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Emerging Evidence

The Association Between Testosterone and Vascular Function in Reproductive-Aged Females With Chronic Kidney Disease

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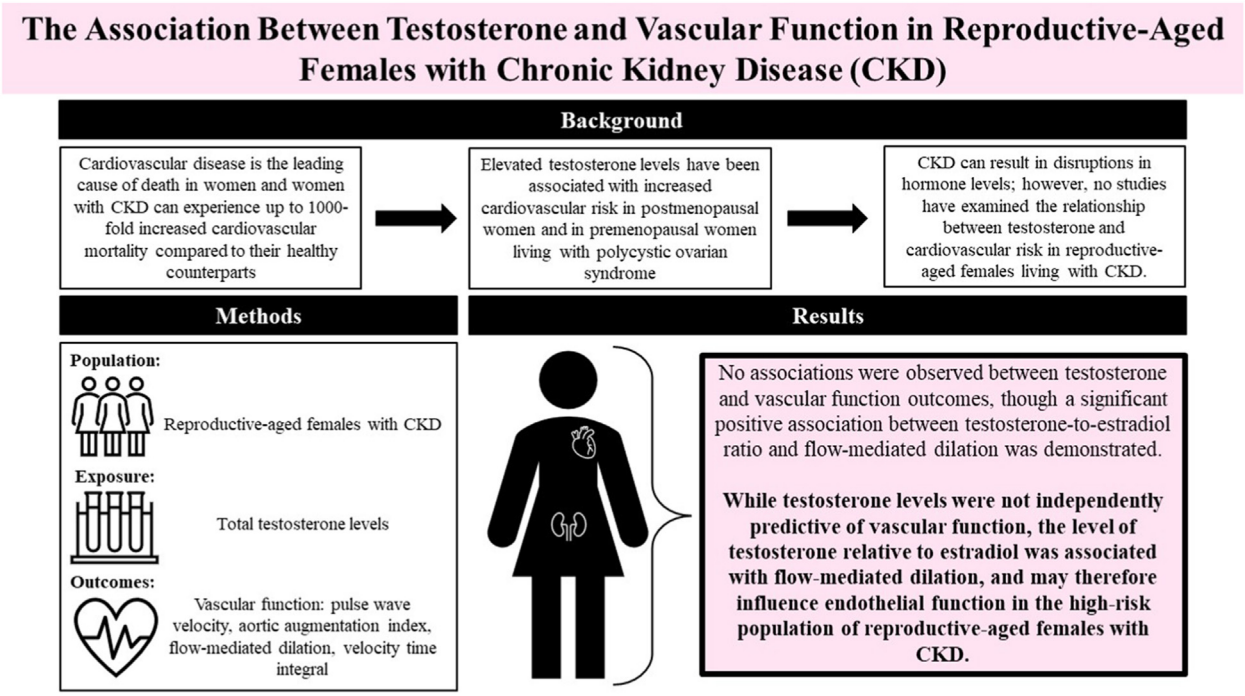

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ABSTRACT

Cardiovascular disease is the leading cause of death in women, and women with chronic kidney disease (CKD) experience especially elevated risk. This study examined the association between testosterone and vascular function in 61 reproductive-aged females with CKD. Testosterone levels and measures of vascular function were assessed, including pulse wave velocity, aortic augmentation, flow-mediated dilation (FMD), and velocity time integral. Multivariable linear regression analyses assessed the relationship between testosterone and each measure of vascular function. No associations were observed between testosterone and vascular function outcomes, although a significant positive association between testosterone-to-estradiol ratio and FMD was demonstrated. Although testosterone levels were not independently predictive of vascular function, the level of testosterone relative to estradiol was associated with FMD and may therefore influence endothelial function in the high-risk population of reproductive-aged female patients with CKD.

RÉSUMÉ

Alors que les maladies cardiovasculaires sont la cause principale de décès chez les femmes, les femmes atteintes d'une maladie rénale chronique (MRC) sont exposées à un risque particulièrement élevé. La présente étude vise à examiner l'association entre la testostérone et la fonction vasculaire de 61 femmes en âge de procréer atteintes d'une MCV. Nous avons évalué les concentrations de testostérone et les mesures de la fonction vasculaire, soit la vélocité de l'onde de pouls, l'augmentation de l'aorte, la dilatation médiée par le flux (DMF) et l'intégrale temps-vitesse. Les analyses multivariées de régression linéaire ont permis d'évaluer la relation entre la testostérone et chacune des mesures de la fonction vasculaire. Aucune association n'a été observée entre la testostérone et les résultats de la fonction vasculaire, bien qu'une association positive significative entre le ratio testostérone/œstradiol et la DMF ait été démontrée. Bien que les concentrations de testostérone n'étaient pas indépendamment prédictives de la fonction vasculaire, les concentrations de la testostérone relativement à l'œstradiol ont été associées à la DMF et peuvent par conséquent influencer la fonction endothéliale au sein de la population exposée à un risque élevé composée de patientes en âge de procréer atteintes d'une MRC.

Lay Summary

Heart disease and stroke are the leading causes of death in women, and women with chronic kidney disease (CKD) are at especially high risk. This study examined the relationship between testosterone and blood vessel function in females of child-bearing age with CKD. Although testosterone was not directly linked to blood vessel function, higher testosterone relative to estrogen was associated with better function and may affect the risk of heart disease in these younger females with CKD.

Cardiovascular disease (CVD) is the leading cause of death in women[1] and a multitude of sex- and gender-specific cardiovascular risk factors play an important role in development of CVD [2] Cardiovascular disease is especially critical for women living with chronic kidney disease (CKD), who experience up to 1000-fold increased cardiovascular mortality compared with their healthy counterparts.[3] CKD affects 1 in 8 women on a global scale,[4] highlighting the urgency for cardiovascular risk reduction in this important population.

Testosterone is a sex hormone that has been associated with cardiovascular risk, in part through direct effects on vascular function.[5] Most commonly studied in men, testosterone may also affect cardiovascular risk in females. Specifically, in postmenopausal women, elevated testosterone has been linked with increased risk for atherosclerosis and incident CVD.[6,7] Furthermore, in premenopausal women living with polycystic ovarian syndrome (PCOS), characterized by hyperandrogenism, higher levels of testosterone have been associated with a disadvantageous cardiovascular risk profile and vascular dysfunction, thereby increasing the risk for cardiovascular events.[8] To explain this relationship, a variety of mechanisms of effect have been described.[9]

CKD often results in disruptions within the hypothalamic-pituitary-gonadal axis, evidenced by reduced levels of gonadal hormones, such as estradiol and testosterone.[10] In male patients living with CKD, there are conflicting data describing the relationship between testosterone and CVD, with some studies reporting increased cardiovascular risk with higher levels of testosterone, others reporting decreased cardiovascular risk, and yet others reporting no association between testosterone levels and CVD.[11] To our knowledge, no studies have examined the relationship between testosterone levels and cardiovascular risk in the high-risk population of reproductive-aged females living with CKD. This study aimed to determine the association between testosterone levels and measures of vascular function, validated cardiovascular risk predictors, in reproductive-aged females living with CKD.

Materials and Methods

Study population

Female patients aged 18 to 51 years living with CKD were recruited from nephrology clinics in Calgary, Alberta. CKD was defined as markers of kidney damage or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 for > 3 months,[12] and confirmation of CKD diagnosis was obtained through participants' nephrologists. Exclusion criteria included pregnancy, breastfeeding, current use of menopausal hormone therapy or gender affirming hormone therapy, or factors that would affect ovarian function such as polycystic ovarian syndrome, premature ovarian insufficiency, ovarian malignancy, gonadotoxic chemotherapy, surgical oophorectomy, or previous radiation to the pelvis.

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See page 537 for disclosure information.

Study protocol

The study was approved by the Conjoint Health Research Ethics Board at the University of Calgary (REB18-0642). Participants underwent 12-hour fasts and abstained from caffeine, alcohol, smoking, and vasoactive medications for 4 hours before the study. All menstruating participants were studied between day 1 and 7 of their menstrual cycle, which was determined by self-report. Participants treated with dialysis were studied on the day following their dialysis sessions. All data collection was completed during a single visit by a consistent research nurse in a temperature-controlled room. All vascular function measurements were taken in supine position after 10 minutes of rest.

Data collection

Baseline data, including demographic and medical history, were collected. A physical examination included height, weight, abdominal circumference, and blood pressure measured per Hypertension Canada guidelines.[13] Baseline laboratory measurements included serum creatinine, eGFR, and urine albumin-to-creatinine ratio (ACR) as well as serum estradiol and progesterone. The lower limit of detection for estradiol and progesterone levels were < 19 pmol/L and < 0.2 nmol/L respectively, and for the purposes of our analyses, levels that were reported as such were assigned a conservative value of 18 pmol/L and 0.19 nmol/L, correspondingly.

The exposure was defined as the total testosterone level of the participant measured with a Cobas 8000 assay (Roche Diagnostics, Indianapolis, Indiana, USA) and competitive chemiluminescent technology, and analyzed by Alberta Precision Laboratories (Calgary, Alberta, Canada). The lower limit of detection for testosterone levels was < 0.2 nmol/L, and for the purposes of our analyses, testosterone levels that were reported as such were assigned a conservative value of 0.19 nmol/L.

Four measures of vascular function were assessed. Carotid-femoral pulse wave velocity (PWV) and aortic augmentation index (AIx) were collected, employing a standardized protocol[14] via noninvasive applanation tonometry, using a piezoresistive pressure transducer (Millar Instruments, Houston, TX) and commercially available acquisition and analysis software (SphygmoCor version 8, AtCor Medical, Sydney, Australia). Using standardized protocols,[15] endothelial function was measured through right brachial artery flow-mediated dilation (FMD), imaged with Doppler ultrasound (Philips, Amsterdam, The Netherlands). Velocity time integral (VTI) was also measured through Doppler images of the first beat of reactive hyperemia. All endothelial function measurements were analyzed using the Brachial Analyzer for Research version 5 (Medical Imaging Applications, Coralville, IA).

Statistical analyses

Baseline characteristics are reported as median (first quartile [Q1], third quartile [Q3]) for continuous data and as numerical values (percentages) for categorical data. Testosterone levels were stratified by CKD treated with or without dialysis and compared using a Mann-Whitney U test. The association between testosterone level and each outcome was examined independently using multivariable linear regression. Furthermore, associations between the testosterone-to-estradiol (TE) ratio and testosterone-to-progesterone (TP) ratio and each outcome were assessed independently using multivariable linear regression; this analysis was not preplanned and was added at reviewer request; therefore, these results should be treated as hypothesis generating. Linear regression assumptions were assessed using an augmented component plus residual plot, Breusch-Pagan test for heteroskedasticity and Shapiro-Wilk W test. Participant age was considered as a covariate, including assessment for effect modification using an interaction term. Sensitivity analyses were completed for each model, in which participants treated with dialysis were removed. All analyses were completed using STATA statistical software (version 17.0, StataCorp LLC, College Station, TX) with a significance level of 0.05.

Reporting of previous literature

Whereas "female" refers to an individual's biological sex, and "woman" refers to an individual's gender identity, these terms have historically been used interchangeably in the literature, making it difficult to firmly ascertain health implications that are specific to either females or women. Within this article, to avoid any assumptions, we have used the terminology from each cited study; however, it is likely that some of the summarized literature has reported findings on "women" from samples of female participants. The authors would like to acknowledge that not all women are biologically female, and not all females identify as women.

Results

Participant characteristics

Participant characteristics are presented in Table 1. In total, 61 participants were included. The median age of the sample was 35 years, ranging from 19 to 51 years, and the majority self-identified as White. More than two-thirds of participants reported menstruation, in keeping with previously reported prevalence estimates of menstruation in CKD.[10,16] Most participants had hypertension, although the median blood pressure was in the normal range. The participants had a wide range of eGFR (13 to 138 mL/min/1.73 m^2), although most were classified as G1 or G2 CKD, and participant ACRs varied between 0.26 and 806.4 mg/mmol. Fifteen percent of participants were treated with dialysis, the majority of those with hemodialysis.

Testosterone and vascular function measurements

The median total testosterone level was 0.5 nmol/L (Q1: 0.3 nmol/L, Q3: 0.9 nmol/L), although measurements ranged widely from < 0.2 nmol/L to 3.4 nmol/L (Fig. 1). There were no statistically significant differences in median testosterone levels when stratified by CKD treated with or without dialysis ($P = 0.74$) (Fig. 1). Further, there was no significant association between testosterone levels and eGFR ($R^2 = 0.03$, $P = 0.21$) (Fig. 2). Median measurements for PWV, AIx, FMD, and VTI were 7.5 m/s (Q1: 6.5m/s, Q3: 8.3 m/s), 22.5% (Q1: 15%, Q3: 31%), 8.2% (Q1: 5.4%, Q3: 11.4%), and 115.0 cm (Q1: 90.0 cm, Q3: 154.0 cm), respectively. Median outcome measurements in the study population did not appear to be markedly different from previously reported measurements in the general population,[17-22] although it is

Table 1. Participant characteristics

	n = 61
Age (y)	35 (32, 44)
Self-identified ethnicity	
White	38 (62%)
Southeast Asian	7 (11%)
Filipina	4 (7%)
Indigenous	3 (5%)
Latina	3 (5%)
South Asian	3 (5%)
Black	2 (3%)
East Asian	1 (2%)
BMI (kg/m^2)	24.7 (21.3, 30.5)
Abdominal circumference (cm)	80.0 (71.0, 96.0)
SBP (mm Hg)	126 (115.5, 135.5)
DBP (mm Hg)	76 (67.5, 81.5)
Cardiovascular comorbidities	
Hypertension	34 (56%)
Diabetes	9 (15%)
Dyslipidemia	13 (21%)
Stroke	3 (5%)
Myocardial infarction	2 (3%)
Coronary artery disease	1 (2%)
Cardiovascular medications	
ACE inhibitor	13 (21%)
ARB	11 (18%)
Diuretic	7 (11%)
β-blocker	4 (7%)
Calcium channel blocker	3 (5%)
α-blocker	1 (2%)
Total cholesterol (mmol/L)	4.4 (3.7, 5.0)
Hemoglobin A1c (%)	5.5 (5.1, 5.8)
Albumin (g/L)	36 (35, 39)
CKD classification	
G1 (eGFR ≥ 90 mL/min/1.73 m^2)	26 (43%)
G2 (eGFR 60-89 mL/min/1.73 m^2)	14 (23%)
G3 (eGFR 30-59 mL/min/1.73 m^2)	9 (15%)
G4 (eGFR 15-29 mL/min/1.73 m^2)	2 (3%)
G5 (eGFR < 15 mL/min/1.73 m^2)	1 (2%)
ACR classification	
A1 (ACR < 3 mg/mmol)	28 (46%)
A2 (ACR 3-30 mg/mmol)	12 (20%)
A3 (ACR > 30 mg/mmol)	14 (23%)
CKD treated with dialysis	9 (15%)
Hemodialysis	8 (13%)
Peritoneal dialysis	1 (2%)
Menstrual status	
Menstruation present	41 (67%)
Menstruation absent	20 (33%)
Hormonal contraception	
IUD	14 (23%)
Oral contraceptive	10 (16%)
Vaginal ring	2 (3%)
Injectable	2 (3%)
Estradiol (pmol/L)	168 (81, 424)
Progesterone (nmol/L)	0.8 (0.6, 1.5)

Data are median (first quartile, third quartile) or number of participants (percentage).

ACE, angiotensin converting enzyme; ACR, albumin to creatinine ratio; ARB, angiotensin II receptor blocker; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IUD, intrauterine device; SBP, systolic blood pressure.

critical to recognize that standardized clinical reference ranges do not exist for any of these outcomes.

Association between testosterone and vascular function

Age was identified as a confounder, and, as such, the associations among total testosterone level, TE and TP ratios, and each measure of vascular function (PWV, AIx, FMD, VTI) was estimated independently and adjusted for age. No statistically significant relationships were identified between testosterone and PWV ($ß_1 = 0.18$, $P = 0.52$), AIx ($ß_1 = 0.42$, $P = 0.86$), FMD ($ß_1 = -0.11$, $P = 0.89$), or VTI ($ß_1 = 4.02$, $P = 0.63$) (Fig. 3). No significant associations were demonstrated between the TE ratio and PWV ($ß_1 = -0.02$, $P = 0.24$), AIx ($ß_1 = -0.12$, $P = 0.46$), or VTI ($ß_1 = 0.70$, $P = 0.20$) (Fig. 4). However, a statistically significant association was identified between the TE ratio and FMD ($ß_1 = -0.19$, $P < 0.001$) (Fig. 4). No significant associations between the TP ratio and PWV ($ß_1 = 0.18$, $P = 0.14$), AIx ($ß_1 = 0.44$, $P = 0.67$), FMD ($ß_1 = 0.54$, $P = 0.13$), or VTI ($ß_1 = -1.35$, $P = 0.71$) were apparent (Fig. 5). A sensitivity analysis, in which participants treated with dialysis were excluded from the analyses, did not result in any change of the relationships. Linear regression assumptions for each model can be found in Supplemental Table S1.

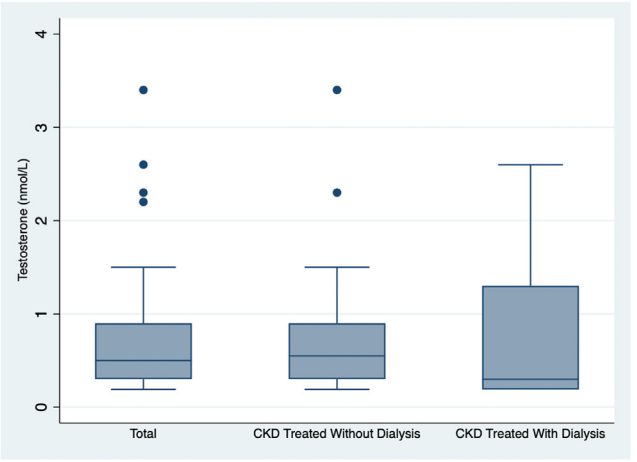

Figure 1. Testosterone levels in study sample, stratified by CKD treated with or without dialysis. CKD, chronic kidney disease.

Discussion

This study aimed to determine the association between testosterone levels and vascular function in reproductive-aged females living with CKD. The key findings were that there was no apparent relationship between testosterone and vascular function, as measured by PWV, AIx, FMD, and VTI and that there was a significant positive relationship between the TE ratio and vascular endothelial function as measured by FMD. These finding suggest that although testosterone levels do not appear to be independently predictive of vascular function, the level of testosterone relative to estradiol may influence endothelial function and predict future cardiovascular risk in this population.

CVD is the leading cause of death among individuals living with CKD, who experience up to a 1000-fold increase in cardiovascular mortality.[3] Furthermore, the CKD-associated risk of cardiovascular mortality is demonstrated earlier in the CKD course in women compared with men,[23] and the relative risk of cardiovascular mortality appears to be higher in reproductive-aged women.[3] This highlights the critical

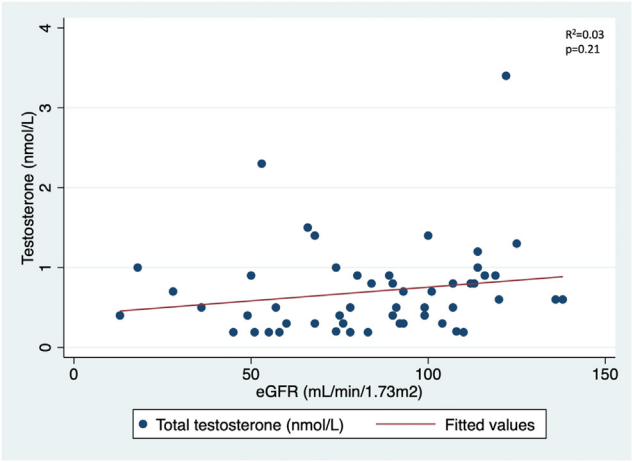

Figure 2. Relationship between testosterone level and eGFR in study sample. eGFR, estimated glomerular filtration rate.

importance of identifying cardiovascular risk factors in this high-risk population.

Testosterone is a sex hormone that contributes to sexual well-being in females,[24] although direct effects on cardiovascular health have also been described.[9] Although endogenous testosterone appears to have a positive effect on male cardiovascular health in a concentration-dependent fashion,[24] it is less clear what the cardiovascular implications of testosterone are in females. Studies in females with PCOS, who often have hyperandrogenism, demonstrate a relationship between increased testosterone levels and a poorer cardiovascular profile.[8] Further, increased testosterone has also been linked to CVD and cardiovascular risk factors in postmenopausal females.[6,7,25] To our knowledge, the relationship between testosterone and cardiovascular risk has not been examined specifically in reproductive-aged females, although 2 studies that have included premenopausal females in the study population suggest that high levels of testosterone—and perhaps low levels as well—are linked to cardiovascular risk, including in premenopausal females.[26,27] In our study, no concentration-dependent relationship was demonstrated between testosterone level and vascular function in females living with CKD. However, this relationship may exist in males with CKD,[11] and the mechanism of this sex difference may result from differences in cellular responses to testosterone. Specifically, similar to males, androgen receptors (ARs) for testosterone are expressed in vascular endothelial cells in females, although whereas activation of ARs in male endothelial cells results in angiogenesis and vascular repair, this effect is not demonstrated in females.[28,29]

Although no independent relationship between testosterone level and vascular function was demonstrated in our

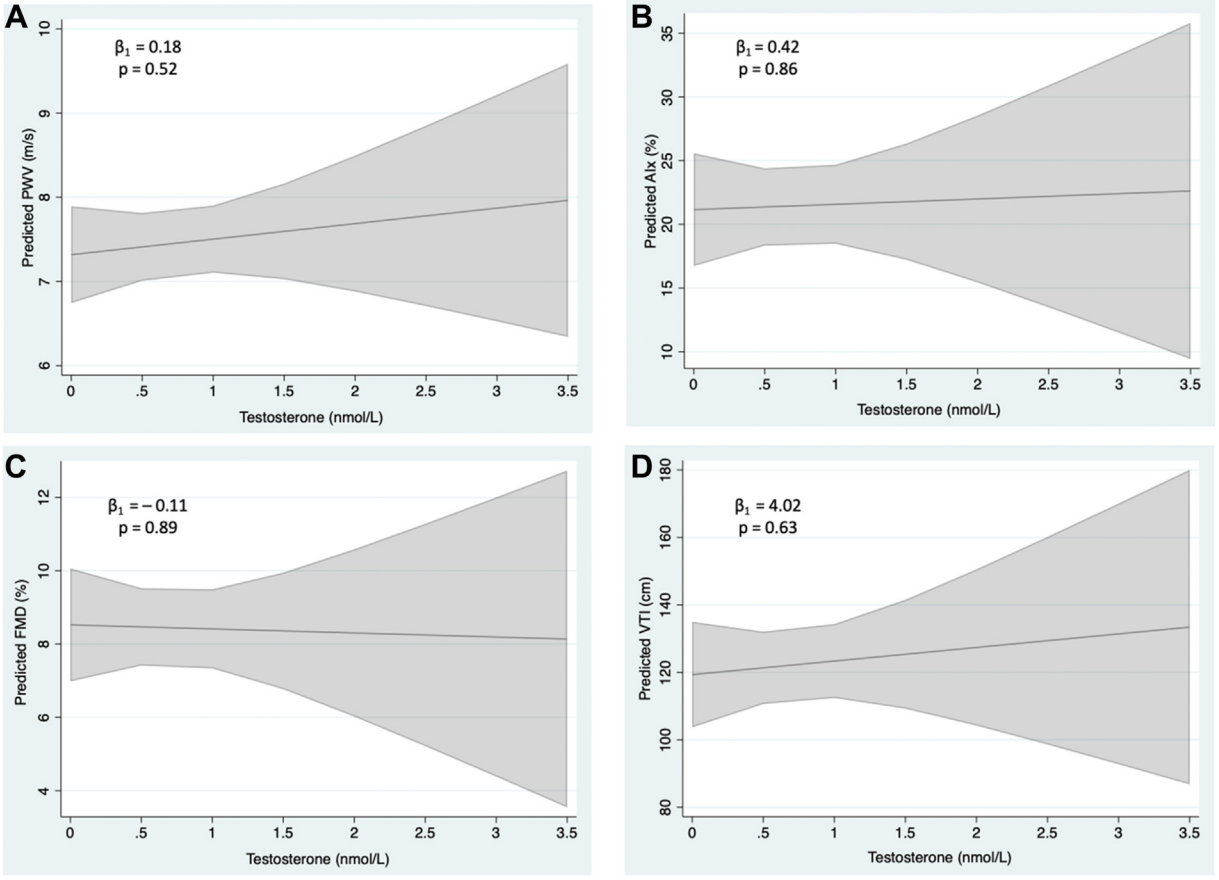

Figure 3. The association between testosterone level and predicted (**A**) PWV, (**B**) AIx, (**C**) FMD, and (**D**) VTI, adjusted for age with 95% confidence band. AIx, aortic augmentation index; FMD, flow-mediated dilation; PWV, pulse wave velocity; VTI, velocity time integral.

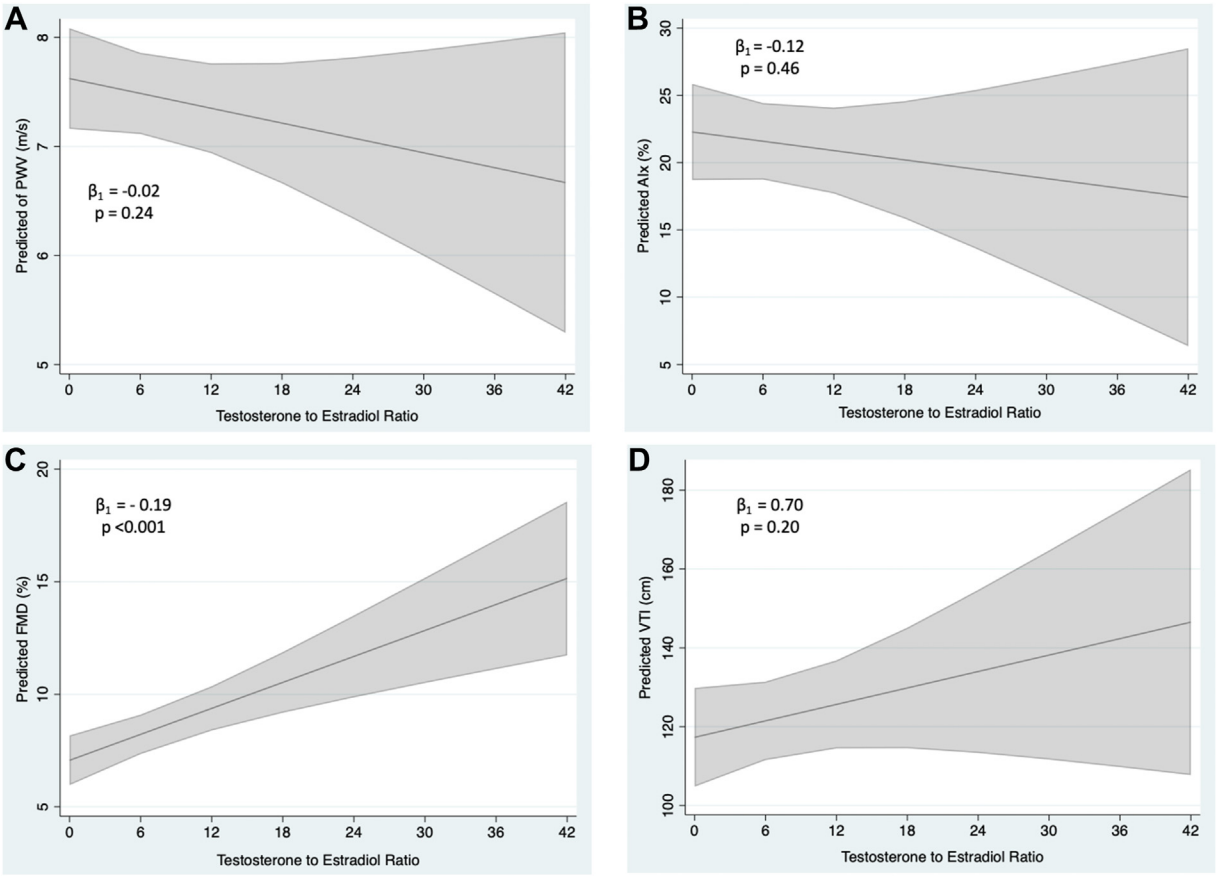

Figure 4. The association between testosterone-to-estradiol ratio and predicted (**A**) PWV, (**B**) AIx, (**C**) FMD, and (**D**) VTI, adjusted for age with 95% confidence band. AIx, aorta augmentation index, FMD, flow-mediated dilation; PWV, pulse wave velocity; VTI, velocity time integral.

study sample, an independent relationship between TE ratio and FMD was demonstrated in post hoc analyses. This finding suggests that higher levels of testosterone relative to estradiol are associated with improved endothelial function in reproductive-aged females living with CKD. This aligns with literature that suggests that both estradiol and testosterone play important roles in regulating endothelial function and vasodilation through estrogen and androgen receptor activation of endothelial nitric oxide (NO) synthase and resultant increase of NO.[30,31] The role of testosterone in females (and also estradiol in males) on vascular health is less well understood, however, and therefore the vascular implications of the balance of these hormones remains less clear. In females with CKD, estradiol has long been regarded as protective against progression of kidney disease[32,33] as well as cardiovascular risk,[11,34] although—interestingly—both markedly low and high levels of estradiol have been associated with cardiovascular disease burden.[35,36] This raises an important question as to whether the relationship between the TE ratio and endothelial function is primarily driven by an altered estradiol level as opposed to a relatively increased testosterone level. Although both hormones likely play an important role in vascular health, further research is necessary to elucidate the specific mechanisms linking the TE ratio and the endothelium in this population.

The levels of total testosterone measured in our study participants were comparable with levels expected in reproductive-aged females in the general population,[37] highlighting that although females with CKD often have a disrupted hypothalamic-pituitary-gonadal axis,[10] testosterone levels appear to be unaffected. This finding itself may help to explain why no relationship was demonstrated between testosterone and vascular function, as it is possible that the relationship in females may only be apparent in the extremes of testosterone levels, as suggested by Benn and colleagues,[26] as well as the PCOS literature.[8] Further, females living with CKD have exceptionally elevated cardiovascular risk caused by multiple factors,[38] all of which have potential to mask the effect of less influential factors.

Strengths and limitations

This study had multiple strengths; it is the first to address the relationship between testosterone and CVD in females living with CKD, a population with very high cardiovascular risk. Also, we used standardized protocols for outcome measures and collected study data at consistent time points related to CKD treatment (ie, dialysis) and menstruation to limit data variability related to these factors. In addition, the study cohort was diverse in terms of age, CKD classification, and

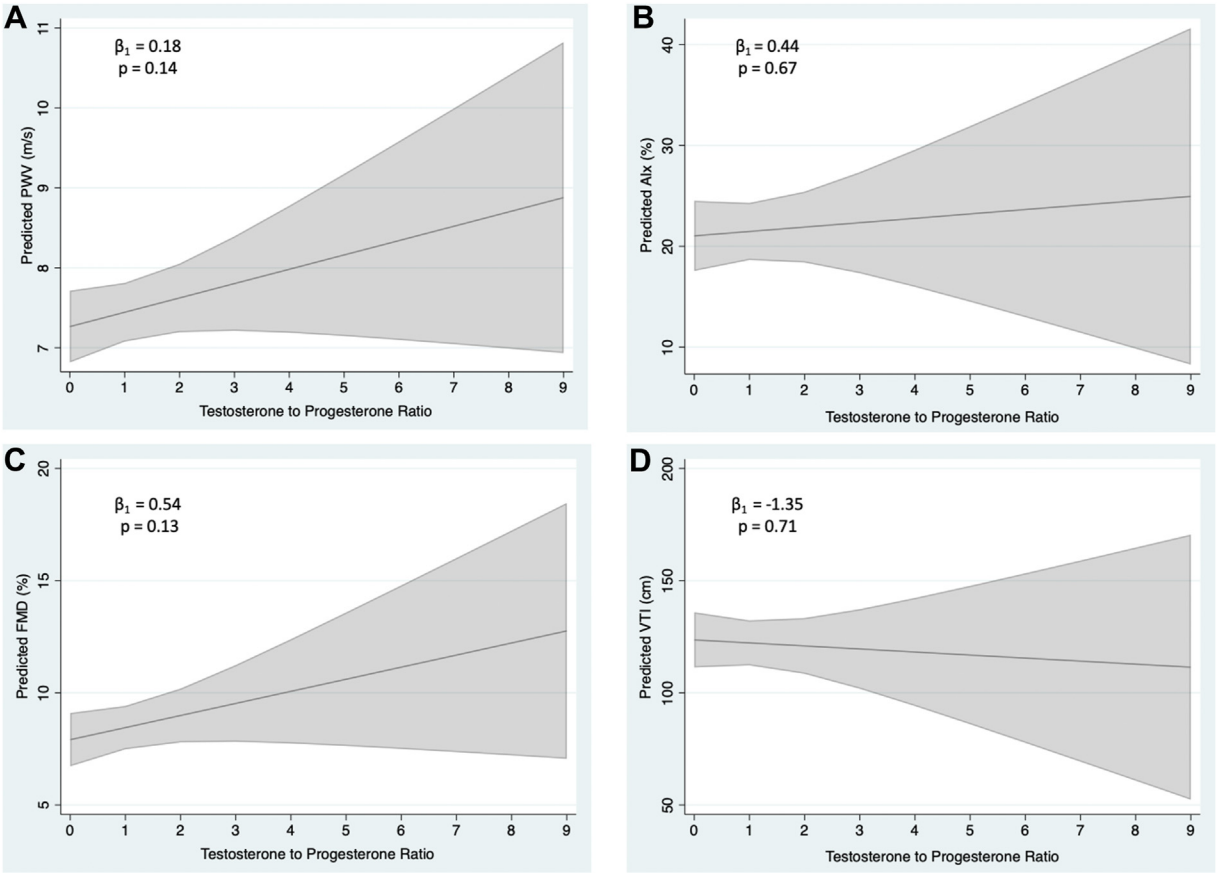

Figure 5. The association between testosterone-to-progesterone ratio and predicted (**A**) PWV, (**B**) AIx, (**C**) FMD, and (**D**) VTI, adjusted for age with 95% confidence band. AIx, aortic augmentation index; FMD, flow-mediated dilation; PWV, pulse wave velocity; VTI, velocity time integral.

self-identified ethnicity, all of which strengthen the generalizability of the study findings; however, we recognize that generalizability was restricted by the single-centre study design that was conducted in an urban setting, using volunteer sampling. In this context, it is likely that there is reduced representation of rural- and remote-dwelling participants and that the generalizability outside of this single-centre is unknown. There are also other important limitations. This was a cross-sectional study; therefore, we were not able to infer causality. In addition, the study design did not include a healthy control group; hence, no direct comparisons of outcomes or associations can be assessed between those with CKD and the general population. Further, the small sample size restricted inclusion of other potential covariates in our analysis, and the results should be interpreted with caution. Finally, our study sample had a high prevalence of hypertension, which has the potential to confound the relationship examined. However, the prevalence of hypertension in individuals living with CKD is estimated between 60% and 90%,[39] which limited our ability to address this in our exclusion criteria.

Conclusions

Overall, this study demonstrated no independent association between testosterone level and vascular function in reproductive-aged females living with CKD; however, a positive association between TE ratio and FMD was identified. Females living with CKD are at very high risk for cardiovascular mortality,[3] and although testosterone has been postulated as a direct mediator of vascular health,[9] it does not appear to be a biomarker of cardiovascular risk in this population. The balance between testosterone and estradiol, however, may be related to endothelial function, highlighting that further research is warranted to identify and characterize sex hormone-specific cardiovascular risk predictors in females living with CKD to optimize cardiovascular risk reduction in this important population.

Ethics Statement

The reported research has adhered to all relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent forms have been obtained for this article.

Funding Sources

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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