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Endogenous sex steroid hormones and measures of chronic kidney disease in a nationally representative sample of men

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Abstract

Context—Sex steroid hormones may play a role in the pathogenesis of chronic kidney disease (CKD).

Objective—To determine whether sex steroid hormone concentrations are associated with kidney function or kidney damage in men in the general US population. We hypothesized that lower serum testosterone and estradiol concentrations are associated with CKD.

Design, Patients and Measurements—Serum sex steroid hormones were measured by electrochemiluminescence immunoassays for 1470 men who attended the morning session of Phase I of the Third National Health and Nutrition Examination Survey (NHANES III). We used two measures of CKD, estimated glomerular filtration rate (eGFR) < 60mL/min/1.73m^2 calculated using serum creatinine or cystatin C levels and the abbreviated Modification of Diet in Renal Disease Study formulae and urinary albumin to creatinine ratio (UACR) ≥ 17 mg/g.

Results—Mean free testosterone concentration was higher in men with an eGFR < 60mL/min/1.73m^2 than in men with a higher eGFR. In multivariable adjusted models, the odds of an eGFR < 60mL/min/1.73m^2 or UACR ≥ 17 mg/g did not differ across tertiles of hormones with the exception of free estradiol; those in the highest vs. lowest tertile had an elevated odds of decreased eGFR (OR: 3.04, 95% CI (1.22, 7.57); p-trend=0.02).

Conclusions—In a nationally representative sample of US adult men, higher free estradiol concentration was significantly associated with an eGFR < 60mL/min/1.73m^2 as assessed by serum creatinine or cystatin C even after multivariable adjustment. These findings are in contrast to the hypothesis that estrogens may protect against CKD, though reverse causation cannot be ruled out. Longitudinal investigation of the role of estrogens in kidney hemodynamics, function, and pathophysiology is warranted.

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Introduction

An estimated 26.3 million individuals in the United States have chronic kidney disease (CKD), and of these, the majority suffer from mild to moderate kidney dysfunction.1 The major risk factors for CKD include diabetes, hypertension, obesity, older age and smoking, 2–4 however our understanding of the pathophysiology of CKD is yet incomplete. Due to the population burden of CKD and its sequelae, increasing focus has been placed on understanding the pathways and mechanisms leading to CKD.

Sex steroid hormones may play a role in the development of CKD, as they affect sodium handling and renal hemodynamics, and may be a contributory factor in the more pronounced rates of kidney decline, age-related kidney disease and end stage renal disease observed in men versus women.5, 6 Animal studies have shown higher endogenous testosterone to be detrimental to overall kidney function and vasculature, and that lower levels are protective against hypertension.5, 7, 8 In contrast, studies in humans (males) have found low levels of circulating testosterone to be associated with hypertension and elevated serum cholesterol and glucose9, as well as with diabetes.10 Endogenous estrogens are believed to protect the kidneys and the vascular wall against damage in both men and women in human and animal studies.11, 12 Sex steroid hormones may also mediate the effect of some of the risk factors (e.g. smoking) for CKD. Elucidation of the effect of sex steroid hormones on the development of CKD is further complicated by reverse causation; that is, men with CKD have been found to have disturbances in sex steroid hormone levels. More specifically, total and free testosterone concentrations are reduced while total plasma estrogen levels are elevated, and sex hormone binding globulin (SHBG) levels are normal.13

The relation between sex steroid hormones and kidney disease has not been well explored in epidemiological studies. The purpose of the current investigation was to determine whether sex steroid hormone concentrations are associated with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or a urinary albumin creatinine ratio ≥ 17 mg/g, both indicators of CKD, in men in the general US population. We hypothesized that lower serum testosterone and estradiol concentrations are associated with worse kidney function and a high prevalence of kidney damage.

Methods

Study population

Between 1988 and 1994, the National Center for Health Statistics conducted the Third National Health and Nutrition Examination Survey (NHANES III).14 This cross-sectional survey used a multistage stratified, clustered probability sample of the US civilian non-institutionalized population. Mexican-Americans, non-Hispanic blacks, and the elderly were oversampled to allow more precise estimates for these subgroups. Subjects participated in an interview, an extensive physical examination, and provided blood and urine samples

NHANES III was conducted in two phases; 1988–1991 and 1991–1994. Unbiased national estimates of health and nutrition characteristics can be independently produced for each phase. Within each phase, subjects were randomly assigned to participate in either the morning or afternoon/evening examination session. In total, 7,772 men age 20 years or older were interviewed and had a physical examination in Phase I of NHANES III. Of these, 1,998 participated in the morning session of Phase I. Morning session participants were chosen for this study to reduce extraneous variation due to diurnal production of hormones. Stored serum samples were available for 1,470 of these men, including 674 non-Hispanic whites, 363 non-Hispanic blacks, 376 Mexican-Americans, and 57 participants of other race/ethnicity.

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Weight, height, bioelectrical impedance analysis resistance, systolic and diastolic blood pressures were measured and 24-hour dietary recalls were performed during the examination. Cigarette smoking and medication use were assessed by interview. Serum cholesterol (calculated low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides), urinary albumin and creatinine, serum albumin and creatinine, and serum C-reactive protein (CRP), were measured as previously described.15–17 Detailed information regarding the data collection in the NHANES III is available elsewhere.17

Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, self-report of a diagnosis of hypertension or use anti-hypertensive medications. Hypertension medication use included antihypertensives, diuretics, calcium channel blockers, beta blockers, alpha blockers, and ACE inhibitors. Diabetes was defined as having a fasting plasma glucose ≥ 126 mg/dL, or of having been told by a doctor that they had diabetes.

Hormone measurements

The specific sex steroid hormones assessed were selected for the following reasons: 1) testosterone is the primary male androgen; 2) estradiol is the primary estrogen in men; and 3) SHBG is the primary carrier of testosterone and estradiol in the peripheral circulation, and testosterone and estradiol concentrations corrected to SHBG and albumin (a non-specific binder of sex hormones) provide good estimates of free testosterone and estradiol, respectively.18, 19 In addition, previous literature points to the relative relation between sex steroid hormones rather than individual hormones themselves, as being relevant to renal hemodynamics.5 Thus, we also evaluated the molar ratio of estradiol to testosterone.

Blood was drawn after an overnight fast for participants in the morning sample. After centrifugation, the serum was aliquotted and stored at −70° C. In 2005, stored samples for hormone measurements were shipped on dry ice directly from the National Center for Health Statistics' main serum repository in Atlanta, GA, to Children's Hospital Boston, MA for analysis.

Serum concentrations of total testosterone, estradiol, and SHBG were measured by competitive electrochemiluminescence immunoassays on the 2010 Elecsys autoanalyzer (Roche Diagnostics, Indianapolis, IN). Samples were tested in a random order, and laboratory technicians were blinded to the identity and characteristics of the participants. The lowest detection limit of the assays was 0.07 nmol/L for testosterone, and 18 pmol/L for estradiol. The coefficients of variation for quality control specimens (pooled plasma with known concentrations) included during the analyses of the NHANES III specimens were as follows: testosterone, 5.9 and 5.8% at 8.7 and 19.1 nmol/L; estradiol, 6.5 and 6.7% at 377.0 and 1740.4 pmol/L; and SHBG, 5.3 and 5.9% at 5.3 and 16.6 nmol/L. Quality control samples with a mean estradiol concentration of 144.6 pmol/L, which is in the range of typical male estradiol concentrations, resulted in an interassay coefficient of variation of 2.5%. Serum testosterone could not be measured for eight, estradiol for five, and SHBG for seven men. Serum concentrations of testosterone and estradiol detected in this study population were generally within what is considered reference values in adult men in the United States (testosterone, 6.73–28.91 nmol/L; estradiol, ≤183.6 pmol/L).20 We estimated free testosterone and free estradiol concentrations from measured testosterone, SHBG, and albumin.18

Measures of Kidney Function and Kidney Damage

The main outcomes of interest were an eGFR <60 mL/min/1.73 m^2, and a UACR of ≥ 17 mg/g (sex specific cutoff in men),21 which are related but measures of different

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physiological processes. Serum creatinine values were calibrated to the Cleveland Clinic Research Laboratory by multiplying by 0.96 and subtracting 16.27 μmol/L.22 Estimated GFR was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) Study formula, reexpressed for standardized serum creatinine:23, 24

$$eGFR = 175 \times (standardized\ serum\ creatinine)^{-1.154} \times (age)^{-0.203} \times 0.742(if\ female) \times 1.212(if\ black).$$

Serum cystatin C was also used to calculate eGFR using the following equation25:

$$eGFR_{Cys} = 127.7 \times (serum\ cystatin\ C)^{-1.17} \times (age)^{-0.13} \times 0.91(if\ female) \times 1.06(if\ black).$$

Urinary albumin to creatinine ratio (UACR; mg/g) was calculated after conversion of units, by dividing urinary albumin levels by urinary creatinine levels. Cystatin C data were available on a subsample (N=549) of the participants included in this analysis.

Statistical Analysis

Participants who were < 20 years of age or missing any of the major covariates (age, serum or urinary creatinine, serum or urinary albumin) were excluded (N=163). The final sample size for the current analysis was 1,307 men. Due to sample size limitations, analysis of race/ethnic differences was limited to a comparison of non-Hispanic whites to all other races.

We categorized the distributions of testosterone, estradiol, estradiol:testosterone, free testosterone, and free estradiol into tertiles. Levels of related covariates were examined in age-adjusted analyses by kidney function and kidney damage. Age adjustment was performed using linear regression prediction models, adjusting to mean age of the study sample. Crude mean hormone levels were examined as well as age- and multivariable adjusted (age, race, blood pressure, percent body fat, smoking status, diabetes, hypertension medication use) means. Multivariable adjusted odds ratios were calculated using logistic regression for associations between tertiles of hormones and kidney dysfunction or damage. The p-trends for each regression were calculated using the median value for each tertile of hormone. We conducted sensitivity analyses to validate the serum creatinine-based results using cystatin C-based measures of eGFR to define kidney dysfunction in the subset of participants in which both cystatin C and hormones were measured. All analyses were performed using the Phase I morning fasting sampling weights and standard errors were estimated using the Taylor series (linearization) method to account for the complex sample survey design as recommended by the National Center for Health Statistics in the NHANES III documentation.26 Analyses were performed using Stata 8.0 svy commands (Stata Corp, College Station, TX).

Results

An eGFR < 60mL/min/1.73m^2 as determined by serum creatinine was present in 3.1% (standard error [SE] = 0.4) of the population. A UACR ≥ 17 mg/g was present in 10.0% (SE = 1.0). After age adjustment, individuals with eGFR <60mL/min/1.73m^2 and a UACR ≥ 17 mg/g had a higher prevalence of hypertension and use of antihypertensive medications (Table 1). Men with reduced eGFR were less likely to be current smokers and men with elevated UACR were more likely to have diabetes.

Crude, age-, and multivariable-adjusted mean hormone levels by eGFR and UACR (binary) are displayed in Table 2. Crude mean total and free testosterone concentrations were

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statistically significantly lower and mean SHBG levels were higher in men with an eGFR <60mL/min/1.73m^2 and a UACR ≥ 17 mg/g as compared to men with normal eGFR or UACR, although these differences were attenuated and were no longer significant after adjustment for age. After multivariable adjustment, free testosterone and total and free estradiol levels were higher in men with eGFR <60mL/min/1.73m^2 than in men with a higher eGFR. Results did not differ when testosterone and estradiol were adjusted for each other and for SHBG or when estradiol:testosterone molar ratio was adjusted for SHBG (data not shown).

The odds ratios of kidney dysfunction and kidney damage by tertile of hormone are displayed in Table 3. In multivariable adjusted models, the odds of an eGFR <60mL/min/1.73m^2 or a UACR ≥ 17 mg/g were not significantly decreased across tertiles of total testosterone, total estradiol, SHBG, estradiol:testosterone molar ratio, or free testosterone. With free estradiol, however, odds of an eGFR <60mL/min/1.73m^2 were increased in men in the highest tertile of free estradiol as compared to those in the lowest tertile (OR: 3.04, 95% CI (1.22, 7.57); p-trend=0.02), contrary to our initial hypothesis. Free estradiol was not associated with a UACR ≥ 17 mg/g. Results did not differ after mutual adjustment for the other hormones. Subgroup analyses were also performed by age group (</≥60 years of age), smoking status, diabetes and race (data not shown), with no differences in results observed.

An eGFR <60mL/min/1.73m^2 as determined using cystatin C values was present in 9.6% (SE=1.3) of the subsample. Men with a higher estradiol:testosterone molar ratio and higher free estradiol were more likely to have a decreased $eGFR_{Cys}$ (Table 4). No patterns were observed for tertiles of the other hormones with decreased $eGFR_{Cys}$ in multivariable adjusted models, although the power for detecting an association in this subpopulation was limited.

The present analysis examined whether sex steroid hormones are associated with an eGFR <60 mL/min/1.73m^2 and a UACR ≥ 17 mg/g in a nationally representative population of adult men in the US. In crude analyses, lower serum total testosterone and higher SHBG concentrations were associated with these outcomes, but after adjustment for age, these associations were attenuated and no longer statistically significant.. Multivariable-adjusted mean free testosterone concentration was significantly higher in men with an eGFR <60 mL/min/1.73m^2 than in men with a higher eGFR In all multivariable analyses, higher free estradiol was significantly associated with an eGFR <60mL/min/1.73m^2 as assessed by serum creatinine and by cystatin C. These findings are contrary to our hypotheses. Previous studies have observed sex differences in kidney function, and studies have attributed such differences to effects of androgens and estrogens on renal function, kidney disease progression, and other cellular and molecular mechanisms.[5, 6, 27]

Discussion

The exact role of androgens in the development of cardiovascular and kidney diseases is unclear. Androgens are thought to mildly increase blood pressure and oxidative stress,[5, 28] although evidence for the relation between testosterone and blood pressure indicates an inverse relation in population-based studies.[29–32] Furthermore, while low testosterone is associated with less favorable cardiovascular risk factors, such as hypertension, increased diabetes and mortality in some studies,[9, 10, 33] it is not associated with cardiovascular disease events.[31, 34, 35] Given the strong relation between blood pressure and renal function, we expected to see differences in androgen concentrations between those with and without kidney disease. In addition, androgen levels are affected by kidney function, with evidence of hypotestosteronism among renal patients.[13, 36] Contrary to this, we found

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elevated levels of free testosterone in those with eGFR <60 mL/min/1.73m^2 but no association between tertiles of total and free testosterone and kidney dysfunction or damage.

In the animal model and in studies of women, endogenous estrogens are hypothesized to protect the kidneys and vascular wall11 and to protect against development of cardiovascular disease in clinical studies.28 Like testosterone, estradiol's relation with blood pressure is unclear: animal studies point to a decrease in blood pressure with administration of estradiol,11 while studies in humans have not found estrogen and blood pressure to be associated in men.30, 31 Based on this evidence, we hypothesized that lower levels of estradiol would be associated with a worsening of kidney function. Instead, we observed that higher free estradiol was associated with poorer kidney function, although not kidney damage, after multivariable adjustment. It is possible this observation is due to reverse causation, since estrogen levels in male renal patients tend to be elevated.13, 36 It has been proposed that protection of the vasculature by estradiol may depend on the degree of damage or stage of vascular disease11 or on estradiol metabolites as opposed to estradiol itself. In addition, estradiol is believed to interact with renal handling of sodium and to influence renal hemodynamics but only at certain phases of the menstrual cycle in women5; these effects have not been well characterized in males. It is possible that endogenous estradiol behaves differently in males, perhaps through modification of the lipid profile or other cardiovascular risk factors.

To our knowledge, this is one of the first epidemiologic studies investigating the relation between endogenous sex steroid hormones and kidney function and damage. Previous studies on renal function and sex steroid hormones have focused on physiological mechanisms,5, 11 sex differences in kidney function27, 37 or in clinical kidney disease populations.38, 39 One of the strengths of this study is that our investigation was conducted in a nationally representative sample of men not selected for kidney function.29 An additional strength is all samples assayed were collected at the morning examination, which minimized within-person variability due to diurnal production of these hormones. In addition, this is one of the first studies to present results for both free (estimated) and total hormones; for testosterone, free levels may be more clinically relevant as they reflect the portion available for biological action.18, 19 Lastly, we were able to conduct sensitivity analysis using available cystatin C data. Cystatin C is a novel marker of kidney function increasingly being used in clinical practice and research, and has many qualities of an ideal measure of GFR including constant rate of production, free filtration at the glomerulus and a lack of an effect of age, sex, or muscle mass on its production.40 Cystatin C has the potential to be a more accurate and sensitive measure of kidney function and predictor of endpoints than serum creatinine-based estimates.40, 41

A limitation of this study is the cross-sectional design, which limits our ability to make statements regarding the temporality of the relation of hormone levels with kidney function or damage. This point is relevant because overt kidney disease is associated with disturbance of sexual function and changes in sex steroid hormone levels at even moderately decreased levels of GFR13, and thus, our results may be due to reverse causation. We measured the men's hormone levels once; a single measurement may be affected by short or long-term variability. Similarly, GFR and UACR were determined using serum creatinine and albumin values from a single spot-urine sample. In addition, the analyses involving free testosterone and free estradiol, which were estimated using serum albumin, and UACR as an outcome may be affected by the effects of kidney disease on albumin excretion. Both testosterone and estradiol target the renin-angiotensin system by directly influencing levels of angiotensin, angiotensin II and angiotensin converting enzyme (ACE).6, 11 We were unable to explore the possibility of effect modification by use of ACE inhibitors and other types of antihypertensive medications due to the small subgroups of individuals taking specific types

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of these drugs. Relatedly, subgroup analyses by age, smoking, diabetes, specific diabetes medication use and race were limited due to small sample size. In particular, we were concerned with our treatment of race as a binary variable considering previously observed racial variation in hormone levels in this cohort42 and that CKD incidence varies by race and ethnicity. However results did not differ when analysis was restricted to whites only (data not shown). We were also concerned with the possibility of confounding by smoking considering its relationships with both CKD and hormone levels; though results did not differ when stratified by smoking status or when multivariable analyses were additionally adjusted for serum cotinine levels.

In conclusion, in a nationally representative sample of US adult men, we found no independent association between total testosterone with either kidney dysfunction or damage, while higher endogenous estradiol level, especially free estradiol, was associated with kidney dysfunction. Higher mean values of free testosterone concentration was also associated with kidney dysfunction. Further investigation of these hormones in other epidemiologic studies will help to elucidate estrogen's role in kidney hemodynamics, function and pathophysiology in men.

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Table 1

Characteristics of the study population by kidney function and kidney damage, US men aged ≥ 20 years, NHANES III, 1988–1991[†]

		Kidney Dysfunction		Kidney Damage	
	Overall	**Normal eGFR ≥ 60 mL/min/1.73 m^2**	**Decreased eGFR < 60 mL/min/ 1.73 m^2**	**Elevated UACR ≥17 mg/g[‡]**	**Normal UACR < 17 mg/g**
N	1307	1224	83	189	1118
Age, mean ± SE (years)	41.9 ± 0.7	41.0 ± 0.7	69.7 ± 1.4	53.9 ± 2.9	40.6 ± 0.6
Non-Hispanic White, % ± SE	78.0 ± 3.3	77.9 ± 3.4	82.9 ± 3.1	72.7 ± 5.2	78.6 ± 3.3
Blood Pressure, mean ± SE (mm Hg)					
Systolic	124.4 ± 0.5	124.4 ± 0.4	127.1 ± 2.0	131.7 ± 1.4**	123.7 ± 0.4
Diastolic	75.7 ± 0.5	75.8 ± 0.5	72.8 ± 1.8	76.4 ± 1.2	75.6 ± 0.5
History of Hypertension, % ± SE	28.9 ± 1.4	28.7 ± 1.5	42.2 ± 8.4	51.8 ± 4.7**	26.5 ± 1.6
Use of Antihypertensive Medications, % ± SE	10.2 ± 1.0	9.4 ± 1.0	38.7 ± 6.4**	20.5 ± 4.4*	9.2 ± 1.0
% Body Fat, mean ± SE	24.9 ± 0.3	24.9 ± 0.3	24.6 ± 1.1	24.6 ± 0.8	25.0 ± 0.3
History of Diabetes, % ± SE	6.2 ± 0.8	6.2 ± 0.8	5.8 ± 5.5	21.1 ± 4.3**	4.5 ± 0.7
Current Smoker, % ± SE	34.3 ± 2.2	34.9 ± 2.2	15.2 ± 4.6	30.0 ± 6.0	34.7 ± 2.3

*p<0.05 compared to eGFR ≥ 60mL/min/1.73 m^2

**p<0.0001 compared to eGFR ≥ 60 mL/min/1.73 m^2 or UACR <17 mg/g where appropriate

[†]Estimates are weighted using the Phase I morning fasting sampling weights; All estimates by kidney dysfunction and damage besides age are age-adjusted

[‡]UACR ≥ 17 mg/g is sex-specific cutoff for kidney damage in males

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Table 2

Adjusted mean serum hormone concentrations by kidney dysfunction and kidney damage, US men aged ≥ 20 years, NHANES III, 1988–1991

	Kidney Dysfunction		Kidney Damage	
	Normal eGFR ≥ 60 mL/min/1.73 m^2	**Decreased eGFR < 60 mL/min/1.73 m^2**	**Elevated UACR ≥ 17 mg/g**	**Normal UACR < 17 mg/g**
Testosterone (nmol/L)				
Crude	19.3 ± 0.3	15.1 ± 0.7*	16.7 ± 0.6**	19.5 ± 0.3
Age-Adjusted	19.1 ± 0.2	19.5 ± 1.1	18.5 ± 0.7	19.2 ± 0.3
Multivariable Adjusted†	18.0 ± 0.3	18.5 ± 0.8	17.3 ± 0.7	18.0 ± 0.3
Estradiol (pmol/L)				
Crude	137.7 ± 2.7	135.9 ± 4.9	134.7 ± 6.7	137.9 ± 2.5
Age-Adjusted	137.3 ± 2.7	145.7 ± 5.7	138.6 ± 7.4	137.4 ± 2.4
Multivariable Adjusted†	124.7 ± 3.3	137.3 ± 5.8*	125.8 ± 8.5	125.2 ± 3.0
SHBG (nmol/L)				
Crude	38.0 ± 0.8	48.9 ± 3.0**	42.9 ± 2.2*	37.9 ± 0.7
Age-Adjusted	38.4 ± 0.8	36.9 ± 2.9	37.9 ± 2.1	38.4 ± 0.76
Multivariable Adjusted†	37.8 ± 0.9	35.9 ± 2.7	37.8 ± 2.3	37.8 ± 0.9
Molar Estradiol:Testosterone (x 10^3)				
Crude	9.9 ± 1.3	15.0 ± 3.8	15.6 ± 5.2	9.5 ± 1.2
Age-Adjusted	10.1 ± 1.3	10.6 ± 3.8	13.9 ± 5.4	9.7 ± 1.3
Multivariable Adjusted†	10.8 ± 2.3	11.9 ± 3.6	15.7 ± 6.5	10.3 ± 2.1
Estimated Free Testosterone (nmol/L)				
Crude	0.39 ± 0.006	0.26 ± 0.007**	0.32 ± 0.014**	0.39 ± 0.007
Age-Adjusted	0.38 ± 0.004	0.40 ± 0.015	0.39 ± 0.014	0.38 ± 0.004
Multivariable Adjusted†	0.36 ± 0.004	0.39 ± 0.011*	0.36 ± 0.015	0.36 ± 0.004
Estimated Free Estradiol (pmol/L)				
Crude	3.54 ± 0.08	3.38 ± 0.10	3.39 ± 0.13	3.55 ± 0.07
Age-Adjusted	3.52 ± 0.08	3.81 ± 0.13	3.56 ± 0.16	3.53 ± 0.07
Multivariable Adjusted†	3.17 ± 0.09	3.59 ± 0.14*	3.19 ± 0.16	3.18 ± 0.08

*p<0.05 compared to eGFR ≥ 60mL/min/1.73 m^2

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** $p<0.0001$ compared to eGFR ≥ 60 mL/min/1.73 m^2 or UACR <17 mg/g where appropriate

† Adjusted for age, race, systolic and diastolic blood pressures, percent body fat, smoking status, diabetes, hypertension medication use

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Table 3

Odds ratios* (95% CI) of decreased kidney function and kidney damage by tertiles of serum hormone concentrations, US men aged ≥ 20 years, NHANES III, 1988–1991

	Tertile of Serum Hormone Concentration**			
	T1	**T2**	**T3**	**p-trend**
Kidney Dysfunction (eGFR <60 mL/min/1.73 m^2)				
Testosterone	Ref	1.42 (0.67, 2.97)	1.45 (0.59, 3.53)	0.33
Estradiol	Ref	1.80 (0.93, 3.48)	1.81 (0.86, 3.81)	0.12
SHBG	Ref	0.58 (0.17, 1.94)	0.58 (0.21, 1.65)	0.42
Molar Estradiol: Testosterone (x 10^3)	Ref	0.55 (0.21, 1.42)	1.37 (0.52, 3.62)	0.23
Estimated Free Testosterone	Ref	1.96 (0.96, 3.99)	0.38 (0.07, 2.08)	0.39
Estimated Free Estradiol	Ref	2.02 (0.98, 4.18)	3.04 (1.22, 7.57)	0.02
Kidney Damage (UACR ≥ 17 mg/g)				
Testosterone	Ref	1.07 (0.60, 1.92)	0.79 (0.38, 1.63)	0.52
Estradiol	Ref	0.69 (0.34, 1.37)	0.73 (0.35, 1.52)	0.43
SHBG	Ref	0.85 (0.40, 1.79)	0.94 (0.41, 2.19)	0.95
Molar Estradiol:Testosterone (x 10^3)	Ref	0.63 (0.30, 1.31)	0.93 (0.51, 1.68)	0.95
Estimated Free Testosterone	Ref	1.62 (0.78, 3.36)	2.15 (0.84, 5.51)	0.10
Estimated Free Estradiol	Ref	0.79 (0.34, 1.82)	0.84 (0.45, 1.57)	0.60

*Adjusted for age, race, systolic and diastolic blood pressures, percent body fat, smoking status, diabetes, hypertension medication use

**Median, [tertiles]: testosterone, nmol/L: 17.6, [<14.86, 14.86–20.86, >20.86]; estradiol, pmol/L: 128.7, [<113.5, 113.5–146.7, >146.7]; estradiol:testosterone molar ratio (x 10^3): 7.38, [<6.39, 6.39–8.65, >8.65]; estimated free testosterone, nmol/L: 0.35, [<0.283, 0.283–0.419, >0.419]; estimated free estradiol, pmol/L: 3.26, [<2.87, 2.87–3.77, >3.77

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Table 4

Odds ratios* (95% CI) of kidney dysfunction ($eGFR_{Cys}$<60 mL/min/1.73 m^2) as determined by cystatin C in subset of the study population (N=544) by tertiles of serum hormone concentrations, US men aged ≥ 20 years, NHANES III, 1988–1991

	Tertile of Serum Hormone Concentration***			
	T1	T2	T3	p-trend
Kidney dysfunction ($eGFR_{Cys}$ <60 mL/min/1.73 m^2)				
Testosterone	Ref	0.91 (0.42, 1.98)	0.33 (0.09, 1.29)	0.15
Estradiol	Ref	1.05 (0.46, 2.40)	1.38 (0.63, 3.04)	0.41
SHBG	Ref	0.90 (0.27, 3.02)	0.96 (0.27, 3.38)	0.99
Molar Estradiol:Testosterone (x 10^3)	Ref	1.13 (0.45, 2.87)	2.56 (0.91, 7.24)	0.05
Estimated Free Testosterone	Ref	0.98 (0.48, 1.96)	0.10 (0.01, 1.28)	0.30
Estimated Free Estradiol	Ref	0.71 (0.34, 1.51)	2.48 (1.14, 5.40)	0.03

* Adjusted for age, race, systolic and diastolic blood pressures, percent body fat, smoking status, diabetes, hypertension medication use

** Within subset of NHANES III that had both cystatin C and hormone measurement; n=79 individuals had eGFR<60

*** Median, [tertiles]: testosterone, nmol/L: 17.6, [<14.86, 14.86–20.86, >20.86]; estradiol, pmol/L: 128.7, [<113.5, 113.5–146.7, >146.7]; estradiol:testosterone molar ratio (x 10^3): 7.38, [<6.39, 6.39–8.65, >8.65]; estimated free testosterone, nmol/L: 0.35, [<0.283, 0.283–0.419, >0.419]; estimated free estradiol, pmol/L: 3.26, [<2.87, 2.87–3.77, >3.77

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