Advancing Kidney Health Equity
Influences of Gender-Affirming Hormone Therapy on Kidney Function

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In the United States, >800,000 transgender and gender diverse individuals (TGD) have CKD and face a disproportionate burden of morbidity and stark sociopolitical and health-related inequities when compared with their cisgender counterparts (1–4). Providing high-quality compassionate care to TGD individuals often involves the prescription of gender-affirming hormonal therapies (GAHT) (1,5). GAHT help align gender identity with gender expression for TGD individuals who have a gender identity that differs from the sex that was assigned to them at birth. Provision of GAHT has been associated with improved psychologic outcomes, including anxiety and depression, quality of life, and overall satisfaction (1). GAHT is designed to decrease endogenous sex hormones and sex characteristics associated with sex at birth in a way that minimizes risks (*e.g.*, deep vein thrombosis [DVT], cardiovascular risk) and achieves desired gender expression (1,5). In so doing, it may influence body composition (including muscle mass) and other biochemical parameters (2,6). Prior studies have demonstrated that testosterone-based masculinizing GAHT can increase lean mass by 3.9 kg in transgender men and estradiol-based feminizing GAHT (with or without antiandrogenic adjuncts) can decrease lean mass by 2.4 kg in transgender women (7). Serum creatinine, the most commonly used biomarker to estimate GFR, is derived from skeletal muscle and is influenced by non-GFR determinants (*i.e.*, diet, medications). Understanding if and how GAHT affects serum creatinine and other kidney function biomarkers is imperative for delivering optimal care to the growing TGD population.

In a systematic review and meta-analysis published in this issue of *CJASN*, Krupka and colleagues explore this topic by characterizing changes in serum creatinine, GFR, and biomarkers measuring kidney function among adult TGD individuals who initiated masculinizing and feminizing GAHT and whose data were published within the context of randomized controlled clinical trials, observational cohort studies and case series between 1998 and 2019 (8). Studies were included in the review if they reported serum creatinine, creatinine clearance, BUN, measured GFR, albuminuria, proteinuria, estimated GFR (eGFR), and/or serum cystatin C before GAHT initiation and after a follow-up period of 3, 6, and/or 12 months.

Consistent with prior (6) and subsequent studies (7), this meta-analysis found that among 488 transgender men, serum creatinine significantly increased at 12 months after GAHT initiation (0.15 ml/dl, 95% confidence interval, 0 to 0.29), with nonsignificant increases noted at 3 and 6 months. However, they found that among 520 transgender women, serum creatinine demonstrated variable, but nonsignificant declines at 3, 6, and 12 months. Only two studies reported 24-hour urine creatinine excretion; significant changes were again noted among transgender men, but not transgender women, at 4 and 12 months of follow-up. No significant changes in BUN were observed after GAHT therapy, although fewer participants (94 transgender men and 198 transgender women) contributed to this analysis. Notably, no studies examined the effect of GAHT on serum cystatin C, measured GFR, or eGFR performance, or on measures of albuminuria or proteinuria.

Although this seminal review provides important insights into the role of GAHT on serum creatinine, and thus considerations for interpreting changes in creatinine-based eGFR estimates after GAHT initiation, important limitations reduce the generalizability and applicability of its findings. First, the analysis lacked information regarding creatinine assay standardization and calibration across studies. Additionally, GAHT may have involved treatments of different doses, formulations (*e.g.*, intramuscular, transdermal), durations, and combinations (*e.g.*, spironolactone and assorted formulations of estradiol), thereby limiting associations or precise characterization of GAHT doses and creatinine changes. None of the studies included individuals who identify as nonbinary or otherwise gender diverse, who may microdose or use varied formulations of GAHT. Study participants were all adults with normal kidney function at baseline, with a mean baseline creatinine (SD) before GAHT of 0.77 mg/dl (0.49) among transgender men and 0.93 mg/dl (0.58) among transgender women. The effect of GAHT on serum creatinine among TGD individuals with CKD and among pediatric TGD individuals could thus not be examined. Most included studies were of poor or fair quality due to the nonexistent sample-size calculations, poor cohort generalizability, and substantial loss to follow-up. Finally, a lack of individual-level data alongside the small

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number of studies limited investigators' capacity to identify associations between patient-level factors including age, achieved sex hormone levels, and baseline serum creatinine and serum creatinine change.

This analysis raises several important questions that should be the focus of subsequent investigations, most notably the mechanism through which GAHT is associated with changes in serum creatinine and whether GAHT independently affects kidney function. Some have postulated that changes in serum creatinine reflect changes in body composition due to GAHT. However, the possible effects of GAHT on BP, incident diabetes, major adverse cardiovascular events, body mass index, and volume status remain poorly understood and may independently affect GFR and thus serum creatinine levels (9,10). Understanding the effect of GAHT on cystatin C, other biomarkers of kidney function, and measured GFR will be instrumental to answering these questions. Further studies are also needed to explore the association between sex hormones on kidney function and cardiovascular risks, particularly among individuals with CKD, for whom age, etiology of kidney disease (*i.e.*, nephrotic syndrome affecting sex hormone binding protein levels), severity of kidney disease, and degree of proteinuria may modify these effects (6). Finally, future studies must consider the influence of stress from marginalization/discrimination, and well-documented disparities in access to care between gender minority and cisgender individuals, on kidney disease risk and morbidity among TGD individuals (4).

Until new data are available, clinical teams involved in TGD care (*e.g.*, primary care providers, nephrologists, and endocrinologists) must consider the most comprehensive methods for assessing kidney function among TGD individuals to minimize potential contributions of inaccurate eGFR values to health care disparities. eGFR is limited by imprecision in the setting of AKI, and creatinine-based eGFR values are influenced by several conditions that affect tubular secretion of creatinine and/or creatinine production (*e.g.*, high-protein diets, medications, pregnancy, obesity, conditions such as rhabdomyolysis or liver disease, and sepsis). Just as our community has carefully reckoned with the inclusion of race, a sociopolitical and nonbiologic variable, in kidney function estimation, Krupka and colleagues pose an opportunity to reconsider the way in which sex is embedded into clinical decision making involving kidney health, especially in the context of individuals receiving GAHT. Although a multiplier associated with "female sex" improved precision of creatinine-based estimates of kidney function in prior studies that suggested lower serum and urine creatinine measures in female versus male participants (11), this must be interpreted within the context of gender-affirming care and a recognition and reconsideration of what "sex" represents in such clinical algorithms. To avoid exacerbating disparities in care delivery and outcomes among TGD individuals, the nephrology community must address the potential harms of imprecise eGFR, which may result in inappropriate GAHT dosing, delays in nephrology care, inappropriate withholding of kidney and cardiovascular disease modifying therapies (*e.g.*, sodium-glucose cotransporter-2 inhibitors, renin-angiotensin-aldosterone system inhibition), and delayed referrals for kidney transplant evaluation. One key step involves universally implementing standard practices for obtaining sexual orientation and gender identity information from patients in an affirming, inclusive manner. Sexual orientation and gender identity data collection, which may include careful history taking regarding GAHT, is essential to ensuring equitable, comprehensive care delivery for all patients, alongside investigations of long-term kidney outcomes associated with sex hormones and other gender-affirming therapies. TGD affirming care also requires appropriate interpretation of laboratory test results (*e.g.*, hemoglobin, serum creatinine, eGFRcr). In situations of clinical ambiguity regarding the use of a female sex coefficient for GFR estimation, clinicians should estimate GFR more precisely using additional tools (*e.g.*, 24-hour urine creatinine and urea measurements).

Finally, as we seek greater precision to estimate kidney function and predict kidney failure risk, we must include data from populations with a range of sexual and gender identities (including individuals on GAHT) to ensure measure optimization and validation. These efforts must complement future initiatives that carefully characterize and combat kidney risk factors uniquely affecting TGD individuals, and their complex underpinnings, which often relate to disproportionate structural inequities (*e.g.*, in housing, insurance and health care access). As the nephrology community continues to strive for kidney health equity, we must advocate for gender-affirming care practices and a continued pursuit of evidence-based practice in all aspects of our care, including kidney function estimation.

Disclosures

D. Mohottige reports employment with Duke University Medical Center; having an ownership interest in non–health care entities; receiving honoraria from MedScape (Continuing Medical Education); serving in an advisory or leadership role for the National Kidney Foundation (NKF) Health Equity Committee and the NKF Transplant Advisory Committee Member; and having other interests or relationships as an NKF Health Equity Advisory Committee member, NKF Transplant Advisory Committee Member, and with the National Institutes of Health Social Determinants of Health PhenX Workgroup. D.S. Tuot reports receiving honoraria from American Society of Nephrology and serving in an advisory or leadership role for the NKF Bay Area Medical Advisory Board and the BluePath Health eConsult Workgroup.

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Author Contributions

D.S. Tuot conceptualized the study and provided supervision, D. Mohottige wrote the original draft, and D.S. Tuot reviewed and edited the manuscript.

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