Glomerular filtration rate estimation in transgender and gender-diverse adults using gender-affirming hormone therapy: an exploratory cross-sectional study

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Assessment of kidney function with estimated glomerular filtration rate (eGFR) equations using serum concentrations of creatinine (Cr) or cystatin C (CysC) is commonly performed as part of routine clinical care. Most eGFR equations use sex/gender interchangeably; however, it is unclear whether sex assigned at birth (SAAB) or gender identity should be used in calculations, leading to uncertainty surrounding how best to estimate glomerular filtration rate (GFR) in transgender and gender-diverse (TGD) adults. TGD individuals (SAAB differs from gender identity) may use gender-affirming hormone therapy (GAHT), resulting in body composition changes.[1] In 1 meta-analysis, GAHT was associated with small but significant increases in serum creatinine in transgender men (TM; individuals assigned female sex at birth who identify as men) using testosterone therapy, but not in transgender women (TW; individuals assigned male sex at birth who identify as women) using estrogen therapy.[2] In a recent cohort study of transgender individuals using GAHT, estrogen use was associated with a decrease in CysC, whereas testosterone use was associated with an increase.[3] Whether these observations correspond to changes in true GFR or simply reflect non-GFR determinants of these serum biomarkers of GFR is unclear. These uncertainties, coupled with the critical importance of appropriate GFR evaluation to guide optimal clinical care prompted our exploratory cross-sectional assessment of eGFR equation performance using both SAAB and gender identity as the sex/gender covariate compared with measured GFR (mGFR) in healthy TGD adults using GAHT.

METHODS

Healthy TGD adults, aged ≥18 years, on GAHT for ≥3 months were recruited. We evaluated the bias, precision, and accuracy of Cr- and CysC-based eGFR equations using SAAB

and gender identity compared with mGFR. Seven eGFR equations (2021 Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]Cr,[S1] CKD-EPICysC,[S1] and CKD-EPICr-CysC,[S1] 2023 CKD-EPICysC,[S2] European Kidney Function Consortium [EKFC]Cr,[S3] EKFCCysC,[S4] and EKFCCr-CysC) were assessed in comparison to mGFR. Two eGFR values were obtained and compared with mGFR for each participant, 1 using SAAB and 1 using a binary gender identity. A full description of the methods is provided in Supplementary Materials.

RESULTS

Demographics

Participant characteristics are summarized in Table 1. mGFR values were similar between TM and TW ($P = 0.12$). Serum creatinine ($P = 0.042$) and CysC ($P = 0.026$) were higher in TM compared with TW. Urine albumin-to-creatinine ratio and protein-to-creatinine ratio were within normal ranges in all participants, with no differences observed between groups. Participants were normotensive, with similar blood pressure and body mass index observed between TM and TW. Route of

Table 1 | Participant demographics and gender-affirming hormone therapy characteristics

Variable	Transgender men (n = 10)[a]	Transgender women (n = 14)
Age, yr	23 (13) [19–39]	29 (6) [18–65]
Self-identified race, n		
East Asian	0	1
Latinx	1	0
Pacific Islander	0	1
White	9	8
Smoking status, n		
Current	4	6
Past	1	2
Never	5	6
Systolic blood pressure, mm Hg	116 (13) [105–129]	110 (19) [92–130]
Diastolic blood pressure, mm Hg	67 (7) [56–76]	66 (11) [53–82]
Weight, kg	79 (29) [53–103]	73 (15) [55–100]
Height, cm	165 (8) [160–174]	180 (11) [166–189][b]
Body mass index, kg/m^2	28 (9) [20–39]	22 (5) [17–32]
GAHT duration of exposure, mo	42 (49) [5–72]	23 (46) [6–114]
GAHT route of administration, n		
Oral	0	7
Non-oral	10	7
Progesterone use, n	0	9
Anti-androgen use, n		
Spironolactone	0	5
Cyproterone	0	1
Serum estradiol, pmol/l[c]	153 (152) [53–1103]	390 (1243) [115–3490][b]
Serum progesterone, nmol/l	1 (0.6) [0.5–2]	2 (4) [0.8–28][d]
Serum testosterone, nmol/l[c]	19 (12) [7–25]	0.5 (7) [0.2–29][b]
Serum creatinine, μmol/l[d]	81 (9) [77–84]	73 (12) [49–88][b]
Serum creatinine, mg/dl	0.9 (0.11) [0.7–1.1]	0.8 (0.14) [0.6–1.0][b]
Serum cystatin C, mg/l[d]	0.9 (0.16) [0.8–1.1]	0.8 (0.19) [0.5–1.0][b]
Urine albumin-to-creatinine ratio, mg/g[e]	25 (14) [10–82]	19 (24) [7–229]
Urine protein-to-creatinine ratio, mg/g[e]	50 (19) [40–74]	53 (19) [42–93]
24-h Urine sodium, mmol/d	257 (126) [156–411]	341 (101) [106–542][b]
mGFR, ml/min per 1.73 m^2	91 (14) [77–116]	99 (24) [76–128]

GAHT, gender-affirming hormone therapy; mGFR, measured glomerular filtration rate.
Values are reported as median (interquartile range) and [range] unless otherwise indicated.
[a]Three participants on testosterone therapy identified as nonbinary/gender nonconforming.
[b]$P < 0.05$ compared with transgender men.
[c]Target levels as per World Professional Association for Transgender Health Standards of Care for the Health of Transgender and Gender Diverse People, version 8. Serum estradiol, 367–734 pmol/l for transgender women; serum testosterone, 14–24 nmol/l for transgender men; <2 nmol/l for transgender women.
[d]Sex-specific reference ranges as per Alberta Precision Laboratories, except for cystatin C, which was as per University of Minnesota Advanced Research and Diagnostic Laboratory. Serum creatinine, 50–120 μmol/l for male and 40–100 μmol/l for female; serum cystatin C, 0.54–0.94 mg/l for male and 0.48–0.82 mg/l for female.
[e]Other reference ranges: urine albumin-to-creatinine ratio, <30 mg/g; urine protein-to-creatinine ratio, <150 mg/g.

GAHT administration (oral vs. non-oral; $P = 0.26$) or concurrent use of progesterone ($P = 0.61$) and/or spironolactone ($P = 0.80$) use was not associated with mGFR in TW. Serum testosterone levels were higher, and serum estradiol and progesterone were lower, in TM compared with TW.

eGFR equation performance

In TM, most eGFR equations had lower bias using SAAB compared with gender identity (Figure 1a, Supplementary Table S1, and Supplementary Figure S1). Differences in bias between eGFR were less pronounced with $eGFR_{CysC}$ compared with $eGFR_{Cr}$. Precision was suboptimal and similar regardless of covariate across all equations. Accuracy (P_{30}) was higher with use of SAAB compared with gender identity in $eGFR_{Cr}$ and $eGFR_{Cr\text{-}CysC}$ equations. Accuracy (P_{30}) was similar in all $eGFR_{Cys}$ irrespective of covariate, and results were comparable to sex/gender agnostic equations.

Unlike TM, bias was significantly lower when using gender identity compared with SAAB (Figure 1b, Supplementary Table S1, and Supplementary Figure S1) in TW. As in TM, $eGFR_{CysC}$ equations demonstrated the least pronounced differences in bias when using SAAB or gender identity. Precision was suboptimal across all equations and similar regardless of covariate. Accuracy (P_{30}) was higher with use of gender identity compared with SAAB in $eGFR_{Cr}$ and $eGFR_{Cr\text{-}CysC}$ equations. Accuracy (P_{30}) was similar in all $eGFR_{Cys}$ irrespective of covariate, and results were comparable to sex/gender agnostic equations.

DISCUSSION

In this exploratory study, we examined the bias, precision, and accuracy of eGFR equations compared with mGFR in healthy TGD adults using GAHT. Our key findings were as follows: (i) serum Cr and CysC were higher in TM compared

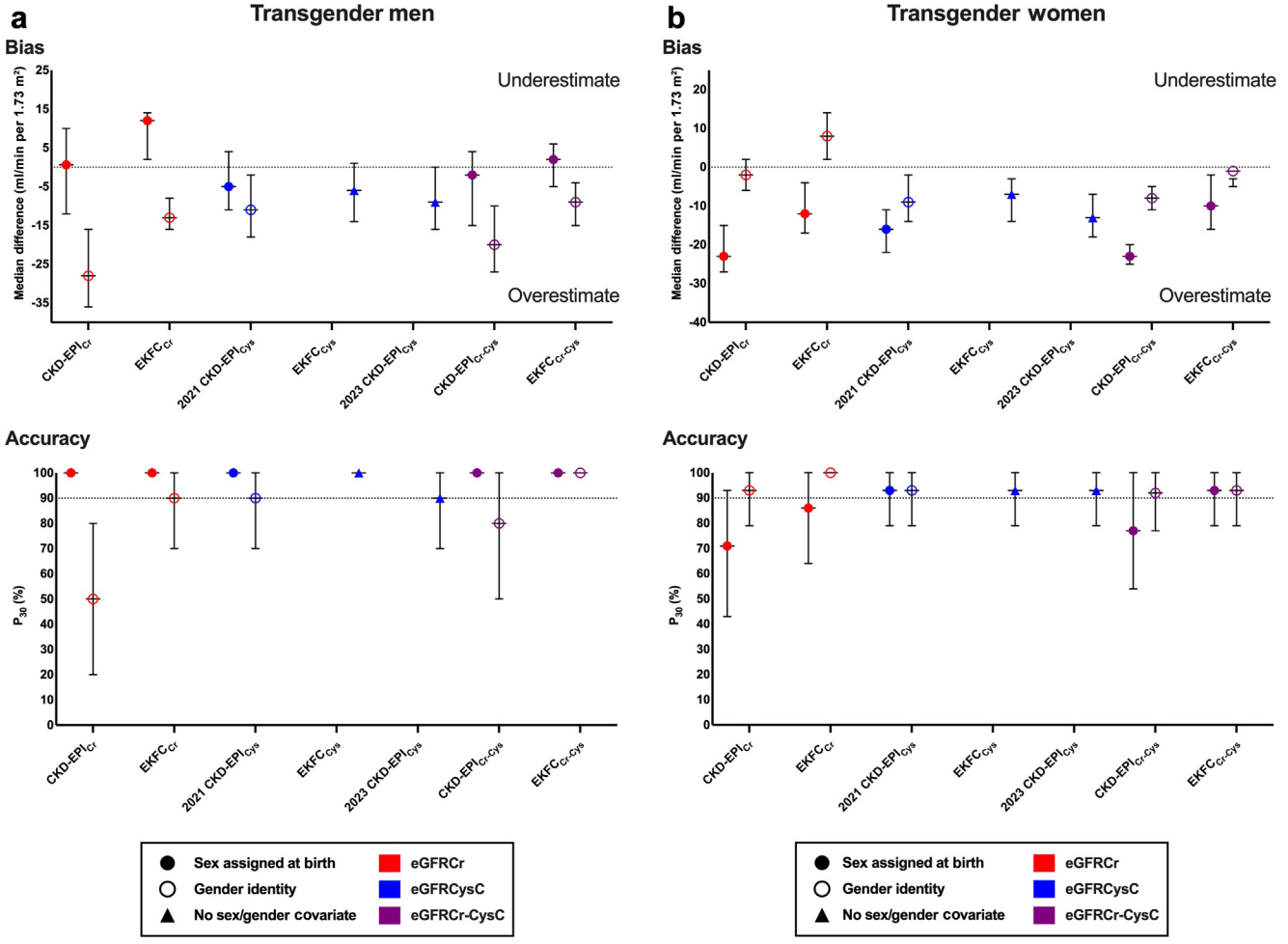

Figure 1 | Bias and accuracy in estimating glomerular filtration rate (eGFR) equations by covariate sex assigned at birth and gender identity in (a) transgender men and (b) transgender women. Bias (systematic error) was assessed as the median of the difference between measured glomerular filtration rate (mGFR) and eGFR (mGFR – eGFR). Red symbols represent creatinine (Cr)–based equations, and blue symbols represent cystatin C (CysC)–based equations. Purple symbols represent combined Cr- and CysC-based equations. A P_{30} ≥90% is desirable. I bars indicate 95% confidence intervals. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EKFC, European Kidney Function Consortium.

with TW, (ii) use of SAAB or gender identity influenced eGFR equation performance differently in TM compared with TW, and (iii) CysC-based, compared with Cr-based, eGFR equations may be less dependent on whether SAAB or gender identity is used to calculate eGFR.

Increased CysC concentrations in TM compared with TW are consistent with findings of a recent cohort of transgender individuals using GAHT.[3] Relative to creatinine, CysC may be less influenced by muscle mass and diet.[4] Although non-GFR determinants of CysC are less studied, inflammation, smoking, fat mass, sex, and GAHT appear to impact CysC levels.[4] Observed differences in CysC may be associated with the lean and fat mass changes observed with GAHT use[1] independent of GFR, although this remains speculative.

This work has limitations. Our small sample size, consisting solely of healthy and predominantly White adults, limits the generalizability of our results in a diversity of populations with established kidney disease and precludes definitive comparisons of eGFR equation performance. Because of the cross-sectional nature of this study, we cannot comment on any potential effect of GAHT on GFR.

Substantial differences in eGFR equation performance exist between TM and TW. However, the performance of CysC-based compared with Cr-based eGFR equations may be less dependent on whether SAAB or gender identity is used in the calculation. As outlined in greater detail elsewhere, laboratory information management systems do not currently incorporate both SAAB and gender identity in data collection.[5] When approaching important thresholds for clinical decision-making in TGD individuals using GAHT, a holistic approach taking into account both SAAB and gender identity in GFR estimation is essential,[6,7] and sex/gender agnostic equations[8,9] warrant consideration. The performance of eGFR equations may change with GAHT-associated alterations in body composition, particularly in the transition period.[1] At critical clinical decision points, measuring GFR in the TGD population using clearance of exogenous filtration markers may be important. These data may inform ongoing discussions on use of eGFR equations in TGD individuals.

DISCLOSURE

All the authors declared no competing interests.

DATA STATEMENT

Data supporting this study are not publicly available to protect the privacy of participants. Please contact the corresponding author with inquiries about deidentified data access.

Supplementary material is available online at www.kidney-international.org.

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