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Kidney Function in Obesity – Challenges in Indexing and Estimation

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Abstract

As the prevalence of obesity continues to rise worldwide, an increasing number of people are at risk for kidney disease. Thus, there is a critical need to understand how best to assess kidney function in this population, and several challenges exist. The convention of indexing glomerular filtration rate (GFR) to body surface area (BSA) attempts to normalize exposure to metabolic wastes across populations of differing body size. In obese individuals, this convention results in a significantly lower indexed GFR than unindexed GFR, which has practical implications for drug dosing. Recent data suggests that "unindexing" eGFR (multiplying by BSA/1.73m^2) for drug dosing may be acceptable, but pharmocokinetic data to support this practice are lacking. Beyond indexing, biomarkers commonly used for estimating GFR may induce bias. Creatinine is influenced by muscle mass, whereas cystatin C correlates with fat mass, both independent of renal function. Further research is needed to evaluate the performance of estimating equations and other filtration markers in obesity, and determine whether unindexed GFR might better predict optimal drug dosing and clinical outcomes in patients whose BSA is very different than the conventional normalized value of 1.73 m^2.

Introduction

The prevalence of obesity [body mass index (BMI) ≥ 30 kg/m^2) continues to increase in both developed and developing countries.[1] Recent estimates from the National Health and Nutrition Examination Survey (NHANES) (2013–2014) report prevalence of obesity of 37.7%, and class III obesity (BMI ≥ 40 kg/m2) of 7.7%, up from 33.9% and 5.7% in 2007–2008.[2,3] Among the U.S. population with CKD, the prevalence of obesity and class III obesity is even higher, at 44.1% and 22.2%, respectively.[4] Both kidney disease and obesity have important implications in terms of prognosis and drug dosing; however, methods for

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estimating kidney function in the setting of obesity—particularly severe obesity—remain uncertain. In this review, we examine the rationale for indexing GFR to body surface area (BSA), methods to estimate GFR, and the accuracy and clinical implications of these conventions in the obese population. Finally, we highlight areas requiring additional research in the growing population of obese individuals.

Rationale for indexing GFR to BSA

In order to fully understand the issues inherent to the assessment kidney function in obesity, we must first discuss the rationale underlying the convention of indexing GFR to BSA. Across mammalian species, GFR increases as kidney and body mass increases. This relationship follows the power law equation ($y = aX^b$), where y is GFR, a is a constant, X is body mass, and the coefficient b is estimated to be 0.77–0.79.[5,6] This ". power" relationship between GFR and body mass is similar to the relationship between metabolic rate and body mass, suggesting that GFR increases proportionally to metabolic needs, which makes physiologic sense. In a similar manner, higher glomerular number (power law coefficient 0.57–0.62) and, to a lesser extent, glomerular capillary tuft volume (power law coefficient 0.26–0.29) are associated with higher body mass.[5]

BSA provides a critical role in dissipating heat produced through metabolic processes, although recent literature suggests that scaling of metabolism is complicated and that substantial variation exists in animals. [6,7] Because BSA is a 2-dimensional variable whereas volume (body mass) is a 3-dimensional variable, smaller animals have a higher BSA:body mass ratio than larger animals. For example, a mouse has a relatively higher metabolic rate and GFR per body mass (0.2 ml/min, or about 0.007 ml/min/g body weight) than a horse (390 ml/min, or about 0.0008 ml/min/g body weight).[6] Allometric scaling was first used to standardize GFR in humans in studies published in the early 20th century, based on the observation that correction for BSA tended to normalize rates of urea excretion. [8,9]

However, there is controversy over the most appropriate scaling variable, as physiologic rationale exists for other factors such as REE or TBW since the kidneys help excrete metabolic wastes and regulate fluid and electrolyte balance. Ellam et al. used data from the Chronic Renal Insufficiency Cohort (CRIC) study and the Modification of Diet in Renal Disease (MDRD) study, to examine gender differences in metabolic burden.[10] Men had higher 24-hour urine urea excretion and serum urea nitrogen levels than women; indexing to BSA only slightly attenuated these gender differences. When GFR was indexed to estimated REE, differences between 24-hour urine urea nitrogen and serum urea nitrogen levels were mostly abolished. When GFR was indexed to estimated TBW, serum urea nitrogen levels were similar between genders, but the relationship was reversed for 24-hour urea nitrogen (higher in women than men). Thus, indexing to BSA results in a greater metabolic burden in men compared to women whereas indexing to REE or TBW may help reduce these differences.

Daugirdas et al. used data from 1551 potential kidney donors evaluated between 1973 and 2005 to examine different methods of indexing GFR measured with ^{125}I-iothalamate.[11] Mean BMI was 27.2 for men and 26.3 kg/m^2 for women. Scaling parameters included

equation-based estimates of BSA, TBW, metabolic rate, and liver size. Mean unindexed GFR was 122 ml/min in men and 106 ml/min in women. Indexing to TBW resulted in women having higher indexed GFR (119 ml/min) than men (105 ml/min) whereas indexing to BSA, or liver size, resulted in similar mean indexed GFR for men and women (113 ml/min/1.73m^2 for men and women using both methods). Further, indexing to BSA resulted in the most uniform indexed GFR across quintiles of BSA (Q1–5: 107, 103, 106, 103, and 104 ml/min/1.73m^2, respectively). Thus, if GFR, adjusted for a body size scaling variable, should be similar across a population, then BSA seems to be appropriate.

Evidence for indexing to BSA from the dialysis population

Another interesting way to compare different methods of indexing GFR is to examine patient outcomes by hemodialysis adequacy, which is commonly assessed as Kt/V (K = urea clearance of dialyzer, t = dialysis time, V = volume of distribution of urea, which approximates TBW). Several studies have identified limitations of using V as an indexing variable; for a given BSA, V is lower in smaller individuals than larger individuals.[6,12] This may have resulted in hemodialysis treatment disparities for smaller individuals. For instance, V is on average lower in women than men, and women are often prescribed treatments of shorter duration.

Port et al. examined the association between dialysis dose and body size with mortality in 45,967 incident hemodialysis patients.[13] Dialysis dose was divided into 5 groups—urea reduction ratio (URR) <60, 60–65, 65–70, 70–75, >75, corresponding to single pool Kt/V KT/V cutpoints of <1.1, 1.2, 1.32, 1.5, >1.7. Lower BMI and lower dialysis dose were both associated with increased risk of death. When stratified by tertiles of body size (small: BMI <23.1, medium: 23.2–27.8, large: >27.8 kg/m^2), higher dialysis dose was associated with lower mortality in all three categories. However, small and medium BMI groups had significantly lower mortality at the highest dose compared to the next highest dose (URR >75 compared to URR 70–75), whereas the large BMI group had similar mortality at URR>75 and URR 70–75.

In the Hemodialysis (HEMO) Study, a multi-center randomized controlled trial of dialysis dose and membrane flux, women randomized to the higher dialysis dose of single pool Kt/V (spKT/V) of 1.65, had significantly lower mortality than women randomized to the conventional lower dose of spKT/V 1.25 (RR 0.81, p=0.02) whereas there was no significant effect of the higher dialysis dose on men (RR 1.16, p=0.2) compared to the standard dose.[12] The same investigators examined whether rescaling dialysis dose to BSA helped explain the different responses in women vs. men.[14] Dose of dialysis, when BSA-adjusted, was on average, 12.3% lower in women compared to men in the conventional dialysis dose group. The ratio V/BSA modified the effect of dialysis dose on mortality; higher dialysis dose was associated with decreased mortality among those with lower V/BSA and marginally associated with increased mortality among those with higher V/BSA. These studies would suggest that for scaling metabolic wastes in dialysis patients, TBW may not be an optimal scaling variable; consideration of other scaling variables such as BSA may be helpful.

Problems with indexing GFR to BSA in the setting of obesity

When the process of indexing GFR to BSA first came into favor, average American BSA at 25 years of age was 1.73$m^{2.8}$8 This value is still used in indexing today even as weight and BSA distributions have shifted higher (NHANES 2011–2014: women 1.81m^2, men 2.05m^2). [15] In obese patients, indexed GFR is substantially lower than unindexed GFR and thus could have implications in CKD staging and drug dosing.[16] For instance, a hypothetical 5′10″ man with unindexed GFR of 90 ml/min would have a similar indexed GFR of 87 if he had a BMI of 20 kg/m^2, using the DuBois equation (Table 1). However, if he were 40 or 60 kg/m^2, indexed GFR would be 65 or 54 ml/min/1.73m^2, respectively. Another issue is the validty of BSA-estimating equations, which were not derived in obese populations. Hypothetical results for the example using formulas by Mostellar et al. and Haycock et al. are also shown in Table 1.[17,18]

Some investigators have also questioned the appropriateness of scaling to BSA in the setting of severe obesity as this practice may mask “glomerular hyperfiltration.” [16] Since nephron number does not increase as individuals gain weight, an increase in total GFR in severe obesity results in increased single nephron GFR. This compensatory mechanism has been hypothesized to be maladaptive, potentially increasing glomerular capillary pressure and renal injury. In animal models, obesity has been shown to increase GFR, renal plasma flow (RPF), and intraglomerular capillary pressure.[19–21] For instance, in a study by Henegar et al, obese dogs fed a high-protein diet had 38% higher GFR and 61% higher RPF, than lean dogs fed a standard diet.[20] Obese dogs also had significantly higher blood pressure, insulin levels, renin-angiotensin system activation, and structural changes (increased mesangial matrix, thickening of glomerular and basement membranes, hypercellularity).

Obesity-associated glomerular hyperfiltration has also been observed in humans. Chagnac et al. measured GFR and RPF using inulin and p-aminohippuric acid (PAH) in 12 nondiabetic adults with BMI ≥ 38 kg/m^2 before and after bariatric surgery, and 9 healthy, lean adult controls.[22] Prior to bariatric surgery, morbidly obese adults had 61% higher GFR, 32% higher RPF, and 19% higher filtration fraction compared to healthy, lean adult controls ($p<0.05$ for all comparisons). After bariatric surgery, mean BMI decreased from 48 kg/m^2 to 32 kg/m^2, mean GFR decreased from 145 to 110 ml/min, and RPF decreased from 803 ml/min to 698 ml/min ($p<0.05$ for both comparisons), suggesting obesity-associated glomerular hyperfiltration may be reversible. Interestingly, when GFR is indexed to BSA, this reduction in glomerular hyperfiltration after bariatric surgery is “masked”.[16,23–25] For instance, in a study by Friedman et al. GFR decreased from 117 to 100 ml/min after bariatric surgery whereas GFR indexed to BSA remained unchanged at 87 ml/min/1.73m^2 before and after bariatric surgery.[25]

Similar findings have been noted in population-based cross-sectional studies. In a study designed to examine genetics of hypertension, GFR and RPF were measured in 301 non-diabetic adults of African descent with a family history of hypertension from the Seychelles Islands.[26] Prevalence of glomerular hyperfiltration (defined as GFR ≥ 140 ml/min) increased across BMI categories (lean 7.2%, overweight 14.8%, obese 27.1%), as did mean GFR, renal plasma flow, and filtration fraction ($p \leq 0.01$ for all comparisons). When GFR was

adjusted for BSA, BMI was no longer associated with GFR or RPF. In another study by the same group, creatinine clearance was determined by 24-h urine collection in 1339 adults in a population-based Swiss survey. Prevalence of glomerular hyperfiltration (CrCl > 140 ml/min) again increased across BMI categories (lean 10.4%, overweight 20.8%, obese 34.7%). When indexed to BSA, prevalence of glomerular hyperfiltration (CrCl > 140 ml/min/1.73m^2) was more similar across BMI categories (lean 6.5%, overweight 6.5%, obese 14.0%).

However, one may argue that identifying obesity-associated hyperfiltration is of limited practical importance. Obesity itself is a known risk factor for CKD and ESRD, and should prompt optimization of CKD risk factors like hypertension and diabetes. Adverse effects of obesity on the kidney may not depend solely on glomerular hyperfiltration. In a study by Kasiske et al., obese Zucker rats developed increased mesangial matrix, glomerulomegaly, and focal glomerulosclerosis, even in the absence of significantly increased GFR, RPF, or intraglomerular hydraulic pressure.[21,27] Factors other than obesity are associated with glomerular hyperfiltration, including high protein and salt intake, and hyperfiltration is a heterogenous condition that occurs in other diseases (diabetes, polycystic kidney disease) and also in the normal physiologic state of pregnancy.[28]

Other clinical implications of indexing GFR in obese patients

Fotheringham et al. used data from 3611 participants in the CRIC Study (42% black, 48% diabetes, 56% obese, 14% with BMI ≥ 40 kg/m^2) to examine the performance of eGFR, urine albumin/creatinine ratio (ACR), and excretory burden in obesity.[29] Higher BMI was associated with higher BSA and excretory burden (24-hour urine urea nitrogen, and estimated dietary sodium, potassium, and phosphorus intake). Interestingly, for a given eGFR, obese individuals tended to have higher unindexed GFR and lower risk of CKD-related complications (anemia, hyperkalemia, hyperphosphatemia) than normal weight individuals, despite having higher excretory burden. To our knowledge, no study has examined whether unindexed GFR or indexed GFR is superior in predicting long-term outcomes such as ESRD, cardiovascular disease, and mortality. Thus, it is unclear whether using indexed or unindexed is the most appropriate approach for CKD staging.

How do estimating equations account for body size?

The Cockcroft-Gault Equation

Several creatinine-based estimating equations have been used to estimate kidney function and have accounted for differences in body size in various ways. The Cockcroft-Gault (CG) equation (1973) was derived from a study of 249 men who had creatinine clearance measured by 24-hour urine collection.[30] A formula to estimate creatinine clearance was created and included weight in the numerator: [(140 – age in years) × weight in kg / (72 × serum creatinine in ml/min) × (0.85 for women)]. Note that the CG equation estimates creatinine clearance, which is slightly higher than GFR since a small amount of creatinine is secreted in the tubules. This formula calculates unindexed creatinine clearance (ml/min), which is often normalized per 1.73 m^2 of BSA.

The MDRD study and CKD-EPI collaboration equations

Levey et al. developed a creatinine-based eGFR equation using data from the MDRD study, which included 1628 predominantly white (88%) patients with non-diabetic CKD (32% glomerular diseases, 22% polycystic kidney disease, 7% tubulointerstitial diseases, 39% other/unknown).[31] Mean BSA was 1.91 (0.23) m^2; mean BMI (reported in another manuscript) was 27.6 (4.2) kg/m^2 for men and 26.6 (5.4) kg/m^2 for women.[32] Stepwise multiple regression was used to determine a set of variables (including weight) to predict GFR (indexed to 1.73 m^2 BSA). The final 4-variable model included age, sex, race, and serum creatinine. The authors noted that although body size was associated with urine creatinine excretion, neither weight nor height independently predicted GFR, likely because the outcome variable (GFR/1.73m^2 BSA) accounted for body size.

To improve upon limitations of the MDRD study equation in estimating GFR in patients with higher levels of GFR, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was derived from 10 studies (8254 participants) and validated separately using 16 studies (3896 participants).[33] Participants were racially diverse and included kidney donors, transplant recipients, and individuals with and without CKD and diabetes. Mean BMI was 28 (6) kg/m^2 and mean BSA was 1.92 m^2. Methods for the CKD-EPI collaboration equation were similar to that of the MDRD study equation, and again the final model included age, sex, race, and serum creatinine. When weight was added as an additional variable to the CKD-EPI collaboration equation, there was no improvement in bias.[34]

Relationship between creatinine and cystatin C with muscle and fat mass

Serum creatinine is commonly used in clinical practice to estimate GFR but may be biased in individuals at extremes of muscle mass.[35] This relationship was examined in detail by Fotheringham et al. in the CRIC study; higher BMI was associated with higher 24-hour urine creatinine excretion (and hence creatinine generation).[36] For instance, women and men with class III (BMI ≥ 40 kg/m^2) obesity had 31% and 34% higher creatinine excretion than women and men with normal BMI (18.5–24.9 kg/m^2). Further, BSA did not increase as much as creatinine excretion as BMI increased above 30 kg/m^2. Thus, at very high levels of BMI, equations which standardize eGFR to BSA may overestimate GFR (Table 2). This relationship between BMI and higher creatinine excretion also impacts interpretation of urine albumin/creatinine ratio. For a given ACR value, a severely obese individual would be expected to have greater 24-hour urine albumin excretion than a normal weight individual, and some have proposed the use of an estimating equation for albuminuria.[37,38]

While serum creatinine is influenced by muscle mass, serum cystatin C is not.[39–42] However, epidemiologic studies suggest that cystatin C is associated with BMI, even after adjusting for renal function, likely because of a direct relationship between cystatin C and fat mass. [40,43–45] Naour et al. examined this relationship in 485 individuals (51.1% obese), who were stratified by tertiles of eGFR estimated by serum creatinine.[40] In each tertile of eGFR, obesity was associated with higher serum cystatin C but not serum creatinine. In support of this finding, cystatin C mRNA expression was twice as high in human adipose cells compared to nonadipose cells. Thus, creatinine and cystatin C both have limitations related to BMI. Use of the CKD-EPI combined creatinine and cystatin C equation may

provide more accurate estimates of GFR than an equation using either creatinine or cystatin C alone.[46]

Performance of estimating equations in obesity

The Cockcroft Gault Equation and Weight Descriptors

The CG equation is widely used in drug dosing. However, its performance is suboptimal, especially among obese patients, where it tends to overestimate creatinine clearance and GFR.[47–50] For example, in a study of 54 morbidly obese patients (mean BMI 50.5 kg/m^2) who had creatinine clearance measured by 24-hour urine collection, the CG equation overestimated creatinine clearance by a mean of 107.4 ml/min. Some have attempted to reduce bias of the CG equation in obesity by substituting ideal body weight for total body weight; unfortunately, this tends to underestimate creatinine clearance.[51–54] Other experimental weight adjustments include the use of "adjusted" body weight [0.4 × (actual body weight – ideal body weight) + ideal body weight] or lean body weight, which seems to improve the CG equation in obesity in some, but not all studies.[50,55] There are challenges to making comparisons to studies examining performance of the CG equation with that of GFR estimating equations. Many studies evaluating performance of the CG equation use 24 hour urine creatinine clearance rather than measured GFR as the reference, and the CG equation was developed in a study prior to standardization of creatinine measurements to an isotope dilution mass spectrometry (IDMS) traceable standard.[56]

The CKD-EPI collaboration and MDRD study creatinine equations

While the CG equation (using actual body weight) tends to overestimate GFR in obese individuals, most but not all studies have found that CKD-EPI and MDRD study equations tend to slightly underestimate GFR but with fairly good accuracy [~80% of eGFR values within 30% of measured GFR (mGFR) (Table 2). Table 2 reports bias (difference or relative difference between eGFR and mGFR), precision (interquartile range or SD of bias), and accuracy (% of eGFR values within 30% of mGFR) of the CKD-EPI and MDRD study equations across different BMI categories, with the reference of measured GFR (inulin, iohexol, iothalamate, ^{51}Cr-EDTA, or ^{99m}Tc-DTPA clearance). Some studies have reported significant overestimation with the CKD-EPI and MDRD study equations in patients with class III obesity.[25,36] In a study of 3611 participants in the CRIC study (56% obese, 14% class III obesity), the CKD-EPI equation substantially overestimated GFR in men and women with class III obesity (bias 12.0% and 8.6%), but was fairly unbiased for men and women with BMI 30–34.9 and 35–39.9 kg/m^2 (median bias ranging from −4.3% to 0% in each group).[36] A few studies have reported significant underestimation of GFR with MDRD study and CKD-EPI equations in obese patients with diabetes,[57,58]56,57and obese patients with low fat mass (i.e. muscular).[42] The varying findings for performance of creatinine-based CKD-EPI and MDRD study equations across studies could be explained by differences in study population characteristics (i.e. diabetes) and/or methods of GFR measurement.

Cystatin C and combined creatinine-cystatin C CKD-EPI equations

Friedman et al. examined the performance of creatinine and cystatin C estimating equations in 36 morbidly obese adults before and after bariatric surgery.[25] Mean BMI was 46 kg/m^2 before surgery and 33 kg/m^2 after surgery. Both MDRD study equation and CKD-EPI equation overestimated GFR before surgery (bias 7 and 13.5 ml/min/1.73m^2), and this overestimation was magnified after surgery (bias 15.2 and 18.7 ml/min/1.73m^2) (Table 2). Interestingly, the cystatin C CKD-EPI formula tended to underestimate GFR both before and after surgery (−15.6 ml/min/1.73m^2 for both). The combined creatinine-cystatin C CKD-EPI equation resulted in very little bias before and after surgery (−1.6 and 3.9 ml/min/1.73m^2). While promising, further research is needed in larger cohorts to evaluate the performance of the combined creatinine-cystatin C CKD-EPI equation in severely obese individuals.

"Unindexing" the MDRD study and CKD-EPI Equations

Recognizing the potential bias in estimating GFR in individuals at extreme body sizes, the National Kidney Disease Education Program (NKDEP) suggests that eGFR be "unindexed" in very large or very small patients by multiplying eGFR by BSA/1.73m$^{2.59}$ Stevens et al. compared the concordance of $MDRD_{unindexed}$ and the CG equation with FDA assigned kidney function categories (reference GFR measured by ^{125}I-Iothalamate) in 5,504 participants from 6 research studies and 4 clinical populations.[60] $MDRD_{unindexed}$ was superior to the CG equation, as well as the CG equation using ideal body weight (concordance 78%, 73%, and 66%, respectively), and findings were similar in a subgroup analysis of patients with BMI > 90 kg. Bouquegneau et al. used data from 366 obese adults (14% African origin, 20% BMI ≥ 40 kg/m^2, mean GFR 71 ml/min) to compare CG, $MDRD_{unindexed}$ and $CKD\text{-}EPI_{unindexed}$ equations.[55] In this study, CG adjusted for ideal body weight was superior to CG adjusted for actual body weight (accuracy: 79% vs. 57%) (Table 3). $MDRD_{unindexed}$ and CKD-EPI performed similarly well (accuracy: 80% and 76%). Thus, these results suggest that unindexing MDRD or CKD-EPI may be useful to inform drug dosing. However, this practice of unindexing eGFR may be questionable, particularly when BSA is markedly higher or lower than in the cohorts used to derive the estimating equation. Beyond estimation of GFR, more detailed pharmacokinetic studies are needed in severely obese individuals, who may also have larger volume of distribution or other characteristics that may impact drug dosing.

Conclusions

The rise in obesity prevalence worldwide poses important questions on how to assess kidney function in obese individuals. The standard practice of indexing GFR to BSA stems from the observation that GFR increases with larger body size and increased metabolic demands. Indexing results in obese individuals having lower indexed GFR compared to unindexed GFR, and drug dosing is typically based on unindexed kidney function. In terms of CKD staging and risk prognostication, insufficient data exists to determine whether indexed GFR is superior to unindexed GFR in predicting clinical outcomes. In severe obesity, creatinine-based CKD-EPI and MDRD study equations may overestimate indexed GFR, and the utility of other filtration markers such as cystatin C need further evaluation. Recent studies suggest that unindexed eGFR can be used for drug dosing although more detailed pharmacokinetic

studies are needed. Further research is needed to determine whether indexed GFR is superior to unindexed GFR in determining important clinical outcomes.

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Clinical Summary

- Indexing GFR to BSA results in lower indexed GFR than unindexed GFR in obese individuals, which has implications for drug dosing and risk stratification
- Creatinine levels are directly related to muscle mass, and cystatin C appears to correlate with fat mass, independent of kidney function
- Studies examining the performance of estimating equations in obesity have shown varied results; some have found that creatinine-based CKD-EPI collaboration equation overestimates indexed GFR in severely obese patients
- Limited data suggests that “unindexing” eGFR provides reasonable estimates of unindexed GFR
- More research is needed to determine whether unindexed GFR may better optimize drug dosing or prognosticate risk than indexed GFR, particularly in individuals at extremes of body size

Table 1

Examples of how BSA affects GFR interpretation

Example	Height (cm)	Weight (kg)	BMI (kg/m^2)				GFR (ml/min)			
1	178	63.4	20				90			
2	178	126.7	40				90			
3	178	190.1	60				90			

BSA estimated by three different equations: Dubois, Mostellar, and Haycock.

Abbreviations: BMI (body mass index), BSA (body surface area), GFR (glomerular filtration rate), ACR (albumin/creatinine ratio)

Table 2

Studies reporting performance of estimating equations (indexed GFR) in obesity

Author, y, mGFR method	Study Population, formula used	Estimating Equation*	BMI Categories	Bias, ml/min/ 1.73m^2 or %	Precision, ml/min/ 1.73m^2 or %	Accuracy, (% within 30% mGFR)
Studies using standardized creatinine traceable to IDMS reference						
Lemoine, 2014, inulin or iohexol clearance	397 French adults, 52.6% obese, 23.7% transplant, 19.9% diabetes, mean mGFR 57 ml/min	CKD-EPI	BMI <30 kg/m^2	0.6 (mean)	5.7 (IQR)	92%
			BMI 30–34.9 kg/m^2	10.3	15	82%
			BMI 35–39.9 kg/m^2	5.6	11.5	46%
			BMI ≥ 40 kg/m^2	6.5	14.5	68%
Friedman, 2014, iohexol clearance	36 morbidly obese U.S. adults undergoing bariatric surgery, plasma iohexol clearance, 78% female, 94% white, mean mGFR (pre-surgery 117, post-surgery 100 ml/min)	MDRD	Pre-surgery (BMI 46)	7.0 (median)	33.8 (IQR)	72.2%
			Post-surgery (BMI 33)	15.2	30.4	55.6%
		CKD-EPI	Pre-surgery (BMI 46)	13.5	33.0	58.3%
			Post-surgery (BMI 33)	18.7	29.6	52.8%
		Cys C CKD-EPI	Pre-surgery (BMI 46)	−15.6	36.3	52.8%
			Post-surgery (BMI 33)	−15.6	29.9	66.7%
		Cr-cys C CKD-EPI	Pre-surgery (BMI 46)	−1.0	28.4	80.6%
			Post-surgery (BMI 33)	3.9	23.4	83.3%
Bouquegneau, 2013, ^{51}Cr-EDTA clearance	366 obese French/Belgian adults, 14% African origin, 20% BMI ≥ 40 kg/m^2, mean mGFR 71 ml/min	CKD-EPI	BMI ≥ 30, mGFR<60	0.9 (mean)	11.2 (SD)	73%
			BMI ≥ 30, mGFR 60–89	11.6	17.1	75%
			BMI ≥ 30, mGFR > 90	3.6	16.2	89%
		MDRD	BMI ≥ 30, mGFR<60	−0.2	9.7	80%
			BMI ≥ 30, mGFR 60–89	6.8	17.7	79%
			BMI ≥ 30, mGFR > 90	−1.0	19.0	87%
Chew-Harris, 2013, Tc-DTPA GFR	67 healthy males characterized as: **1** "normal": BMI 18–25 kg/m^2, body fat <30%; mean mGFR 136 mL/min **2** "muscular": BMI ≥30, body fat <20%; mean mGFR 186 mL/min **3** "obese" BMI ≥30 kg/m^2, body fat ≥30%; mean mGFR 159 mL/min	MDRD	BMI 18–25, body fat <30%	−20.1	Not reported	81.8%
			BMI ≥30, body fat <20%	−58.4		26.1%
			BMI >30, body fat ≥30%	−18.6		86.4%
		CKD-EPI	BMI 18–25, body fat <30%	−11.9		90.9%
			BMI ≥30, body fat <20%	−48.7		39.1%

Author, y, mGFR method	Study Population, formula used	Estimating Equation*	BMI Categories	Bias, ml/min/ 1.73m^2 or %	Precision, ml/min/ 1.73m^2 or %	Accuracy, (% within 30% mGFR)
			BMI ≥30, body fat ≥30%	−11.8		95.5%
		Cys C CKD-EPI	BMI 18–25, body fat <30%	23.8		72.7%
			BMI ≥30, body fat <20%	0.4		100%
			BMI ≥30, body fat ≥30%	−3.1		95.5%
		Cr-cys C CKD-EPI	BMI 18–25, body fat <30%	7.0		77.3%
			BMI ≥30, body fat <20%	−27.0		91.3%
			BMI ≥30, body fat 30%	−4.0		95.5%
Nair, 2011, ^{51}Cr-EDTA clearance	111 white patients with diabetes, 66.7% obese, mean mGFR 84 ml/min	MDRD	BMI <30	1.38 (mean)	Not reported	Not reported
			BMI ≥ 30	−9.4		
Nyman, 2011, iohexol clearance	850 adults, 18% obese, mean mGFR 60 ml/min	CKD-EPI	BMI <20	21.5% (median)	Not reported	65.3%
			BMI 20–24.9	7.3%		82.4%
			BMI 25–29.9	3.6%		81.1%
			BMI ≥ 30	1.9%		77.3%
		MDRD	BMI <20	15.4%		64.0%
			BMI 20–24.9	4.0%		81.8%
			BMI 25–29.9	1.9%		81.1%
			BMI ≥ 30	−0.1%		81.3%
Michels, 2010 iothalamate clearance	271 patients, 44% male; 12% black, 18% obese, mean mGFR 72.6 ml/min	CKD-EPI, MDRD, CG	BMI 18.5–24.9, 25–29.9, and ≥ 30	Higher BMI associated with positive bias for CG; no association for MDRD or CKDEPI	Not reported	Obese: CKD-EPI 85.7%, MDRD 77.6%, CG 57.1%
Studies prior to creatinine standardization to IDMS reference						
Fotheringham, 2014, iothalamate clearance	3611 U.S. adults in the CRIC study, 41.5% black, 48.3% diabetes, 56% obese, 14% BMI ≥ 40 kg/m^2, mean mGFR 57 ml/min	CKD-EPI	18.5–24.9 kg/m^2	M 4.9%, F −4.5% (median)	M 28.8%, F 21.4% (IQR)	Not reported
			25–29.9 kg/m^2	M −5.4%, F 3.7%	M 27.2%, F 22.6%	
			30–34.9 kg/m^2	M −4.3%, F 0%	M 26.8%, F 36.5%	

Author, y, mGFR method	Study Population, formula used	Estimating Equation*	BMI Categories	Bias, ml/min/ 1.73m^2 or %	Precision, ml/min/ 1.73m^2 or %	Accuracy, (% within 30% mGFR)
			35–39.9 kg/m^2	M −2.0%, F −1.3%	M 31.6%, F 33.5%	
			≥ 40 kg/m^2	M 12.0%, F 8.6%	M 33.7%, F 32.8%	
Stevens, 2010, iothalamate, iohexol, or EDTA clearance	3896 adults in 16 studies, 10% black, 28% diabetes, 29% transplant, mean BMI 27, mean GFR 75 ml/min	CKD-EPI	BMI <20	6.8% (median)	Not reported	Not reported
			BMI 20–25	−4.2%		
			BMI 26–30	−6.3%		
			BMI >30	−4.4%		
Chudleigh, 2008, ^{51}Cr-EDTA clearance	293 adults newly diagnosed with T2DM, BMI not reported, mean GFR 114.9 ml/min	CG	Wt Tertile 1 (mean 74.3 kg)	−20.6 (mean)	16.3 (SD)	80%
			Wt Tertile 2 (mean 91.2 kg)	−14.7	18.9	84%
			Wt Tertile 3 (mean 110.5 kg)	−5.6	20.9	94%
		MDRD	Wt Tertile 1 (mean 74.3 kg)	−21.3	16.6	88%
			Wt Tertile 2 (mean 91.2 kg)	−24.8	16.5	74%
			Wt Tertile 3 (mean 110.5 kg)	−28.9	16.0	74%
Froissart, 2005, ^{51}Cr-EDTA clearance	2095 non-black adults, 92% CKD, 8% potential kidney donors, mean BMI 25.2, mean GFR 63 mL/min	CG	< 18.5	M 5.1, F 7.4 (mean)	M 14.1, F 16.3(SD)	Not reported
			18.5–24.9	M 1.0, F −2.0	M 13.3, F 15.4	
			25–30	M 0.4, F 5.0	M 13.7, F 14.2	
			>30	M 6.4, F 12.5	M 13.8, F 22.7	
		MDRD	< 18.5	M 12.1, F 12.3	M 16.3, F 29.4	
			18.5–24.9	M 2.1, F −4.1	M 12.1, F 14.7	
			25–30	M −2.7, F −1.8	M 11.5, F 11.1	
			>30	M −2.8, F −2.4	M 9.9, F 13.4	
Verhave, 2005, ^{99m}Tc-DTPA clearance	850 outpatient adults with serum creatinine level <1.5 mg/dL. mean GFR 99.3 mL/min/1.73 m^2, 22% obese (BMI>30 kg/m^2)	CG	BMI <25	−13.0 (mean)	−0.22 (SD)	
			BMI ≥30	10.1	0.17	
		MDRD	BMI <25	−13.7	−0.23	

Author, y, mGFR method	Study Population, formula used	Estimating Equation*	BMI Categories	Bias, ml/min/ 1.73m^2 or %	Precision, ml/min/ 1.73m^2 or %	Accuracy, (% within 30% mGFR)
			BMI ≥30	−11.5	−0.19	

Bias is reported as eGFR-mGFR, and percent bias calculated as (eGFR-mGFR)/mGFR. Thus, a positive bias would indicate overestimation of GFR using estimating equation. Precision is calculated as the interquartile range or SD of bias. Accuracy reported as the proportion of eGFR values within 30% of mGFR.

*Results for CG are indexed to BSA by multiplying by 1.73 m^2/BSA.

Abbreviations: IDMS (isotope dilution mass spectrometry), mGFR (measured glomerular filtration rate), CRIC (chronic renal insufficiency study), BMI (body mass index), MDRD (modification of diet in renal disease study), CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), CG (Cockcroft-Gault), ^{51}Cr-EDTA (chromium-51 labeled ethylenediamine tetraacetic acid), ^{99}mTc-DTPA (technetium 99m-labeled diethylene triaminopentaacetic acid)

Table 3

Studies reporting performance of estimating equations (unindexed GFR) in obesity

Author, y, mGFR method	Study Population, formula used	Estimating Equation*	BMI Categories	Bias, ml/min/ 1.73m^2 or %	Precision, ml/min/ 1.73m^2 or %	Accuracy, (% within 30% mGFR)
Studies using standardized creatinine traceable to IDMS reference						
Bouquegneau, 2016, ^{51}Cr-EDTA clearance	366 obese French/Belgian adults, 14% African origin, 20% BMI ≥ 40 kg/m^2, mean mGFR 71 ml/min	CKD-EPI$_{unindexed}$	BMI ≥ 30, mGFR<60,	−0.7 (mean)	9.6	76.9%
			BMI ≥ 30, mGFR ≥ 60	11.3	12.2	74.8%
		MDRD$_{unindexed}$	BMI ≥ 30, mGFR<60	−1.3	9	82.7%
			BMI ≥ 30, mGFR ≥ 60	5.9	6.3	78.6%
		CG$_{ABW}$	BMI ≥ 30, mGFR<60	9.1	14.1	64.1%
			BMI ≥ 30, mGFR ≥ 60	36.8	37.1	51.4%
		CG$_{AIBW}$	BMI ≥ 30, mGFR<60	−1.9	9.4	77.6%
			BMI ≥ 30, mGFR ≥60	4.2	3.6	80.0%
Friedman, 2014, iohexol clearance	36 morbidly obese U.S. adults undergoing bariatric surgery, plasma iohexol clearance, 78% female, 94% white, mean BMI (pre-surgery 46, post-surgery 33), mean mGFR (pre-surgery 117, post-surgery 100 ml/min)	MDRD$_{unindexed}$	Pre-surgery (BMI 46)	9.0	41.3	72.2%
			Post-surgery (BMI 33)	15.2	27.0	55.6%
		CKD-EPI$_{unindexed}$	Pre-surgery (BMI 46)	18.2	46.9	58.3%
			Post-surgery (BMI 33)	18.7	33.0	52.8%
		cys C CKD-EPI$_{unindexed}$	Pre-surgery (BMI 46)	−22.6	45.1	52.8%
			Post-surgery (BMI 33)	−15.6	28.4	66.7%
		cr-cys C CKD-EPI$_{unindexed}$	Pre-surgery (BMI 46)	−1.6	35.0	80.6%
			Post-surgery (BMI 33)	3.9	21.6	83.3%
Redal-Baigorri, 2013, ^{51}Cr-EDTA clearance	185 Danish patients, mean BMI 24 kg/m^2, mean mGFR 88 ml/min	CKD-EPI$_{unindexed}$	BSA < 1.60	3.66 (mean)	12.85 (SD)	Not reported
			BSA 1.60–1.79	0.31	14.1	
			BSA > 1.80	−0.68	11.8	
		MDRD$_{unindexed}$	BSA < 1.60	3.18	14.2	
			BSA 1.60–1.79	1.08	20.0	
			BSA > 1.80	−1.63	13.3	

Bias is reported as eGFR-mGFR, and percent bias calculated as (eGFR-mGFR)/mGFR. Thus, a positive bias would indicate overestimation of GFR using estimating equation. Precision is calculated as the interquartile range or SD of bias. Accuracy reported as the proportion of eGFR values within 30% of mGFR.

*Results for CKD-EPI and MDRD equations are unindexed by multiplying eGFR by BSA/1.73m^2. Weight descriptors for the CG equation in this table include actual body weight (ABW) and adjusted ideal body weight (AIBW): ideal body weight + {0.4 *[ABW (kg) – ideal weight]}; ideal body weight calculated as [height (cm) – 152.4] *0.9 + 45.5 + 4.5 (if male)]

Abbreviations: IDMS (isotope dilution mass spectrometry), mGFR (measured glomerular filtration rate), CRIC (chronic renal insufficiency study), BMI (body mass index), BSA (body surface area), MDRD (modification of diet in renal disease study), CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), CG (Cockcroft-Gault), ^{51}Cr-EDTA (chromium-51 labeled ethylenediamine tetraacetic acid), ^{99m}Tc-DTPA (technetium 99m-labeled diethylene triaminopentaacetic acid)