Performance of Glomerular Filtration Rate Estimating Equations Before and After Bariatric Surgery

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Rationale & Objective: Evaluation of glomerular filtration rate (GFR) is challenging in adults undergoing bariatric surgery because creatinine and cystatin C levels are influenced by changes in muscle and fat mass. Additionally, indexing of GFR by body surface area (BSA) may by affected by decreases in BSA.

Study Design: Prospective observational study.

Setting & Participants: 27 adults with body mass index (BMI) ≥ 35 kg/m^2 who underwent measurement of GFR before and after bariatric surgery.

Outcomes: Indexed and nonindexed GFRs measured (mGFRs) using plasma iohexol clearance, indexed and nonindexed estimated GFR (eGFR) based on levels of creatinine, cystatin C, or both from Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.

Analytic Approach: Bias and percent of estimates within 20% and 30% of mGFR (P_{20} and P_{30}) for estimating equations were examined.

Results: Mean presurgery BMI was 49.5 (SD, 9.4) kg/m^2, BSA was 2.42 (SD, 0.27) m^2, nonindexed mGFR was 117.3 (SD, 34.1) mL/min, and indexed mGFR was 84.1 (SD, 22.0) mL/min/1.73 m^2. After 6 months, mean BMI changed by −13.8 (95% CI, −15.9 to −11.8) kg/m^2, BSA by −0.30 (95% CI, −0.33 to −0.27) m^2, and nonindexed mGFR by −9.2 (95% CI, −17.2 to −1.1) mL/min, while indexed mGFR was unchanged at 5.1 (95% CI, −0.1 to 10.4) mL/min/1.73 m^2. Nonindexed $eGFR_{cr}$ was unbiased (median bias, 5.0 [95% CI, −4.3 to 11.6] mL/min) before surgery, but overestimated mGFR (8.8 [95% CI, 1.8 to 16.9] mL/min) after surgery. Nonindexed $eGFR_{cys}$ underestimated mGFR before (median bias, −12.1 [95% CI, −21.4 to −1.2] mL/min) and after surgery (−11.2 [95% CI, −21.8 to −7.3] mL/min). Nonindexed $eGFR_{cr\text{-}cys}$ was unbiased before (median bias, −6.0 [95% CI, −11.0 to 1.0] mL/min) and after surgery (−2.0 [95% CI, −8.8 to 4.9] mL/min). Findings were similar for indexed eGFR compared with indexed mGFR.

Limitations: Small, mostly white sample.

Conclusions: Changes in indexed and nonindexed GFRs may be discordant after bariatric surgery in adults because of decreases in BSA. Indexed and nonindexed $eGFR_{cr\text{-}cys}$ may be less biased than indexed or nonindexed $eGFR_{cr}$ or $eGFR_{cys}$ because of opposite biases in estimating mGFR.

Visual Abstract included

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The obesity epidemic continues to expand worldwide, now affecting ∼40% of US adults.[1] The prevalence of severe obesity (body mass index [BMI] ≥ 40 kg/m^2) has also increased from 5.7% in 2007 to 2008 to 7.7% in 2015 to 2016 in US adults, as has the number of bariatric surgery procedures performed in the United States (∼158,000 in 2011 to ∼228,000 in 2017).[2] Persons with severe obesity are at high risk for comorbid conditions, including chronic kidney disease (CKD) and end-stage kidney disease,[3] resulting in high levels of health care use and drug prescriptions.[4] Thus, it is highly important to evaluate glomerular filtration rate (GFR) accurately in this high-risk population, both for prognosticating risk and for safe and efficacious drug dosing.

There are several challenges to accurate GFR evaluation in patients with severe obesity and particularly in the setting of bariatric surgery.[5] First, commonly used GFR estimating equations such as the CKD Epidemiology Collaboration (CKD-EPI) equation and the Modification of Diet in Renal Disease (MDRD) Study equation were created using older data from cohorts when severe obesity was much less common than now.[6] Second, obesity is associated with both creatinine and cystatin C levels, independent of GFR.[7] Creatinine generation is directly related to muscle mass, and skeletal muscle decreases by 20% to 25% after bariatric surgery.[8] Cystatin C is associated with inflammation, which is common in patients with severe obesity. However, studies examining changes in inflammatory factors after bariatric surgery have been inconsistent, and it is unclear whether changes in cystatin C levels after bariatric surgery reflect changes in the generation or GFR.[7,9]

As a result, both estimated GFR based on creatinine level ($eGFR_{cr}$) and eGFR based on cystatin C level ($eGFR_{cys}$) may be biased after bariatric surgery. A study by Friedman et al[10] found that the combined creatinine-cystatin C–based eGFR ($eGFR_{cr\text{-}cys}$) using the CKD-EPI equation was more accurate than using either marker alone pre– and post–bariatric surgery. However, the reported accuracy estimates for $eGFR_{cr}$ and $eGFR_{cys}$ were much lower than what has been reported in other studies of obese patients.[5,10-13] Another study of patients after bariatric surgery suggested that $eGFR_{cys}$ may be the most useful.[9]

A particular concern in evaluating GFR after bariatric surgery is indexing of GFR for body surface area (BSA) because BSA changes substantially with large weight

PLAIN-LANGUAGE SUMMARY

Kidney function estimation is important for determining drug dosing and prognosis. In clinical practice, kidney function is estimated from glomerular filtration rate (GFR) using creatinine level and, less often, with cystatin C level. However, levels of these kidney markers can be influenced by changes in muscle and fat mass, which decrease substantially after bariatric surgery. In this study, we compared directly measured GFR with equations to estimate kidney function in patients with severe obesity before and after bariatric surgery. We found that equations using creatinine level overestimated kidney function after surgery, whereas an equation using both creatinine and cystatin C levels was the most accurate. These findings are important because an increasing number of patients are undergoing bariatric surgery and some drugs can have toxic effects if dosed inappropriately.

changes. Generally, measured GFR (mGFR) and eGFR are expressed indexed to 1.73 m^2 of BSA, with the rationale that GFR is associated with kidney mass, which in turn varies by body mass across mammalian species,[5,14,15] and indexing for BSA reduces variation in kidney function parameters among healthy individuals.[16,17] Indexing to BSA results in significantly lower mGFRs and eGFR in patients with severe obesity and whether BSA indexing is appropriate for patients with severe obesity and after bariatric surgery is controversial.[18] In this study, our main objective was to examine the performance of indexed and nonindexed eGFR using creatinine and/or cystatin C levels compared with indexed and nonindexed mGFRs before and after surgery.

METHODS

Study Population

A total of 44 adults at least 18 years of age with BMI ≥ 35 kg/m^2 undergoing evaluation for bariatric surgery at Geisinger's Center for Nutrition and Weight Management clinic were recruited and gave written informed consent for this study. The study was approved by the Geisinger Institutional Review Board (#2014-0293).

Exclusion criteria included allergy to iodine or contrast dye, pregnancy, $eGFR_{cr}$ < 30 mL/min/1.73 m^2, end-stage kidney disease, history of kidney transplant, current use of trimethoprim or cimetidine, multinodular goiter, Graves disease, autoimmune thyroiditis, cirrhosis, and active treatment for cancer. Of the 44 adults, 34 underwent bariatric surgery, 27 completed a 6-month follow-up visit, and 25 completed a 12-month follow-up visit. For these analyses, we included data from the 27 participants who completed at least 1 post–bariatric surgery research visit.

Measurement of GFR

Participants were instructed to eat a light breakfast the morning of their visit and then had 5 mL of iohexol (Omnipaque-300; GE Healthcare) administered intravenously over 30 seconds, followed by 10 mL of normal saline solution flush. Blood samples were drawn at approximately 10, 30, 240, and 300 minutes (only if eGFR was <60 mL/min/1.73 m^2), with exact times recorded, similar to a protocol used in the Multi-Ethnic Study of Atherosclerosis (MESA) Kidney study.[19] GFR was calculated using plasma iohexol clearance, using all time points in a 2-compartment model.

Laboratory Methods

Serum creatinine was measured at the Geisinger Medical Laboratory using the isotope-dilution mass spectrometry–traceable Roche enzymatic method (Roche Diagnostics) according to manufacturer specifications (interassay coefficient of variation, 1.7%). Iohexol and cystatin C were measured at the University of Minnesota, using thawed serum samples stored at −80 °C. Iohexol concentration was measured using high-performance liquid chromatography (coefficient of variation, 1.8% at 10.2 mg/dL and 2.0% at 42.6 mg/dL). Cystatin C was measured on the Roche COBAS 6000 chemistry analyzer (coefficient of variation, 4.3% at 0.75 mg/L and 3.2% at 3.83 mg/L). The assay for cystatin C is traceable to the international standard.[20] Previously published CKD-EPI estimating equations were used to estimate GFR using creatinine and cystatin C levels, alone or in combination.[6,21] We also estimated creatinine clearance using the Cockcroft-Gault (CG) equation, using actual body weight and "adjusted" body weight [0.4 × (actual body weight − ideal body weight) + ideal body weight].[22]

Other Variables of Interest

Weight, height, and waist circumference were measured during research visits using standardized methods. BSA was calculated using the DuBois equation.[23] Blood pressure was measured using the Omron 907XL after a 5-minute rest period, with an averaged value of 3 readings separated by 1-minute intervals. Hypertension was defined as taking at least 1 antihypertensive medication or having a study systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg. Diabetes was defined as taking at least 1 glucose-lowering agent, most recent hemoglobin A_{1c} level ≥ 6.5%, or having a fasting glucose level ≥ 126 mg/dL; diabetes was considered to be resolved if no longer meeting these criteria for diabetes diagnosis.[24] Electronic health record data were supplemented by patient interview and chart review to ascertain comorbid conditions and medications at each time point. During study visits, a timed 6-hour urine collection was performed, and 24-hour values for urinary sodium, albumin, urea nitrogen, and creatinine were estimated by multiplying values by 24/collection time.

Table 1. Characteristics Presurgery and Approximately 6 Months Postsurgery Among 27 Patients Who Had Bariatric Surgery

	Presurgery	~6 mo Postsurgery
Age, y	46.2 (10.8)	47.1 (10.8)
Female sex	18 (66.7%)	18 (66.7%)
Black race	1 (3.7%)	1 (3.7%)
Hypertension	16 (59.3%)	10 (37.0%)[a]
Diabetes	11 (40.7%)	3 (11.1%)[a]
Coronary artery disease	4 (14.8%)	4 (14.8%)
SBP, mm Hg	115.4 (15.5)	114.9 (15.1)
DBP, mm Hg	74.6 (9.5)	69.0 (9.2)[a]
Weight, kg	140.8 (28.4)	103.1 (21.9)[a]
BMI, kg/m^2	49.5 (9.4)	35.6 (6.6)[a]
Waist circumference, cm	138.8 (15.9)	114.4 (15.0)[a]
BSA, m^2	2.42 (0.27)	2.12 (0.25)[a]
mGFR, mL/min	117.3 (34.1)	108.2 (24.2)[a]
mGFR, mL/min/1.73 m^2	84.1 (22.0)	89.2 (19.9)
mGFR < 60 mL/min/1.73 m^2	3 (11.1%)	2 (7.4%)
Creatinine, mg/dL	0.89 (0.23)	0.78 (0.19)[a]
Cystatin C, mg/L	1.08 (0.32)	1.03 (0.25)
Glucose, mg/dL	124.7 (75.1)	94.6 (26.2)[a]
No. of BP medications	1.2 (1.6)	0.6 (1.0)[a]
ACEi or ARB	11 (41%)	5 (19%)[a]
Diuretic	7 (26%)	2 (7%)
Metformin	9 (33%)	2 (7%)[a]
Insulin	5 (19%)	1 (4%)
NSAIDs	3 (11%)	0 (0%)

Note: Values are reported as number (percent) for categorical variables and mean (standard deviation) for continuous variables. Conversion factors for units: creatinine in mg/dL to μmol/L, ×88.4; glucose in mg/dL to mmol/L, ×0.05551.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; BSA, body surface area; DBP, diastolic blood pressure mGFR, measured glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; SBP, systolic blood pressure.

[a]$P < 0.05$ when compared with presurgery value.

Statistical Analysis

Characteristics were summarized at each time point and differences between the postsurgery and baseline visits were evaluated using generalized estimating equations (clustered by individuals) for continuous variables and exact McNemar test for categorical variables. Performance of estimating equations was assessed pre- and postsurgery at 6- and 12-month visits. Bias was calculated as the median difference between eGFR and mGFR. Precision was reported as the interquartile range (IQR) of the bias. Accuracy was assessed by the percentage of values within 20% (P_{20}) and 30% (P_{30}) of mGFR. For analyses with nonindexed GFR as the reference, we "de-indexed" eGFR values by multiplying by current BSA/1.73 m^2. To better understand the influence of weight change on the performance of GFR estimating equations, we additionally conducted stratified analyses, above and below median weight change at 6 months. STATA/MP 15.1 (StataCorp LLC) was used for analyses. CIs were calculated using bootstrapping (2,000 replications) for bias, precision, P_{20}, and P_{30}. The significance of the differences between equations compared with $eGFR_{cr}$ was evaluated using signed rank test for bias and precision and exact McNemar test for P_{20} and P_{30}.

RESULTS

A total of 27 participants underwent research visits presurgery and approximately 6 months postsurgery, with 25 returning for a research visit approximately 12 months postsurgery. Median number of days from the time of bariatric surgery were −140 (IQR, −180 to −80), 193 (IQR, 182 to 217), and 376 (IQR, 351 to 384) for the baseline, 6-month, and 12-month visits. At the presurgery visit, mean age was 46.2 (standard deviation [SD], 10.8) years, mean BMI was 49.5 (SD, 9.4) kg/m^2, mean BSA was 2.42 (SD, 0.27) m^2, mean nonindexed mGFR was 117.3 (SD, 34.1) mL/min, and mean indexed mGFR was 84.1 (SD, 22.0) mL/min/1.73 m^2. Two-thirds were women, 59% had hypertension, 41% had diabetes, 15% had coronary artery disease, 11% had mGFRs < 60 mL/min/1.73 m^2, and 48% had albuminuria with albumin excretion ≥ 30 mg/d (Table 1). The most common bariatric surgery was Roux-en-Y gastric bypass (74%), followed by biliopancreatic diversion with duodenal switch (15%) and then laparoscopic sleeve gastrectomy (11%).

Changes After Bariatric Surgery

After 6 months, mean BMI decreased by −13.8 (95% CI, −15.9 to −11.8) kg/m^2, mean BSA decreased by −0.30 (95% CI, −0.33 to −0.27) m^2, nonindexed mGFR decreased by −9.2 (95% CI, −17.2 to −1.1) mL/min, and indexed GFR tended to increase by 5.1 (95% CI, −0.1 to 10.4) mL/min/1.73 m^2 (Fig 1). The proportion of patients with diabetes decreased from 44% to 11% at 6 months after surgery ($P = 0.002$) along with the proportion of patients with hypertension (59% to 37%; $P = 0.008$). There were also decreases in study visit glucose levels, diastolic blood pressures, numbers of antihypertensive medications, metformin use, and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use (Table 1). Serum cystatin C level was unchanged, whereas serum creatinine level decreased by 0.11 (95% CI, −0.15 to −0.06) mg/dL at 6 months. Estimated urinary creatinine excretion (−329; 95% CI, −461 to −197) mg/d decreased, but the decline in urinary albumin excretion was not significant (−38.1%; 95% CI, −64.4% to 7.6%). These changes remained consistent at the 12-month visit (Table S1).

Estimating Equation Performance Presurgery

Presurgery, median bias significantly differed between nonindexed $eGFR_{cr}$, $eGFR_{cys}$, and $eGFR_{cr\text{-}cys}$ ($P < 0.05$ for all comparisons; Table 2; Fig 2). There was significant underestimation of mGFR with nonindexed $eGFR_{cys}$ by a median of −12.1 (95% CI, −21.4 to −1.2) mL/min,

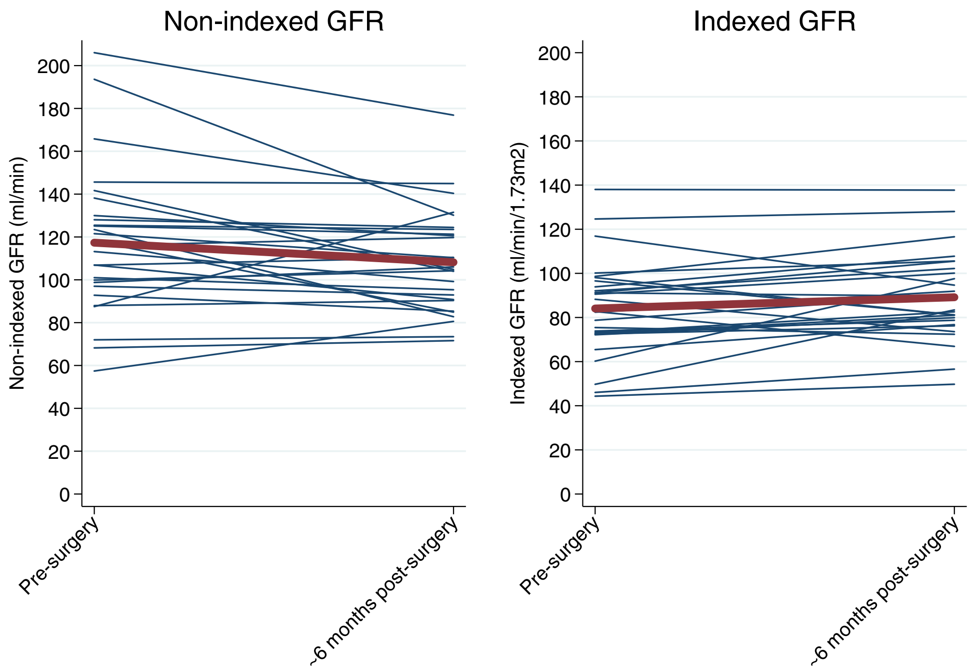

Figure 1. Changes in glomerular filtration rate (GFR) from presurgery to approximately 6 months postsurgery. The red line shows mean GFR presurgery and approximately 6 months postsurgery. Blue lines depict each individual's GFR values.

Table 2. Performance of eGFR and Estimated Creatinine Clearance Nonindexed and Indexed for BSA at Baseline and 6 Months After Surgery

	Nonindexed GFR		Indexed GFR		Nonindexed and Indexed GFR	
	Median Bias, mL/min	IQR of Bias, mL/min	Median Bias, mL/min/1.73 m^2	IQR of Bias, mL/min/1.73 m^2	P_{20}, %	P_{30}, %
Presurgery						
$eGFR_{cr}$ (reference)	5.0 (−4.3 to 11.6)	25.9 (12.5 to 39.1)	3.6 (−3.2 to 8.9)	20.6 (8.8 to 30.2)	78% (63% to 93%)	85% (70% to 96%)
$eGFR_{cys}$	−12.1 (−21.4 to −1.2)[a]	31.2 (19.3 to 47.8)[a]	−8.1 (−16.1 to −0.9)[a]	21.8 (13.7 to 35.8)[a]	59% (41% to 78%)	78% (59% to 93%)
$eGFR_{cr\text{-}cys}$	−6.0 (−11.0 to 1.0)[a]	21.9 (10.4 to 29.6)[a]	−4.0 (−8.0 to 0.7)[a]	16.2 (8.2 to 21.9)[a]	85% (70% to 96%)	93% (81% to 100%)
eCL_{cr}	72.9 (51.3 to 81.2)[a]	43.5 (23.5 to 89.5)[a]	52.9 (42.7 to 66.4)[a]	40.4 (19.7 to 57.7)[a]	7% (0% to 19%)[a]	19% (4% to 33%)[a]
eCL_{cr}, adjusted for IBW	8.9 (1.2 to 20.9)[a]	33.4 (14.6 to 50.6)[a]	6.5 (0.8 to 15.0)[a]	27.0 (11.0 to 37.5)[a]	67% (48% to 82%)	81% (67% to 96%)
~6 mo Postsurgery						
$eGFR_{cr}$ (reference)	8.8 (1.8 to 16.9)	26.3 (12.2 to 32.5)	8.4 (1.5 to 12.3)	21.6 (9.4 to 28.0)	70% (52% to 89%)	85% (70% to 96%)
$eGFR_{cys}$	−11.2 (−21.8 to −7.3)[a]	22.2 (11.2 to 32.0)[a]	−10.7 (−16.2 to −5.5)[a]	16.8 (10.2 to 26.5)[a]	59% (41% to 78%)	93% (81% to 100%)
$eGFR_{cr\text{-}cys}$	−2.0 (−8.8 to 4.9)[a]	21.2 (10.6 to 27.5)[a]	−1.9 (−7.6 to 3.8)[a]	16.4 (8.6 to 22.0)[a]	85% (70% to 96%)	93% (81% to 100%)
eCL_{cr}	44.7 (29.2 to 55.8)[a]	41.9 (23.6 to 65.6)[a]	37.8 (24.6 to 44.4)[a]	38.1 (18.1 to 47.6)[a]	22% (7% to 41%)[a]	37% (19% to 59%)[a]
eCL_{cr}, adjusted for IBW	12.1 (0.3 to 22.4)[a]	31.3 (18.0 to 48.7)[a]	9.4 (0.3 to 16.6)[a]	25.3 (15.3 to 40.3)[a]	67% (48% to 85%)	81% (67% to 96%)

Note: Bias calculated as eGFR − measured GFR. Accuracy calculated as P_{20} or P_{30}; results are the same for both indexed and nonindexed GFRs. We calculated eCL_{cr}, indexed to 1.73 m^2 using the Cockcroft-Gault equation, with actual body weight and "adjusted" body weight [0.4 × (actual body weight − IBW) + IBW].[22]
Abbreviations: BSA, body surface area; cr, creatinine; cys, cystatin C; eCL_{cr}, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; IBW, ideal body weight; IQR, interquartile range; $P_{20(30)}$, percent of values within 20% (30%) of measured glomerular filtration rate.
[a]$P < 0.05$ for comparison to $eGFR_{cr}$.

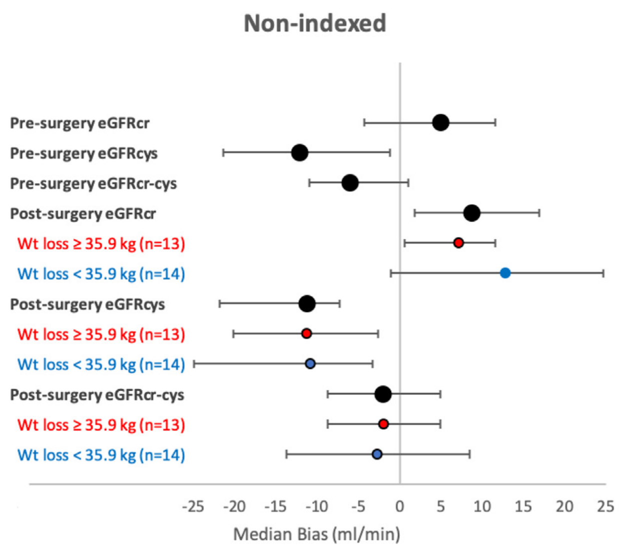

Figure 2. Median bias of estimating equations pre- and postsurgery. Median bias (estimated glomerular filtration rate [eGFR] − measured GFR) and 95% CIs are shown presurgery overall and then approximately 6 months postsurgery, overall and then stratified by weight (Wt) loss (above and below median 6-month weight loss). Abbreviations: BSA, body surface area; eGFRcr, eGFR based on creatinine level; eGFRcr-cys, eGFR based on creatinine and cystatin C levels; eGFRcys, eGFR based on cystatin C level.

whereas nonindexed $eGFR_{cr}$ and nonindexed $eGFR_{cr\text{-}cys}$ were unbiased (5.0; 95% CI, −4.3 to 11.6; and −6.0; 95% CI, −11.0 to 1.0 mL/min, respectively). Nonindexed $eGFR_{cr\text{-}cys}$ was the most precise (IQR of bias, 21.9 mL/min), followed by nonindexed $eGFR_{cr}$ (IQR of bias, 25.9 mL/min) and nonindexed $eGFR_{cys}$ (IQR of bias, 31.2 mL/min; Table 2). Results for indexed eGFR compared with indexed mGFR were qualitatively the same (Table 2; Fig 2). Point estimates for P_{20} were numerically highest with $eGFR_{cr\text{-}cys}$ (85%), followed by $eGFR_{cr}$ (78%) and then $eGFR_{cys}$ (59%), though P_{20} for $eGFR_{cr\text{-}cys}$ and $eGFR_{cys}$ were not significantly different from P_{20} for $eGFR_{cr}$. Point estimates for P_{30} were $eGFR_{cr\text{-}cys}$ (93%), $eGFR_{cys}$ (78%), and $eGFR_{cr}$ (85%). CG estimated creatinine clearance using actual body weight performed poorly presurgery (median bias, 72.9; 95% CI, 51.3-81.2 mL/min/1.73 m^2).

Estimating Equation Performance Postsurgery

At the 6-month postsurgery visit, nonindexed $eGFR_{cr\text{-}cys}$ was unbiased (−2.0; 95% CI, −8.8 to 4.9 mL/min), whereas nonindexed $eGFR_{cr}$ overestimated mGFR (median bias, 8.8; 95% CI, 1.8 to 16.9 mL/min) and nonindexed $eGFR_{cys}$ underestimated mGFR (median bias, −11.2; 95% CI, −21.8 to −7.3 mL/min; Table 2; Fig 2). Nonindexed $eGFR_{cr\text{-}cys}$ was the most precise (IQR of bias, 21.2 mL/min), followed by $eGFR_{cys}$ (IQR of bias, 22.2 mL/min) and $eGFR_{cr}$ (IQR of bias, 26.3 mL/min). Results for indexed eGFR compared with indexed mGFR were qualitatively the same (Table 2; Fig 2). Point estimates for P_{20} were numerically highest for $eGFR_{cr\text{-}cys}$ (85%), followed by $eGFR_{cr}$ (70%) and $eGFR_{cys}$ (59%), though P_{20} for $eGFR_{cr\text{-}cys}$ and $eGFR_{cys}$ were not significantly different from P_{20} for $eGFR_{cr}$. Point estimates for P_{30} were $eGFR_{cr\text{-}cys}$ (93%), $eGFR_{cys}$ (93%), and $eGFR_{cr}$ (85%). CG estimated creatinine clearance using actual body weight performed poorly postsurgery (median bias, 44.7; 95% CI, 29.2-55.8 mL/min).

Results at the 12-month postsurgery visit for the 25 patients with available data were largely consistent with the 6-month postsurgery visit. Again, nonindexed $eGFR_{cr\text{-}cys}$ was unbiased (0.4; 95% CI, −9.3 to 6.0 mL/min), whereas nonindexed $eGFR_{cr}$ overestimated mGFR (7.6; 95% CI, 2.2 to 19.6 mL/min) and nonindexed $eGFR_{cys}$ underestimated mGFR (−11.5; 95% CI, −17.0 to −2.1 mL/min; Table S2). Interestingly, the equation at the approximately 12-month postsurgery visit with the best precision was nonindexed $eGFR_{cys}$ (IQR of bias, 17.2 mL/min), followed by nonindexed $eGFR_{cr}$ (IQR of bias, 18.9 mL/min) and nonindexed $eGFR_{cr\text{-}cys}$ (IQR of bias, 22.9 mL/min). Despite the lower precision, $eGFR_{cr\text{-}cys}$ had the numerically highest P_{20} (88%), followed by $eGFR_{cys}$ (72%) and $eGFR_{cr}$ (60%).

Estimating Equation Performance 6-Months Postsurgery by Weight Loss Groups (above and below median weight loss)

Estimating equations performed fairly similarly for the lesser weight loss subgroup and the greater weight loss subgroup (Fig 2; Table S3). At the approximately 6-month postsurgery visit, nonindexed $eGFR_{cr\text{-}cys}$ was unbiased for both the lesser weight loss subgroup (−1.9; 95% CI, −8.8 to 4.9 mL/min) and the greater weight loss subgroup (−2.7; 95% CI, −13.7 to 8.5 mL/min), whereas nonindexed $eGFR_{cr}$ overestimated mGFR and nonindexed $eGFR_{cys}$ underestimated mGFR for both weight loss subgroups.

DISCUSSION

In this study of 27 patients with a wide range of baseline GFRs, mean nonindexed mGFR declined but there was a trend for mean indexed mGFR to increase because of the decrease in BSA. Performance of indexed and nonindexed CKD-EPI equations for $eGFR_{cr\text{-}cys}$ was better than that of $eGFR_{cr}$ and $eGFR_{cys}$ before and after surgery. Before surgery, both $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$ were unbiased, whereas $eGFR_{cys}$ tended to underestimate mGFR. After surgery, $eGFR_{cr\text{-}cys}$ was unbiased, whereas $eGFR_{cr}$ significantly overestimated mGFR and $eGFR_{cys}$ underestimated mGFR. $eGFR_{cr\text{-}cys}$ was most precise both before and approximately 6 months after bariatric surgery, and point estimates for P_{20} and P_{30} were numerically higher for $eGFR_{cr\text{-}cys}$ than for $eGFR_{cr}$ and $eGFR_{cys}$. These findings are important because the prevalence of severe obesity continues to increase worldwide and inaccurate GFR evaluation in the severely obese could result in errors in drug dosing.

Ongoing debate exists over the level of accuracy needed for estimating GFR in clinical care.[25-27] Cost, availability, and convenience must be considered when considering whether to use $eGFR_{cr}$, $eGFR_{cr\text{-}cys}$, or direct measurement of GFR. Our study suggests that the current clinical standard, $eGFR_{cr}$ using the CKD-EPI equation, is a reasonable option for estimating GFR in severely obese patients who have not undergone bariatric surgery. However, in the setting of bariatric surgery, clinicians should consider using $eGFR_{cr\text{-}cys}$ or direct measurement of GFR when more accurate estimation of GFR is required (ie, drugs excreted by the kidney with narrow therapeutic windows).[26,28,29] Results from other literature also suggest that $eGFR_{cr\text{-}cys}$ may be preferable in severely obese patients undergoing bariatric surgery, though we found overall higher accuracy,[10,30] which may reflect the rigor of our methods of measuring GFR in a research setting at a single site. Other studies of severely obese (non–bariatric surgery) individuals have shown either overestimation, underestimation, or minimal bias when using creatinine-based estimating equations.[10,11,13,31-33] Postsurgery, weight loss results in a decrease in creatinine production due to loss of muscle mass accompanying loss of fat mass. It is interesting that cystatin C levels tended to underestimate GFR both before and after bariatric surgery. Reasons for this underestimation both pre- and postsurgery are unclear but suggest a relative increase in cystatin C production after bariatric surgery, although other inflammatory markers such as serum C-reactive protein, interleukin 6, and tumor necrosis factor α have been shown to decrease it.[34]

In addition to bias related to GFR-independent changes in levels of filtration markers, GFR evaluation in severely obese individuals is challenging due to substantial changes in BSA accompanying surgical weight loss. Although indexing to BSA reduces variation in GFR in healthy individuals,[16,17] there is controversy whether indexing GFR to BSA for individuals with severe obesity undergoing bariatric surgery is appropriate.[18] Use of nonindexed GFR might be preferable for patients who have bariatric surgery because a decline in BSA leads to changes in opposite directions of indexed versus nonindexed mGFR and eGFR and could mask a decline in nonindexed mGFR. A recent study of 3,506 participants from 9 cohorts found that nonindexed $eGFR_{cr}$, $eGFR_{cys}$, $eGFR_{cr\text{-}cys}$ performed reasonably well, and using nonindexed eGFR should be considered when appropriate.[35] Using indexed GFR in patients with severe obesity could result in errors in drug dosing.[5] For example, indexed mGFR in our cohort was 28% lower before surgery and 17% lower 6 months after surgery than unindexed mGFR at these times.

Because many clinicians still use the CG equation for drug dosing, we also examined its performance, both unadjusted and using the "adjusted" body weight that is recommended for individuals for whom actual body weight exceeds ideal body weight by >30%.[36] The rationale for using CG in drug dosing is that most older drugs were studied using CG estimates and it is not indexed for BSA. However, there are several reasons to avoid using the CG equation. First, use of the unadjusted CG equation results in exceptionally large bias in severe obesity because weight is in the equation, and this bias persists even after marked weight loss after bariatric surgery. Second, the CG equation lacks face validity in this setting because it was derived from a study of 249 white men in 1973 when average BMI was much lower,[22] and it has not been re-expressed for use with serum creatinine values that are standardized to international reference values.[37] Third, several studies have shown that use of nonindexed $eGFR_{cr}$ equations results in better accuracy than the CG equation.[29,38-40]

There were several strengths of our study. We examined estimating equations using creatinine and cystatin C levels before and after bariatric surgery, compared to a gold standard reference. We also compared eGFR with indexed mGFR and nonindexed eGFR with mGFR because nonindexed eGFR should be used for assessing drug dosing in severely obese individuals.

The main limitation is that our research cohort consisted of a relatively small sample of mostly white individuals at a single institution, and only 3 participants had baseline mGFRs < 60 mL/min/1.73 m^2, which may have limited statistical power and generalizability of our findings. However, research participants in this study were fairly similar to the general bariatric surgery population at Geisinger with the exception of slightly higher BMI and lower eGFR (Table S4).[41] Larger studies including severely obese individuals pre– and post–bariatric surgery with mGFR could be helpful but may not be completed due to the burdensome nature of measuring GFR. Additional research is needed assessing the utility of other filtration markers unaffected by muscle or fat for improving GFR evaluation in this population.

In conclusion, changes in indexed and nonindexed GFR may be discordant after bariatric surgery in adults because of decreases in BSA. Indexed and nonindexed $eGFR_{cr\text{-}cys}$

may be less biased than indexed or nonindexed $eGFR_{cr}$ or $eGFR_{cys}$ because of opposite biases in estimating mGFR.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Characteristics at 12 month among 25 patients who completed all visits

Table S2: Performance of eGFR and eCL_{cr} indexed and nonindexed for BSA at 12 months after surgery

Table S3: Performance of eGFR indexed and nonindexed for BSA at 6 months, by weight loss ≥ 35.9 and <35.9 kg

Table S4: Characteristics compared with general bariatric surgery population at Geisinger

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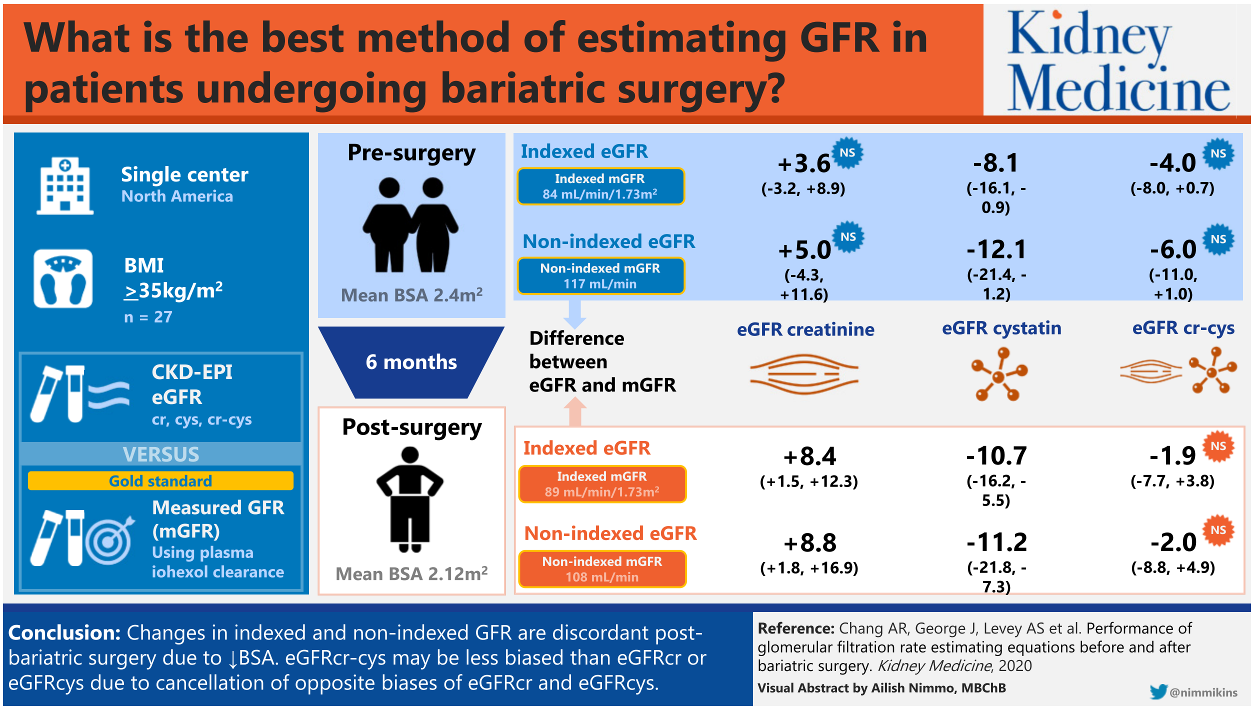
What is the best method of estimating GFR in patients undergoing bariatric surgery?
Kidney Medicine
Single center
North America
BMI
≥35kg/m²
n = 27
CKD-EPI
eGFR
cr, cys, cr-cys
VERSUS
Gold standard
Measured GFR
(mGFR)
Using plasma
iohexol clearance
Pre-surgery
Mean BSA 2.4m²
6 months
Post-surgery
Mean BSA 2.12m²
Indexed eGFR
Indexed mGFR
84 mL/min/1.73m²
+3.6 NS
(-3.2, +8.9)
-8.1
(-16.1, -0.9)
-4.0 NS
(-8.0, +0.7)
Non-indexed eGFR
Non-indexed mGFR
117 mL/min
+5.0 NS
(-4.3, +11.6)
-12.1
(-21.4, -1.2)
-6.0 NS
(-11.0, +1.0)
Difference between eGFR and mGFR
eGFR creatinine
eGFR cystatin
eGFR cr-cys
Indexed eGFR
Indexed mGFR
89 mL/min/1.73m²
+8.4
(+1.5, +12.3)
-10.7
(-16.2, -5.5)
-1.9 NS
(-7.7, +3.8)
Non-indexed eGFR
Non-indexed mGFR
108 mL/min
+8.8
(+1.8, +16.9)
-11.2
(-21.8, -7.3)
-2.0 NS
(-8.8, +4.9)
Conclusion: Changes in indexed and non-indexed GFR are discordant post-bariatric surgery due to ↓BSA. eGFRcr-cys may be less biased than eGFRcr or eGFRcys due to cancellation of opposite biases of eGFRcr and eGFRcys.
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