Published in final edited form as:
Am J Hypertens. 2009 January ; 22(1): 100–105. doi:10.1038/ajh.2008.307.

Inverse Associations Between Androgens and Renal Function: The Young Men Cardiovascular Association (YMCA) Study

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Abstract

BACKGROUND—Men exhibit higher risk of nondiabetic renal diseases than women. This male susceptibility to renal disease may be mediated by gender-specific factors such as sex hormones.

METHODS—We have undertaken a cross-sectional examination of associations between renal function (creatinine clearance estimated based on Cockcroft–Gault equation) and circulating levels of sex steroids (total testosterone, total estradiol, estrone, androstenedione, dehydroepiandrosterone sulfate (DHEA-S), and dihydrotestosterone) in 928 young (mean age: 18.5 ± 1.2 years) men.

RESULTS—Both androstenedione and DHEA-S showed inverse linear associations with renal function in the crude analysis of lean men (those with body mass index (BMI) less than median). However, only DHEA-S retained its association with renal function in lean subjects after adjustment—assuming no changes in other independent variables 1 s.d. increase in DHEA-S was associated with 13%-s.d. decrease in creatinine clearance ($P = 0.004$). Testosterone decreased across tertiles of creatinine clearance only in the crude analysis of nonlean (BMI greater than median) subjects ($P < 0.001$). The adjusted regression analysis that assumed no changes in other independent variables showed that 1 s.d. increase in total testosterone was associated with 11%-s.d. decrease in creatinine clearance of nonlean men ($P = 0.006$). Factor analysis confirmed an inverse association of renal function with both sex steroids and a different pattern of their loadings on glomerular filtration–related factors in lean (DHEA-S) and nonlean (testosterone) subjects.

CONCLUSIONS—Our data may suggest that androgens are inversely associated with estimated renal function in apparently healthy men without history of cardiovascular disease.

Men have significantly higher risk of nondiabetic renal complications than age-matched women.[1] Microalbuminuria, a hallmark of kidney damage, is more common among men than women in the population screening.[2] Consistently, in epidemiological surveys of the general population, men exhibit a higher incidence of chronic kidney disease than premenopausal women.[3] In males with increased risk of chronic kidney disease but without overt nephropathy, urinary excretion of albumin shows a stronger association with cardiovascular morbidity[4] and mortality[5] than in females. In addition, men with advanced renal impairment (stage 4 and 5 of chronic kidney disease) initiate renal replacement therapy

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Disclosure: The authors declared no conflict of interest.

faster then women.[6] Most importantly, the mortality related to chronic kidney disease is also higher in men than in women.[7] The associations between male sex and predisposition to renal disease may be, at least in part, independent on the well-documented sexual dimorphism in hypertension and blood pressure (BP). Although males exhibit significantly higher BP then age-matched females in childhood,[8,9] adolescence,[9] and through middle-age[10,11] and the overall prevalence of hypertension is higher in men than in women[12] adjustment for BP does not completely abolish the apparent sexual dimorphism in renal risk.[13] Similarly, predisposition to renal damage in experimental models exhibits a clear pattern of "male-disadvantage," independent of BP.[14] Finally, the deterioration of renal function related to nephropathies in which hypertension is not a primary etiological factor[15] is consistently more rapid among men than women. Collectively, these data suggest that irrespective of the level of renal or in fact BP-related risk, there is an apparent male predisposition to structural and functional nondiabetic kidney damage.

Sex steroids are one of the most obvious biological factors that could contribute to the increased male susceptibility to renal injury. Indeed, in experimental studies androgens were shown to affect renal hemodynamics[16] and promote glomerular and tubular injury in males.[17,18] However, little is known how circulating concentrations of testosterone and other sex hormones may affect renal parameters in men in context of other traditional cardiovascular risk factors. We have hypothesized that higher concentrations of testosterone and/or other androgens will correlate with decreased renal function in a large cohort of men recruited from young male Polish population.

METHODS

Subjects

Young Men Cardiovascular Association (YMCA) study is a cohort of young male subjects recruited in Silesia (Southern Poland), as previously reported.[19,20] The following were criteria of inclusion to the YMCA study: male sex, age ≥17 years, Polish origin, and readiness to participate. Exclusion from the original study was based on lack of blood sample suitable for laboratory analyses.[19] Of 1,157 subjects who satisfied these criteria in the YMCA study,[19] 229 were excluded because of unavailability of biological material needed for hormonal examination in the current analysis.

An approval from the local Bioethical Committee has been obtained for this study and all subjects have given a written consent for participation.

Clinical and biochemical phenotyping

Each subject was phenotyped for conventional cardiovascular risk factors using the standard protocol (basic demographic data, physical examination, anthropometric measurements, blood biochemistry), as reported previously.[19] In brief, weight and height measurements (using the electronic digital scales and stadiometers) were taken in participants wearing light clothes and without shoes. Body mass index (BMI) was calculated as the ratio of weight (in kilograms) to height^2 (in meters). As described elsewhere,[19] BP was taken in a sitting position using mercury sphygmomanometer with a cuff size individually adjusted to the arm after 20 min of rest. Systolic BP (SBP) was taken at the return of arterial sounds (Korotkoff phase 1), and disappearance of sounds (Korotkoff phase 5) indicated diastolic BP (DBP).[19] BP was measured in triplicate during a single appointment and the average of three readings was used in estimation of final SBP and DBP.[19] Mean BP (MAP) was calculated based on the following formula: MAP = DBP + 1/3 (SBP − DBP). Hypertension was defined as taking antihypertensive treatment and/or BP readings ≥140 mm Hg and/or 90 mm Hg on

three separate occasions (one of which was obtained during the recruitment and two others before or after the recruitment as per clinical records).

Fasting lipid profile (total cholesterol, high-density lipoprotein–cholesterol, and triglycerides) was evaluated using enzymatic methods on an automated Cobas Bio-Autoanalyzer and low-density lipoprotein–cholesterol was calculated based on the Friedewald formula. Hypercholesterolemia was defined as total cholesterol >200 mg/dl (in subjects aged >19 years) or according to sex- and age-specific thresholds in those aged ≤19 years.[21]

Circulating concentrations of creatinine were measured based on the kinetic Jaffe reaction on a Cobas Bio-Autoanalyzer. Creatinine clearance was estimated with the use of the Cockcroff–Gault formula[22] and not indexed by body surface area to avoid a potential underestimation of renal function that may be introduced by body surface area indexing, in particular among obese individuals.[23,24]

Circulating concentrations of sex steroids (total testosterone, total estradiol, estrone, androstenedione, dehydroepiandrosterone sulfate (DHEA-S), and dihydrotestosterone) were measured in plasma samples collected in the morning hours (9.00–12.00 AM) and stored in −70 °C. Apart from dihydrotestosterone levels that were assessed by enzyme-linked immunosorbent assay (DHT-ELISA; Biosource, Brussels, Belgium); plasma concentrations of other sex steroids were evaluated using radioimmunoassays (TESTO-RIA-CT, E2-RIA-CT, ESTRONE-RIA-CT, ANDROSTENEDIONE-RIA-CT, DHEA-S-RIA-CT, all Biosource). Each assay was highly specific—the crossreactivity of a measured hormone with other sex steroids was minimal (generally below 1.0%), except for DHT-ELISA that showed ~8.7% crossreactivity with testosterone. However, this crossreactivity had no influence on the results of the ELISA test due to a specific complexing buffer system that blocked the binding of testosterone to the antibody. Estradiol plasma levels were measured by an ultra-sensitive assay specifically designed for studies in men and children. The other assays also had sufficient sensitivity to measure circulating concentrations of sex steroids in men.

The intra- and interassay precision was good—the coefficients of variation assessed for at least two different levels of hormones concentrations were all below 12.1%. Dihydrotestosterone showed the highest 11.4 and 12.1% intra- and interassay coefficients of variation. The other intra- and interassay coefficients of variation were: 4.1 and 5.5% (total testosterone), 5.4 and 8.2% (total estradiol), 6.3 and 8.6% (estrone), 3.9 and 7.5% (androstenedione), 2.8 and 5.1% (DHEA-S), 10.7 and 11.6% (dihydrotestosterone), respectively.

Statistical analysis

Kolmogorov–Smirnov test was used to examine whether the distribution of all clinical and biochemical quantitative variables was normal. Phenotypes that were not normally distributed underwent log-transformation before further analysis.

Spearman’s correlation was used to examine associations between sex steroids and renal function in the entire study group.

Given that relationships between sex steroids and renal function may be affected by body weight (fat-free mass is a key correlate of plasma creatinine and fat mass—a well-documented associate of sex steroids), we stratified our further investigations on the median BMI—the well-accepted clinical indicator of total body weight (the sum of fat-free mass and fat mass). Unadjusted analysis of associations between renal function and sex steroids was

based on examination of trends in hormones concentrations across tertile distribution of creatinine clearance. Dependent on the distribution, one-way analysis of variance with weighted partitioning of the between-groups variation into linear trends or nonparametric analysis of variance (Kruskal–Wallis test) were used to assess statistical significance of the crude associations. Data from log-transformed variables in these tests were presented as geometric means (anti-logs of the mean of the logged data) and respective 95% confidence intervals.

Multiple analyses of associations between renal function and sex steroids were conducted using linear regression and factor analysis. Multiple linear regression models with creatinine clearance as a dependant variable were constructed based on forward entry of all available demographic, clinical, and biochemical variables as independent predictors (criterion of entry—probability of *F*-statistics <0.05). The magnitude of associations between renal function and sex steroids was expressed by standardized β-coefficients (change in the dependent parameter resulting from a change of 1 s.d. of an independent variable).

Factor analysis was used to segregate the available quantitative variables into fractions (factors) that reflect independent clusters of correlated phenotypes within the data stratum.[25] In brief, clustering of the individual phenotypes within the same factor is likely to reflect biologically meaningful correlations and relative contribution of the individual parameters to the extracted factors is reflected by their loadings.[25] A principal component method was employed to extract three independent factors from the available data and an orthogonal varimax rotation was used to maximize the variance of the squared loadings within factors and increase the interpretability of the data.[25] Loadings exceeding |0.4| were considered as statistically significant in the factor analysis.

RESULTS

Clinical data of 928 men included in this study (Table 1) are consistent with the characteristics of the sample recruited from young male population. Only five men in this cohort had creatinine clearance <60 ml/min.

Of six examined sex hormones, only total testosterone showed a week inverse correlation with renal function in the entire study group ($R = -0.1$, $P = 0.003$).

Stratification on the median BMI (22.5 kg/m^2) has revealed differences in the pattern of associations between sex steroids and renal function in lean (those whose BMI <22.5 kg/m^2) and nonlean (those with BMI >median) men (Table 2). Androstenedione was associated with creatinine clearance only in subjects with low BMI and total testosterone showed association with renal function only in nonlean subjects (Table 2). DHEA-S was linked to renal function in both lean and non-lean subjects (Table 2). All three sex steroids showed consistent decreasing trends across escalating tertiles of estimated creatinine clearance (Table 2). Exclusion of five subjects with creatinine clearance <60 ml/min had no effect on the associations between renal function and sex steroids (data not shown).

After adjustment for other covariates (age, BMI, total cholesterol) in the multiple regression models, total testosterone retained its association with renal function in nonlean men. Specifically, 1 s.d. increase in testosterone was associated with an 11%-s.d. decrease in creatinine clearance in the multivariate model that assumed no changes in the other independent predictors of estimated renal function (standardized $\beta = -0.11$, $P = 0.006$).

Multiple regression analysis has also revealed an independent, statistically significant association between DHEA-S and creatinine clearance in lean subjects. One standard deviation increase in DHEA-S was associated with 13%-s.d. decrease in creatinine clearance

in the model in which other independent predictors of renal function (age, BMI, MAP, total cholesterol, triglycerides) were held as constant (standardized $\beta = -0.13$, $P = 0.004$).

Associations between both androgens and estimated creatinine clearance retained their statistical significance after exclusion of BMI as a covariate from multiple regression models (data not shown).

Total estradiol, estrone, androstenedione, and dihydrotestosterone were not associated with renal function in the adjusted analysis.

Factor analysis across the two strata of BMI resulted in extraction of three independent fractions from the collected anthropometric, metabolic, renal and hormonal parameters (Table 3). Consistent with the data from multiple regression analysis the pattern of associations between sex steroids and renal function was different in lean and nonlean subjects. Total testosterone clustered together with renal function and body mass within the same factor (factor 1—maximal testosterone loading of −0.457) only in nonlean subjects whereas in lean men testosterone loading on renal function–related factors (factors 1 and 2) was not statistically significant. DHEA-S showed clustering with renal function only in lean subjects (factor 1). As in the multiple regression analysis, both sex steroids showed a similar inverse direction of association with renal function.

DISCUSSION

To the best of our knowledge our analysis is the first population-based study that shows an association between circulating concentrations of androgens and renal function in men. The most consistent correlations were revealed between DHEA-S and renal function in lean subjects and between total testosterone and glomerular filtration estimate in non-lean subjects. Most importantly, the independent associations between sex steroids and renal function were demonstrated in a young, apparently healthy male population largely unaffected by hypertension, without any history of overt cardiovascular disease.

Our data provide a clinical context to the reported experimental investigations suggestive of the role of androgens in renal injury. Indeed, key enzymatic regulators of androgen biosynthesis and signaling are expressed in the renal tissue.[26,27] Furthermore, data from rodent models directly demonstrate the negative impact of testosterone on renal structure and function in male rats[26] and significant improvement in renal parameters after testosterone depletion (castration).[28] Mechanistically, the adverse effects of androgens on renal outcomes is most likely mediated via activation of the renin–angiotensin–aldosterone system, oxidative stress, proapoptotic and proinflammatory processes,[26,27] all of which are well-known drivers of cardiovascular and metabolic disorders. The inverse association between testosterone and renal function apparent only in nonlean men in our study suggests a permissive contribution of increased body weight to the androgen–renal relationship. Overweight and obesity are indeed increasingly recognized as risk factors for kidney diseases.[29] In addition, increased body weight correlates with oxidative stress[30] and low-grade inflammation[30]—the two most likely intermediate phenotypes on the androgens–renal axis.[26] Whether interactions between overweight and testosterone influence renal function via promotion of prooxidative and proinflammatory phenotype in men remains to be elucidated.

Our study also shows an association between renal function and DHEA-S—the most abundant circulating androgen[31] that has been linked to atherosclerosis,[32] chronic inflammation,[33] and endothelial dysfunction.[34] Given that renal function declines with aging and that endothelial injury is a well-recognized factor underlying kidney damage,[35] association between DHEA-S and creatinine clearance is biologically plausible.

Nonetheless, the direction of the association between DHEA-S and cardiovascular and renal phenotypes remains controversial. The majority,[36] but not all,[37] data suggest a protective effect of endogenous DHEA-S on the well-documented risk factors of renal injury (such as BP and lipids) and a possible negative impact of low DHEA-S on cardiovascular mortality.[36] Low circulating concentrations of DHEA-S were also implicated as a risk factor for progression of glomerular injury in diabetic men.[38] However, evaluation of relationships between DHEA-S and renal function was not examined directly in most of these studies. In addition, most of the reported associations[36] come from cohorts of middle-aged or elderly subjects and as such may be confounded by coexisting disorders or in fact aging—recognized inverse correlates of DHEA-S plasma levels. Given that circulating concentrations of DHEA-S peak at 20–24 years in men and only thereafter decline with age[39] our analysis based on young, apparently healthy subjects is unlikely to be confounded by strong inverse relationships between DHEA-S and aging or cardiovascular diseases.

Our study has a number of limitations. First, the analysis is based on calculated glomerular filtration rather than a direct measurement of renal hemodynamics and as such represents only a surrogate of genuine filtration rates. Second, lack of available sex hormone–binding globulin and albumin levels does not permit us to calculate free and bioavailable fractions of testosterone. Therefore, we cannot exclude that using free rather than total hormonal fraction of testosterone would provide even better estimate of its association with renal function. Third, due to unavailability of urine samples in the YMCA study we could not evaluate associations between androgens and urinary excretion of albumin (a well-recognized marker of renal injury) or verify the extent to which renal clearance of sex steroids contributes to the detected associations. We should also stress that although our data do not support the role of dihydrotestosterone as a mediator of negative effects of androgens on renal function in men, they should be interpreted with caution given that circulating concentrations of dihydrotestosterone may not reflect accurately its bioavailability within peripheral tissue, including the kidney.[40] Future studies should focus on paracrine functions of dihydrotestosterone in the kidney bringing us closer to the full dissection of associations between androgens and renal function. It should be also acknowledged that our analysis was not corrected for multiple testing. However, consistency of associations between renal function and both androgens (in different strata of BMI distribution) in the crude, adjusted and factor analysis suggests a low probability of type 1 error. Finally, lack of prospective observation does not permit to assign a causal context to the demonstrated findings and provide an immediate mechanistic explanation for the observed associations. Further investigations are warranted to elucidate fully the physiological background of relationships between androgens and renal function in men.

Within the interpretational limitations discussed above our data may suggest that androgens are inversely associated with male renal function early in life. Future prospective studies are needed to confirm whether these associations may help to explain the well-documented epidemiological trends in higher incidence and progression of nondiabetic kidney diseases among men than women.

Acknowledgments

This study was supported by NIH Fogarty International Research Collaboration Award (R03 TW007165) (to M.T., C.M. and E.Z.-S.). N.J.S. holds a British Heart Foundation Chair of Cardiology.

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Table 1

Demographic and clinical characteristics of subjects

Phenotype	Values
n	928
Age (years)	18.5 ± 1.2
Weight (kg)	70.0 (65.0–79.0)
Height (m)	1.78 (1.73–1.83)
Body mass index (kg/m^2)	22.5 (20.6–24.2)
Systolic blood pressure (mm Hg)	118 (108–127)
Diastolic blood pressure (mm Hg)	73 (70–80)
Mean arterial pressure (mm Hg)	89 ± 9
Creatinine clearance (ml/min)	131.8 (117.1–149.8)
Creatinine (mg/dl)	0.9 (0.8–1.0)
Total cholesterol (mg/dl)	162.5 (142.6–185.8)
HDL-cholesterol (mg/dl)	42.6 (34.8–50.3)
LDL-cholesterol (mg/dl)	98.9 (78.3–121.0)
Triglycerides (mg/dl)	88.6 (70.9–121.8)
Total estradiol (pg/ml)	19.5 (14.1–25.5)
Estrone (pg/ml)	33.9 (23.4–49.2)
Dehydroepiandrosterone sulfate (μg/dl)	233.8 (176.3–339.3)
Androstenedione (ng/ml)	2.6 (1.8–3.6)
Total testosterone (ng/ml)	5.5 (3.9–7.0)
Dihydrotestosterone (ng/dl)	32.6 (25.9–40.7)
Hypertension, *n* (%)	98 (10.6)
Antihypertensive treatment, *n* (%)	13 (1.4)
↑Total cholesterol, *n* (%)	160 (17.2)
Lipid-lowering medication, *n* (%)	0 (0)

Quantitative phenotypes are shown as means and s.d. or medians and 25–75% interquartile ranges, hypertension was defined as elevation of blood pressure (SBP ≥ 140 mm Hg and/or DBP ≥90 mm Hg on three separate occasions) or/and taking antihypertensive medication. ↑Total cholesterol—elevated total cholesterol (>200 mg/dl or according to sex- and age-specific thresholds in those aged ≤19 years).[21] HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2

Sex steroids across three tertiles of creatinine clearance distribution—crude analysis stratified on median value of BMi

	Lean subjects (BMI < median value)				Nonlean subjects (BMI > median value)			
Phenotype	**1st Tertile (*n* = 155)**	**2nd Tertile (*n* = 154)**	**3rd Tertile (*n* = 154)**	***P* value**	**1st Tertile (*n* = 155)**	**2nd Tertile (*n* = 155)**	**3rd Tertile (*n* = 155)**	***P* value**
Creatinine clearance (ml/min)	11.9–114.6	114.7–130.0	130.1–212.8	—	16.9–134.5	134.6–155.5	155.6–266.8	—
Total estradiol (pg/ml)	18.7 (17.4–20.0)	18.6 (17.2–20.2)	17.6 (16.2–19.1)	0.51	19.2 (17.9–20.6)	18.5 (16.9–20.3)	18.7 (17.3–20.2)	0.87
Estrone (pg/ml)	32.9 (30.0–36.1)	34.9 (32.9–37.9)	31.2 (28.6–34.0)	0.41	35.9 (32.8–39.4)	34.9 (31.8–38.2)	34.7 (31.5–38.2)	0.60
DHEA-S (μg/dl)	245.0 (226.5–264.9)	221.4 (203.0–239.8)	210.3 (195.6–225.1)	0.007	280.4 (258.3–306.3)	265.7 (243.5–284.1)	236.2 (217.7–254.6)	0.003
Androstenedione (ng/ml)	2.6 (2.4–2.8)	2.5 (2.3–2.8)	2.2 (2.0–2.3)	0.004	2.7 (2.5–2.9)	2.6 (2.3–2.8)	2.5 (2.3–2.7)	0.32
Total testosterone (ng/ml)	4.8 (4.3 –5.3)	5.0 (4.6–5.5)	4.8 (4.4–5.2)	0.56	5.5 (5.1–6.0)	4.9 (4.4–5.4)	4.4 (4.1–4.8)	<0.001
Dihydrotestosterone (ng/dl)	32.1 (30.1–34.3)	31.4 (29.5–33.4)	33.5 (31.4–35.7)	0.45	38.8 (35.5–42.3)	33.4 (31.6–35.4)	36.1 (33.4–39.1)	0.09

Log-transformed data are geometric means and 95% confidence intervals, creatinine clearance was estimated based on the Cockcroft–Gault equation. The full ranges of circulating concentrations of creatinine and creatinine clearance were 0.6 mg/dl—9.6 mg/dl and 11.9—266.8 ml/min, respectively.

BMI, body mass index; DHEA-S, dehydroepiandrosterone sulphate.

Am J Hypertens. Author manuscript; available in PMC 2010 January 19.

Table 3

Factor analysis in lean and nonlean subjects—factor loadings after orthogonal varimax rotation

	Lean subjects				Nonlean subjects			
Variable	**Factor 1**	**Factor 2**	**Factor 3**	**Communality**	**Factor 1**	**Factor 2**	**Factor 3**	**Communality**
Age	**0.427**	**0.486**	0.015	0.419	0.007	**−0.549**	0.077	0.308
Body mass index	−0.015	**0.674**	0.175	0.485	**0.754**	0.008	−0.184	0.602
MAP	−0.191	0.372	−0.143	0.196	**0.519**	−0.211	0.199	0.354
Ccr	**−0.625**	**0.439**	0.105	0.594	**0.638**	0.377	0.11	0.561
Triglycerides	**0.68**	−0.014	−0.089	0.47	**0.551**	−0.264	−0.336	0.485
HDL-C	**0.627**	0.039	0.341	0.511	−0.296	−0.344	**0.46**	0.418
Total cholesterol	−0.217	0.033	−0.359	0.177	0.274	**−0.539**	−0.32	0.468
Estradiol	−0.015	−0.078	−0.4	0.166	0.003	0.009	**−0.722**	0.521
Estrone	0.094	0.022	**−0.616**	0.389	−0.107	−0.177	**−0.574**	0.372
Androstenedione	0.343	0.111	**−0.582**	0.468	−0.127	**−0.406**	−0.231	0.234
DHEA-S	**0.439**	0.342	−0.223	0.359	0.032	**−0.673**	0.053	0.457
Total testosterone	−0.049	0.315	**−0.472**	0.325	**−0.457**	−0.099	−0.097	0.228
Dihydrotestosterone	0.066	**0.486**	−0.106	0.252	−0.074	−0.212	−0.174	0.081
% Variance	14.1	11.5	11.4	37.0	15.0	12.9	11.3	39.1

Boldface values represent the significant loadings of variables on the extracted factors.

Ccr, creatinine clearance; DHEA-S, dehydroepiandrosterone sulfate; HDL-C, high-density lipoprotein–cholesterol; MAP, mean arterial pressure.