RESEARCH LETTER

β2-Microglobulin and β-Trace Protein in Patients Undergoing Bariatric Surgery: Non-GFR Determinants and Panel-estimated GFR Performance

To the Editor:

Bariatric surgery is associated with a decrease in serum creatinine concentrations, independent of the measured glomerular filtration rate (mGFR), due to reduced muscle mass, making the interpretation of changes in GFR estimated with the use of creatinine ($eGFR_{cr}$) challenging.[1,2] We previously reported that GFR estimated with the use of creatinine and cystatin C ($eGFR_{cr\text{-}cys}$) may be less biased than $eGFR_{cr}$ or GFR estimated with the use of cystatin C ($eGFR_{cys}$) in the setting of patients with severe obesity who underwent bariatric surgery.[2] Other filtration markers under investigation include serum β2-microglobulin (B2M) and β-trace protein (BTP) concentrations. Like cystatin C, they are low molecular weight proteins that are filtered by the glomeruli and degraded by the tubules; their serum concentrations are less influenced by age, sex, and race and are more strongly associated with death and cardiovascular disease than the serum creatinine concentration.[3] Some studies suggest associations of serum B2M and BTP concentrations with body composition and inflammation, similar to that of serum cystatin C concentrations.[4-7] Data are lacking on the effect of bariatric surgery on serum BTP and B2M concentrations and the performance of eGFR panels incorporating serum BTP and B2M concentrations (GFR estimated with the use of cystatin C-β2-microglobulin-β-trace protein [$eGFR_{cys\text{-}B2M\text{-}BTP}$] and GFR estimated with the use of creatinine and cystatin C-β2-microglobulin-β-trace protein [$eGFR_{cr\text{-}cys\text{-}B2M\text{-}BTP}$]).[3] Our aims were to evaluate the changes in serum BTP and B2M concentrations after bariatric surgery, independent of changes in mGFR, and to compare the performance of estimating equations (CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] 2009 $eGFR_{cr}$ and CKD-EPI 2012 $eGFR_{cr\text{-}cys}$, $eGFR_{cys}$) with CKD-EPI 2020 $eGFR_{cys\text{-}B2M\text{-}BTP}$ and $eGFR_{cr\text{-}cys\text{-}B2M\text{-}BTP}$ using regression calibration to account for measurement error.[8,9]

We prospectively measured the glomerular filtration rate (GFR) using the plasma clearance of iohexol (2-compartment model) in a study cohort of participants undergoing bariatric surgery. Evaluations were carried out at 2 separate visits before surgery and at 6 months and 12 months after surgery.[2] The serum samples were batched together and assayed at the University of Minnesota for creatinine, cystatin C, BTP, and B2M concentrations. This study was approved by the Geisinger Institutional Review Board (#2014-0293; Item S1).

We used data from all 4 visits to estimate the change in log-transformed filtration marker concentrations after bariatric surgery, adjusted for concurrent mGFR values with generalized estimating equations (exchangeable correlation structure) clustered by individual. We used regression calibration, a method that adjusts estimates from regression models for bias due to measurement error.[8] We used data from all 4 visits to evaluate the performance of indexed ($mL/min/1.73m^2$) and nonindexed (mL/min) eGFR compared with indexed and nonindexed mGFR. Nonindexed eGFR values were calculated by multiplying indexed eGFR values by body surface area/$1.73m^2$. We used generalized estimating equations to calculate the mean bias (difference between eGFR and mGFR). Precision was reported as the interquartile range of the difference. Accuracy was assessed by the percentage of eGFR within 20% or 30% of mGFR (P_{20} and P_{30}). Confidence intervals were calculated using bootstrapping (2,000 replications) for bias, interquartile range, P_{20}, and P_{30}. The significance of differences in P_{20} between estimating equations were evaluated using the exact McNemar test. The primary comparisons of interest were between

Table 1. GFR and Filtration Markers Before and After Bariatric Surgery

	Presurgery visit 1[a] (n=26)	Presurgery visit 2 (n=25)	Postsurgery visit 3 (n=27)	Postsurgery visit 4 (n=25)	Postsurgery change (unadjusted)	Postsurgery change in filtration marker adjusted for mGFR, %
Time relative to bariatric surgery, d	−136.2 (65.4)	−75.9 (63.2)	195.0 (26.7)	366.3 (55.2)	N/A	N/A
mGFR (mL/min)	118.1 (34.6)	116.1 (36.4)	108.2 (24.2)	105.4 (25.1)	−9.65 (−15.32, −3.97)	N/A
S_{cr}, mg/dL	0.88 (0.23)	0.90 (0.26)	0.78 (0.19)	0.82 (0.19)	−0.10 (−0.13, −0.07)	−13% (−20%, −5%)
S_{cys}, mg/L	1.06 (0.31)	1.10 (0.33)	1.03 (0.25)	1.05 (0.27)	−0.05 (−0.09, −0.02)	−7% (−15%, 2%)
S_{B2M}, mg/L	2.18 (0.65)	2.24 (0.66)	2.17 (0.55)	2.17 (0.54)	−0.06 (−0.13, 0.00)	−5% (−13%, 11%)
S_{BTP}, mg/L	0.63 (0.18)	0.62 (0.18)	0.56 (0.15)	0.59 (0.21)	−0.06 (−0.09, −0.03)	−13% (−22%, −3%)

Abbreviations: N/A, not applicable; mGFR, measured glomerular filtration rate; S_{B2M}, serum β2-microglobulin concentration; S_{BTP}, serum β-trace protein concentration; S_{cr} serum creatinine concentration; S_{cys} serum cystatin C concentration.
[a]There were only 26 patients included in the presurgery visit 1 because there were technical issues with mGFR measurement for 1 patient during visit 1. Changes in mGFR and filtration markers were estimated using generalized estimating equations, clustered by individuals, and regression calibration was used to account for measurement error. Filtration markers were log-transformed and the β-coefficients were back-transformed and are presented as % change.

Table 2. Performance of Nonindexed eGFR in Bariatric Surgery Patients

	Mean bias (mL/min)	IQR of bias (mL/min)	P_{20} (%)	P_{30} (%)
$eGFR_{cr}$	8.7 (2.9, 14.5)	23.9 (18.1, 29.7)	68% (57%, 79%)	84% (76%, 93%)
$eGFR_{cys}$	−11.5 (−18.7, −4.3)	25.5 (19.6, 31.4)	59% (46%, 73%)	85% (76%, 95%)
$eGFR_{cys\text{-}B2M\text{-}BTP}$	−11.0 (−17.2, −4.8)	20.6 (14.1, 27.0)	75% (64%, 86%)[a]	91% (84%, 98%)
$eGFR_{cr\text{-}cys}$	−3.2 (−8.1, 1.7)	23.6 (19.4, 27.8)	82% (73%, 90%)	91% (85%, 98%)
$eGFR_{cr\text{-}cys\text{-}B2M\text{-}BTP}$	−3.5 (−7.8, 0.9)	18.9 (15.5, 22.3)	86% (79%, 94%)[a]	95% (91%, 100%)

Note: Analyses included 103 measurements in 27 participants at 4 visits because bias, precision, and accuracy for the eGFR equations were similar before and after surgery. The nonindexed GFR was calculated by multiplying indexed GFR values by body surface area/1.73m^2. The bias was calculated as mean difference between eGFR and mGFR, and precision was reported as the IQR of the difference. The accuracy was assessed by the percentage of eGFR within 20% or 30% of mGFR. Bootstrapping (2,000 replications) was used to calculate 95% confidence intervals for each of the parameters.
Abbreviations: B2M, β2-microglobulin; BTP, β-trace protein; Cr, creatinine; cys, cystatin C; IQR, interquartile range; mGFR, measured glomerular filtration rate.
[a]P = 0.004 for the comparison of P_{20} between $eGFR_{cys\text{-}B2M\text{-}BTP}$ and $eGFR_{cys}$. P = 0.04 for the comparison of P_{20} between $eGFR_{cr\text{-}cys\text{-}B2M\text{-}BTP}$ and $eGFR_{cr\text{-}cys}$.

the 3-marker panel to $eGFR_{cys}$ and the 4-marker panel to $eGFR_{cr\text{-}cys}$ in P_{20}, as this metric reflects bias and precision. We considered a P value of <0.05 significant without correction for multiple comparisons. STATA/MP 15.1 (StataCorp LLC) was used for analyses.

The study population included 27 patients, including 18 (66.7%) women. At visit 1, the mean ± standard deviation age was 46.2 ±10.8 years, body mass index was 49.5 ± 9.4 kg/m^2, and body surface area was 2.42 ± 0.27 m^2 (Table S1). Following surgery, the mean (95% confidence interval) nonindexed mGFR declined by 9.65 (−15.32 to −3.97) mL/min. After adjustment for concurrent mGFR, serum creatinine and BTP concentrations decreased by −13% (from −20% to −5%) and −13% (from −22% to −3%), respectively, whereas 95% confidence intervals for serum cystatin C (−7%, [−15%, 2%]) and B2M (−5% [−13%, 11%]) concentrations included zero (Table 1).

The 3-marker panel was more accurate than $eGFR_{cys}$ (75% vs 59% of estimates within 20% of mGFR; $P = 0.004$), and the 4-marker panel was found to be more accurate than $eGFR_{cr\text{-}cys}$ (86% vs 82%; P = 0.04) (Table 2, Table S2). There were similar improvements in P_{20} for the 3- and 4-marker panels before and after surgery (Tables S3, S4).

Our results show that serum creatinine and β-trace protein concentrations declined more than serum cystatin C and B2M concentrations following bariatric surgery, independent of GFR. BTP is a 23-29 kDa glycoprotein enzyme generated in the central nervous system and other tissues that promotes the conversion of prostaglandin H2 to prostaglandin D and is used clinically as a marker for the leakage of cerebrospinal fluid into nasal secretions.[4] B2M is an 11.8 kDa protein found on the surface of all nucleated cells associated with major histocompatibility complex class I molecules and is used as a tumor marker in multiple myeloma.[6,10] Our study does not provide insight into the mechanisms of a decline in BTP after bariatric surgery. These findings should be replicated in other bariatric surgery cohorts with measured GFR and multiple filtration markers.

Our results suggest that the inclusion of B2M and BTP in estimating equations could potentially improve performance of GFR estimation in patients undergoing bariatric surgery. The limitations include small sample size, lack of diversity, and few participants with chronic kidney disease.

B2M and BTP may be useful endogenous filtration markers for GFR estimation in patients with severe obesity and after bariatric surgery. However, the $eGFR_{cr\text{-}cys}$ equation already performed well in our population. Further studies are necessary to confirm these findings.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Supplemental methods.

Table S1: Characteristics at pre-surgery and post-surgery visits.

Table S2: Performance of eGFR indexed for BSA in bariatric surgery patients.

Table S3: Performance of non-indexed eGFR before and after bariatric surgery.

Table S4: Performance of eGFR indexed for BSA before and after bariatric surgery.

ARTICLE INFORMATION

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