NEPHROLOGY

Nephrology (2019)

Brief Communication

De-indexed estimated glomerular filtration rates: A simple step towards improving accuracy of drug dosing of renally excreted medications in moderate to severe obesity

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KEY WORDS:
chronic kidney disease, eGFR, obesity.

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doi: 10.1111/nep.13621

SUMMARY AT A GLANCE

The authors propose that eGFR should be de-indexed in patients with moderate to severe obesity, especially when calculating doses of medications that are excreted by the kidneys. They report that about half of patients in their CKD clinic with BMI 35 had a clinically significant eGFR improvement after de-indexing by dividing eGFR by 1.73 m^2 (the standardized BSA) and multiplying by the actual BSA of the respective patient to re-determine each patient's CKD stage based on the de-indexed GFR.

ABSTRACT:

Kidney function is underestimated in obese individuals when standard equations are applied. Laboratory-reported estimated glomerular filtration rates (eGFR) report glomerular filtration rates corrected for body surface area in mL/min per 1.73 m^2 using modification of diet in renal disease or the chronic kidney disease-Epidemiology Collaboration equations. This may result in premature discontinuation or reduction in dosage of renally excreted medications. Currently, there are no clinical guidelines defining thresholds beyond which physicians should consider de-indexing patient eGFR values. We compared standard and de-indexed eGFR values for 281 consecutive patients seen in our chronic kidney disease clinic. In our study, half of the patients with a body mass index above 35 had clinically significant changes in their eGFR, with an improvement in chronic kidney disease stage, when eGFR was de-indexed. We propose that eGFR de-indexing should be considered in patients with moderate to severe obesity when calculating the dose, especially for medications that are excreted by the kidneys.

The accurate assessment of kidney function is important in all individuals [1] to avoid both over-diagnosis and under-diagnosis of chronic kidney disease (CKD), as well as its staging, especially in individuals at extremes of bodyweight. Moreover, an accurate assessment of kidney function is crucial when medications that are excreted by the kidneys are used to reduce their toxicity while maintaining their efficacy. Glomerular filtration rate (GFR) can be measured (mGFR) directly, with validated gold-standard methodologies, but is cumbersome and costly. In clinical practice, the GFR is mostly estimated (eGFR) using the CKD Epidemiology Collaboration equation (CKD-EPI). However, in cross-sectional studies, the average error of eGFR is ±30% of mGFR[2]. Interestingly, this wide error would be unacceptable if applied to other clinical measurements (e.g. blood pressure). Furthermore, estimating GFR at extremes of body size is challenging, and creatinine-based equations are less accurate as these equations have not been validated, especially in obese individuals[3,4]. This results in underestimation of kidney function when eGFR is standardized to 1.73 m^2 of body surface area (BSA). Cystatin-C-based equations were initially felt to be superior but have not been shown to improve the accuracy of eGFR[5] and are not easily available to the practicing clinician. The accurate estimation of GFR is of particular importance in the current era as the prevalence of obesity (body mass index (BMI) >30) is increasing worldwide[6].

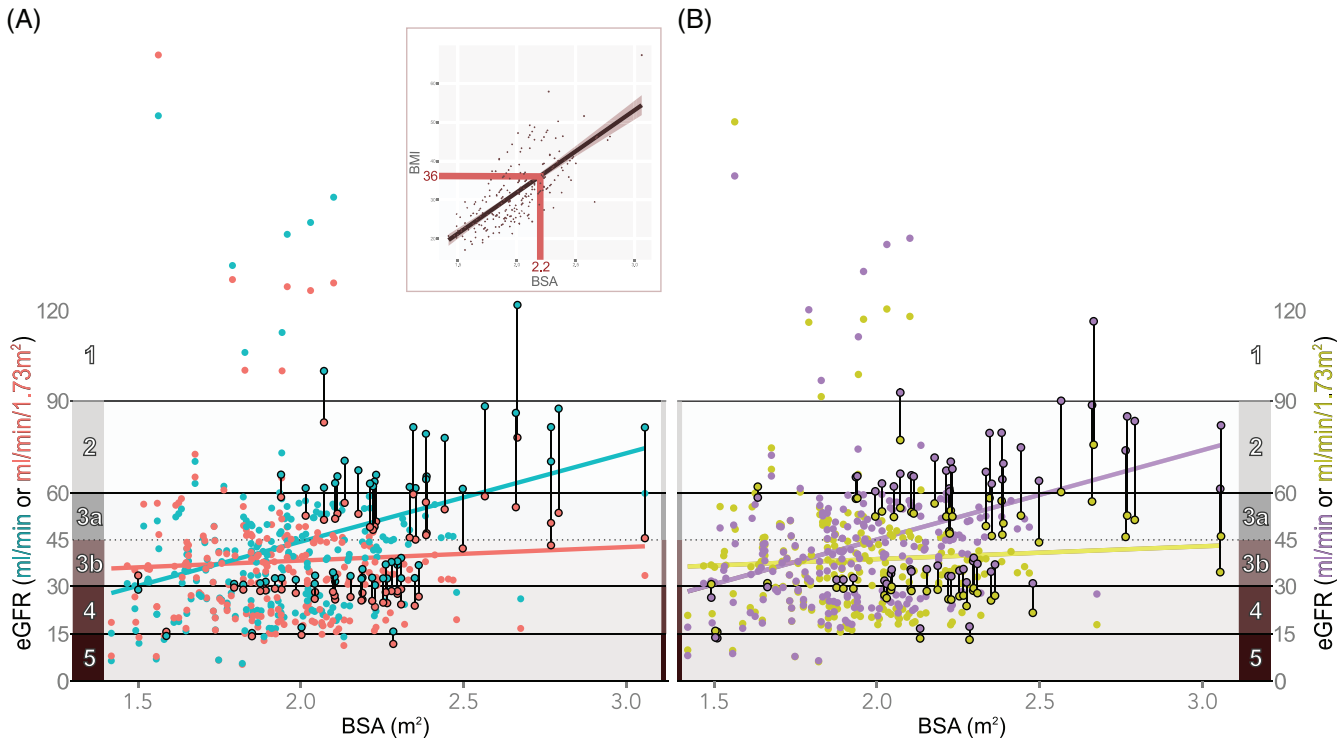

Fig. 1 Panel A – Comparison of estimated glomerular filtration rates (eGFR): CKD Epidemiology Collaboration equation (CKD-EPI) eGFR (pink, in mL/min per 1.73 m^2) and de-indexed glomerular filtration rates (GFR) for body surface area (BSA) (di-$GFR_{CKD\text{-}EPI}$ – blue, in mL/min). Panel B – Comparison of eGFR: modification of diet in renal disease (MDRD) eGFR (lime-green, in mL/min per 1.73 m^2) and de-indexed GFR for BSA (di-GFR_{MDRD} – purple, in mL/min). Vertical/Oblique lines connecting dots, in each panel, indicate a change in kidney function classification after de-indexing for BSA. Stages 3a and 3b of CKD were considered to be a single class in this analysis. Figure Inset – Correlation between body mass index (BMI) (weight in kilograms/(height in meters)^2) and BSA in m^2 calculated by *DuBois and DuBois formula* (0.20247 × (height in meters)$^{0.725}$ × (weight in kilograms)$^{0.425}$). (a) (—●—) CKD-EPI, (—●—) di-$GFR_{CKD\text{-}EPI}$; (b) (—●—) MDRD, (—●—) di-GFR_{MDRD}.

We prospectively analysed the kidney function of 281 consecutive patients presenting to our CKD clinic and collected demographic (age, gender and race), anthropometrical (height and weight) and biochemical (Blood Urea Nitrogen (BUN), serum creatinine and serum albumin) data. We calculated BMI using standard calculation (weight in kilograms/(height in meters)^2) and BSA using *DuBois and DuBois formula* (0.20247 × (height in meters)$^{0.725}$ × (weight in kilograms)$^{0.425}$). We did not measure the GFR using the gold-standard method (being cumbersome and expensive), but used the estimating equations, to calculate the eGFR that are being used in clinical practice around the world on daily basis. We used CKD-EPI and MDRD equations and determined their CKD staging based on the eGFR using both equations. We then calculated the de-indexed GFR for both equations by dividing the eGFR by 1.73 m^2 (the standardized BSA) and multiplied by the actual BSA of the respective patient ((eGFR/1.73) × actual BSA) and re-determined each patient's CKD stage based on de-indexed GFR. When de-indexing the CKD-EPI eGFR, 60 of 281 (21.4%) patients demonstrated a change in their CKD stage. Strikingly, almost half (52.4%) of patients with BSA more than 2.2 m^2 were moved to a less severe CKD stage (Fig. 1), which corresponded to a BMI of 36 kg/m^2 (Fig. 1, inset). Similarly, when de-indexing the MDRD eGFR, 61 of 281 (21.7%) patients demonstrated a change in their CKD stage; again, around half (50.8%) of patients with a BSA of more than 2.2m^2 moved to a less severe CKD stage. We plotted their eGFR (Fig.1) based on both the CKD-EPI equation (Panel A) and the MDRD equation (Panel B) with and without correction (or de-indexed) for their BSA.

Most laboratories now provide eGFR (in mL/min per 1.73 m^2) when serum creatinine is requested, yet physicians rarely de-index the eGFR in obese individuals, leading to some of these patients being labelled with a diagnosis of 'CKD', and many renally excreted medications are withheld or under-dosed. Until 2008, the Cockcroft-Gault (CG) equation was the only equation recommended by the Food and Drug Administration (FDA) for the determination of dose adjustment studies for a new drug. Since 2008, the FDA has accepted use of the Modification of Diet in Renal Disease (MDRD) and the CKD-EPI equations; however, there are no clear data to recommend one over the other, especially in obese populations. In fact, when drug dosing is considered, the various regulatory bodies (Kidney Disease Improving Global Outcomes (KDIGO), European Medicines Agency (EMA) and FDA) recommend a de-indexed eGFR (mL/min), and eGFR that is not adjusted for BSA, but do not provide specific guidance. In a multicentre study, Bjork *et al*[7] also noted a significant discrepancy between mGFR and eGFR at a BMI of less than 20 and a BMI of more than 35 kg/m^2.

De-indexing of eGFR should be considered in patients with moderate (BMI 35–40) to severe (BMI >40) obesity until more robust methods become available for the accurate estimation of kidney function in such individuals to prevent unnecessary withholding or under-dosing of medications[8] that are excreted by the kidneys. Further studies are required to validate these findings.

DISCLOSURE

None, for all authors.

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