD-EPI deindexed in mGFR stage**  **n patients**  **(%) b** | **Classified by**  **MDRD deindexed in mGFR stage**  **n patients**  **(%) b** |
| **mGFR stage**  **n patients (%) a** | **eGFR regarding the cut-off of mGFR**  **n patients**  **(%)** | | | |
| *< 30 mL/min*  *49 patients*  *(13.4%)*  *Metformin*  *Contra indicated* | 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*  *58 patients*  *(15.9%)*  *Dose of metformin to adjust* | 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*  *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%) |

mGFR: measured Glomerular Filtration Rate; eGFR: estimated Glomerular Filtration Rate; MDRD: Modification Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology; CG: Cockcroft & Gault; ABW: Actual Body Weight; AIBW: Adjusted Ideal Body Weight

a percentage of total population

b percentage of subgroup population

**Table 5.** Classification of hyperfiltrating patients according to the different eGFR and the number of patients with an mGFR below the eGFR

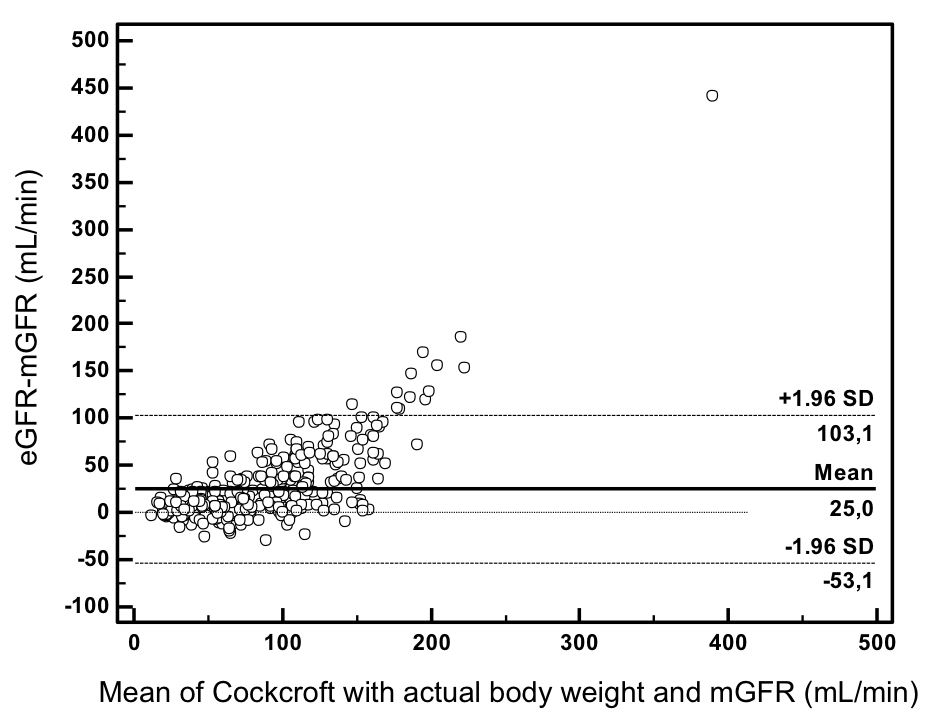
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **mGFR n**  **(%)** a | **CGABW**  **n patients**  **(%)** a | **CGAIBW**  **n patients**  **(%)** a | **CKD-EPI deindexed**  **n patients**  **(%)** a | **MDRD deindexed**  **n patients**  **(%)** a |
| **mGFR<eGFR** b  n patients  (%) | | | |
| *≥ 130*  *mL/min*  *19 patients*  *(5.2%)* | 90 patients  (24.6%) | 36 patients  (9.8%) | 50 patients  (13.7%) | 31 patients  (8.5%) |
| 28 patients  (31.1%) | 21 patients  (58.3%) | 26 patients  (52%) | 22 patients  (71%) |

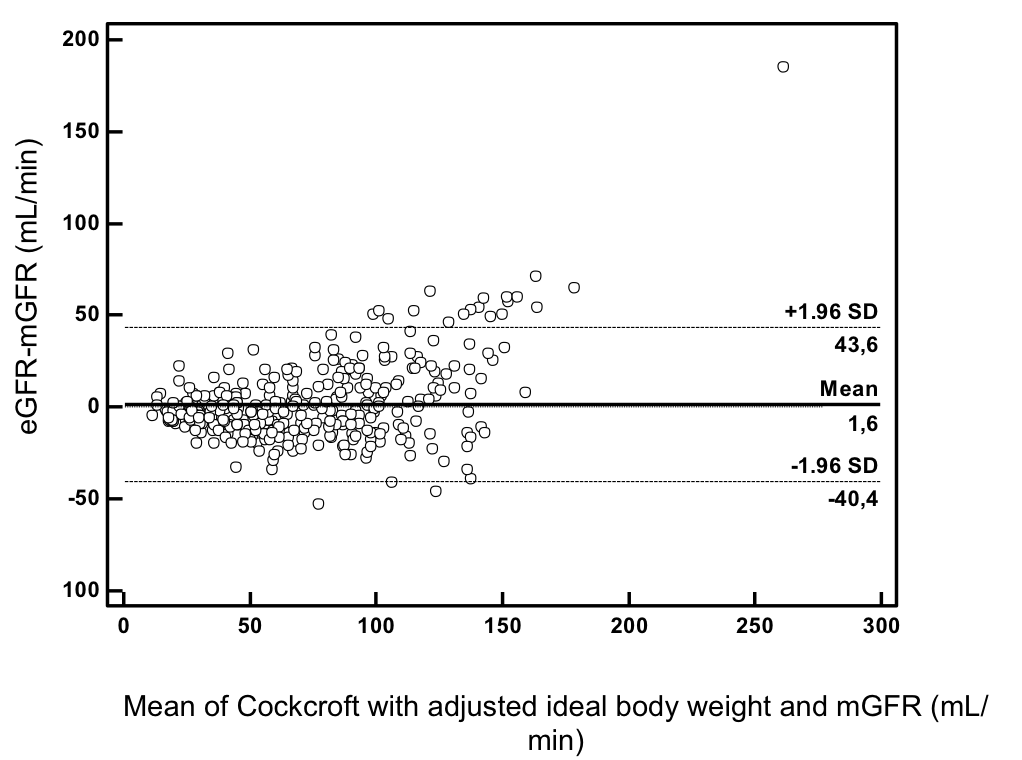
mGFR: measured Glomerular Filtration Rate; eGFR: estimated Glomerular Filtration Rate; MDRD: Modification Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology; CG: Cockcroft & Gault; ABW: Actual Body Weight; AIBW: Adjusted Ideal Body Weight

a percentage of total population

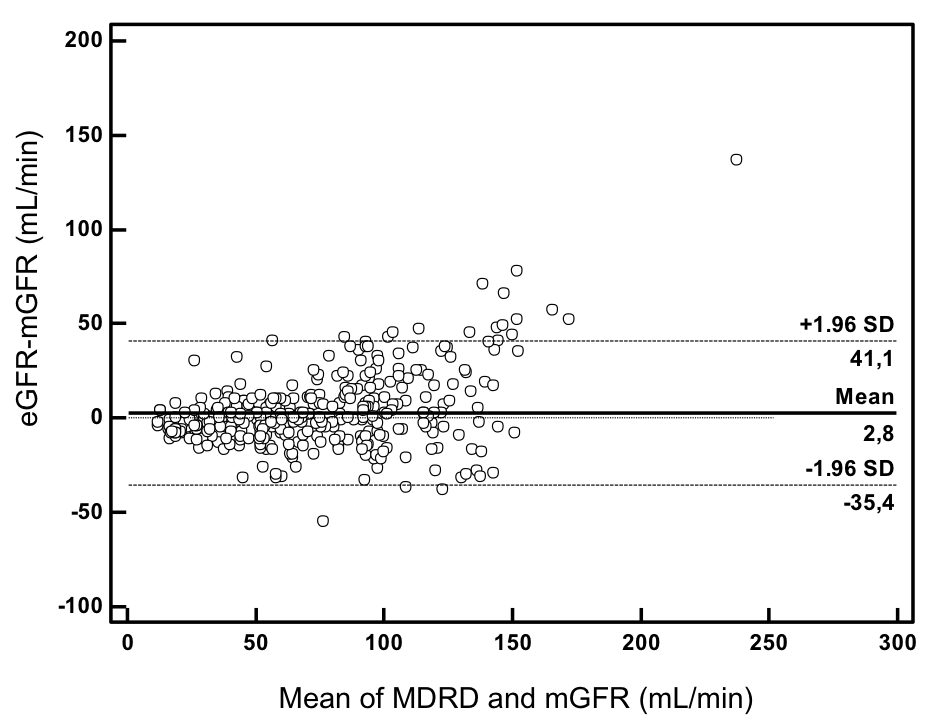
b percentage of subgroup population

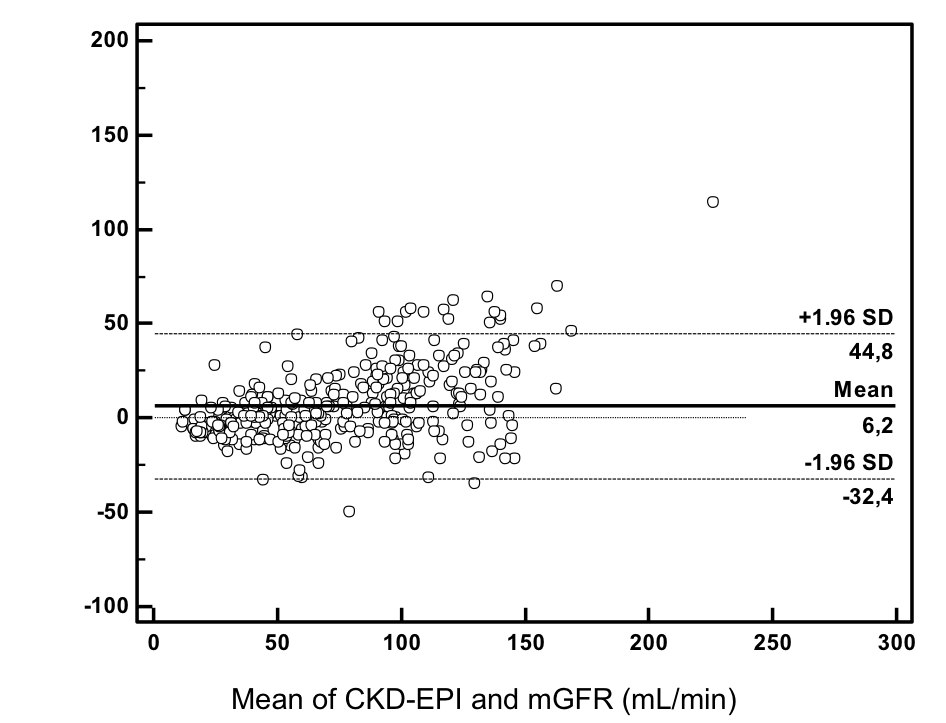
**Figure 1a.** Bland and Altman analysis for the CGABW (upper panel) and CGAIBW (lower panel) compared to mGFR.

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**Figure 1b.** Bland and Altman analysis for the MDRDdeindexed (upper panel) and CKD-EPIdeindexed (lower panel) equations compared to mGFR.

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