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Journal

American Journal of Hypertension, 31(7)

ISSN

0895-7061

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Publication Date

2018-06-11

DOI

10.1093/ajh/hpy024

Peer reviewed

ORIGINAL ARTICLE

Relation of Sex Hormone Levels With Prevalent and 10-Year Change in Aortic Distensibility Assessed by MRI: The Multi-Ethnic Study of Atherosclerosis

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BACKGROUND
Women experience a steeper decline in aortic elasticity related to aging compared to men. We examined whether sex hormone levels were associated with ascending aortic distensibility (AAD) in the Multi-Ethnic Study of Atherosclerosis.

METHODS
We studied 1,345 postmenopausal women and 1,532 men aged 45–84 years, who had serum sex hormone levels, AAD measured by phase-contrast cardiac magnetic resonance imaging, and ejection fraction>50% at baseline. Among these participants, 457 women and 548 men returned for follow-up magnetic resonance imaging 10-years later. Stratified by sex, and using mixed effects linear regression methods, we examined associations of sex hormones (as tertiles) with baseline and annual change in log-transformed AAD (mm $Hg^{-1}10^{-3}$), adjusting for demographics, body size, lifestyle factors, mean arterial pressure, heart rate, hypertensive medication use (and in women, for hormone therapy use and years since menopause).

RESULTS
The mean (SD) age was 65 (9) for women and 62 (10) years for men. AAD was lower in women than men ($P < 0.001$). In adjusted cross-sectional analysis, the highest tertile of free testosterone (compared to lowest) in women was significantly associated with lower AAD [−0.10 (−0.19, −0.01)] and the highest tertile of estradiol in men was associated with greater AAD [0.12 (0.04, 0.20)]. There were no associations of sex hormones with change in AAD over 10 years, albeit in a smaller sample size.

CONCLUSIONS
Lower free testosterone in women and higher estradiol in men were associated with greater aortic distensibility at baseline, but not longitudinally. Sex hormone levels may account for differences in AAD between women and men.

Keywords: aortic distensibility; blood pressure; epidemiology; hypertension; magnetic resonance imaging; sex differences; sex hormones; vascular stiffness.

doi:10.1093/ajh/hpy024

Arterial stiffness is the resistance offered by the vessel wall to deformation[1] and is associated with age and cardiovascular disease (CVD) risk factors.[2,3] Age-related arterial stiffening is an important cause of hypertension in older adults and implicated in the development of heart failure with preserved ejection fraction (HFpEF).[4] HFpEF accounts for approximately half of all heart failure cases, with a greater burden among older women.[4,5] Greater arterial stiffness is seen in HFpEF patients when compared to patients without HFpEF with a similar risk factor profile.[6]

After adjusting for contributing factors like mean arterial pressure, smoking, and body size, arterial stiffness is higher in postmenopausal women compared to similarly-aged men.[6–9] Greater arterial stiffness in females, compared to males, has been observed even prepuberty, with a dramatic increase postmenopause, suggesting sex-specific differences in the

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Initially submitted October 17, 2017; date of first revision January 27, 2018; accepted for publication February 16, 2018; online publication February 19, 2018

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biomechanical properties of the arterial wall throughout the lifespan.[10,11] In this regard, the Anglo-Cardiff Collaborative Trial found that augmentation pressure and augmentation index were higher in women compared to men within each decade of life, a sex-difference that persisted after adjustment for height.[12] However, there were no observed sex differences in aortic and brachial pulsed wave velocity (PWV) in that same study.[12] Moreover, the Framingham Offspring Study also found that women had larger reflected waves that was not fully explained by shorter average height of women compared to men,[13] a finding also seen in a cohort of older hypertensive adults.[14] However, the direct contribution of sex hormone levels to this process has not been extensively studied.

A previous analysis in the Multi-Ethnic Study of Atherosclerosis (MESA)[15] examining the association of sex hormones and carotid stiffness found a more androgenic hormone profile was associated with less distensible arteries and arterial remodeling in women but not men. In contrast, the Baltimore Longitudinal Study of Aging (BLSA) found that in men, higher levels of testosterone were associated with a decrease in arterial stiffness over a 12-year follow-up.[16] These studies suggest that the effect that sex hormones have on arterial stiffness differs by sex. Both the MESA[15] and BLSA[16] analyses examined carotid stiffness; however, stiffness of the proximal aorta, may better correlate with risk for CVD and mortality.[17]

There is a need to further understand the relation of sex hormone levels with aortic stiffness and changes in stiffness over time, particularly among women. Therefore, in a well-characterized cohort of men and postmenopausal women, we examined the associations between sex hormones [estradiol, testosterone, dehydroepiandrosterone (DHEA), and sex hormone binding globulin (SHBG)] and measures of aortic stiffness assessed by magnetic resonance imaging (MRI), both cross-sectionally and longitudinally. We hypothesized that a more androgenic profile (i.e., lower estradiol and higher free testosterone) would be associated with decreased aortic distensibility among women but not men.

METHODS

Study population

MESA is an ongoing prospective cohort study. It consists of 6,814 men and women, aged between 45 and 84 years and free of CVD at baseline, from 4 race/ethnicities (White, African American, Hispanic/Latino, Chinese) and recruited from 6 US centers (Baltimore City/County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota).[18] The baseline exam was conducted between 2000 and 2002. Participants attended up to 4 follow-up exams: Exam 2 (2002–2004), Exam 3 (2004–2005), Exam 4 (2005–2007), and Exam 5 (2010–2012). MRI was performed only at Exams 1 and 5.

Our study population (Figure 1) consisted of cross-sectional and longitudinal components. The cross-sectional component (N = 2,877) included participants with both available aortic MRI and sex hormone data from baseline exam. We included only participants with a preserved left ventricular ejection fraction (≥50%) given our interest in mechanisms that might explain sex differences in HFpEF risk. We restricted our female sample to postmenopausal women, as sex hormone levels differ drastically in premenopausal vs. postmenopausal states. Among those eligible for cross-sectional analyses, the longitudinal component (N = 1,005) consisted of participants who also had interpretable aortic MRI data at Exam 5.

The MESA protocols were approved by the institutional review boards of all collaborating institutions and the National Heart, Lung, and Blood Institute. Participation was voluntary and written informed consent was obtained at each study visit.

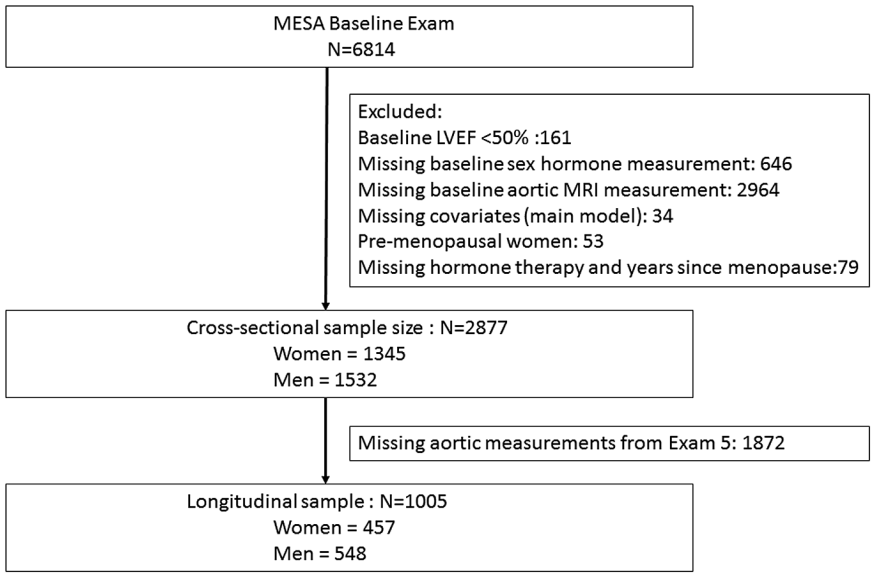

Figure 1. Flowchart of study sample. Abbreviation: MESA, Multi-Ethnic Study of Atherosclerosis.

Sex hormones

Fasting blood samples drawn in the morning at the baseline exam were used to measure serum sex hormone concentrations. Hormone assays were carried out at the University of Massachusetts Medical Center in Worcester, MA. Estradiol was measured using an ultrasensitive radioimmunoassay kit (Diagnostic System Laboratories, Webster, TX). Total testosterone and DHEA were measured directly with radioimmunoassay kits, and SHBG was measured by chemiluminescence enzyme immunometric assay using Immulite kits (Diagnostic Products Corporation, Los Angeles, CA).[19] Free testosterone (reported as percent of total testosterone) was calculated using the Sodergard method.[20] The intra-assay coefficients of variation for total testosterone, SHBG, DHEA, and estradiol were 12.3%, 9.0%, 11.2%, and 10.5%, respectively.

Aortic stiffness measures

Aortic MRI studies were performed using 1.5T MR Systems (MAGNETOM Avanto, Siemens Healthcare, Erlangen, Germany; and Signa, General Electric, Waukesha, WI) with a body-matrix coil and a spine-matrix coil, using 12 coil elements for both baseline and follow-up. As previously described,[3] this was done using the gradient echo phase-contrast cine MRI to evaluate aortic flow and aortic area. Ascending aortic strain (AAS) and ascending aorta distensibility (AAD) were determined from the maximum and minimum cross-sectional area of the aorta,[3] as measured by automated software (ARTFUN, INSERM, LIM).[21] Aortic arch PWV was calculated using transit time and distance between the ascending and descending aorta as described previously.[3,22] Distensibility was calculated using AAS and pulse pressure (PP) measurements made during the MRI scan. The formulas for the aortic stiffness parameters are presented in Supplementary Table 1. Reproducibility of aortic measurements by MRI has been previously described.[23] Intraobserver and interobserver intraclass correlation were: AAD (0.85, 0.70), AAS (0.87, 0.56), and PWV (0.96, 0.90).[3,23] Our primary outcome measure was AAD. Secondary outcomes included AAS (which was used to calculate AAD) and PWV.

Other covariates

Self-reported variables such as race/ethnicity, education level, smoking status, physical activity (intentional exercise in METS * min/week), and age at menopause were assessed using standardized questionnaires. Medication use, including current use of hormone therapy (HT), was determined by a medication inventory. Height and weight were measured per standardized procedures.[24] Resting blood pressure was measured 3 times in the seated position using a Dinamap automated sphygmomanometer, and the average of the 2nd and 3rd readings was used. Menopausal status was determined from an algorithm using self-report, age, age at menopause/hysterectomy/ovariectomy, and use of HT.[25] Only postmenopausal women were included in this analysis.

Statistical methods

Baseline characteristics of the study population by sex were evaluated using *t*-tests and χ^2 tests, respectively. Sex hormones levels were positively skewed and were therefore modeled as sex-specific tertiles with the lowest tertile as reference. Measures of aortic stiffness were also right skewed and log-transformed. In sex-stratified analyses, we examined the cross-sectional and longitudinal associations of each sex hormone separately with aortic stiffness parameters using multivariable-adjusted linear mixed effects models. The coefficients of the sex hormones address the cross-sectional difference of aortic stiffness at baseline by different sex hormones levels. The coefficient for the interactions between sex hormones and time address the difference in the annual rate of change of aortic stiffness measures associated with the sex hormones. We also used adjusted restricted cubic splines to visually depict nonlinear associations between sex hormone levels and aortic parameters at baseline. Our adjusted models included age, race/ethnicity, site, education, physical activity, smoking, height, weight, heart rate, mean arterial pressure, and use of antihypertensive medications. In women, we additionally adjusted for current HT use and years since menopause. Longitudinal models also adjusted for change in these covariates. We performed a supplemental model additionally adjusting for other CVD risk factors of total and HDL cholesterol, use of lipid lowering medications, diabetes, and estimated glomerular filtration rate. We performed a sensitivity analysis excluding women on current HT. Two-sided *P* values <0.05 were considered to be statistically significant. All analyses were performed on Stata version 14.

RESULTS

Participant characteristics

The baseline characteristics of the cross-sectional sample (N = 2,877), stratified by sex, are depicted in Table 1. On average, women were older than men, had lower levels of physical activity, were less likely to be smokers, had higher body mass index, heart rate, systolic blood pressure, and were more likely to be on antihypertensive medications, but had lower mean arterial pressure. One-third of the women were on current HT. As expected, sex hormone levels were significantly different between men and women, with men having higher levels of androgens and estradiol and lower levels of SHBG. Women also had lower average AAD than men ($P < 0.001$) but not PWV or AAS.

The baseline characteristics of the cross-sectional sample were further stratified by those who had a follow-up MRI (N = 1,005) vs. those with a baseline MRI only (N = 1,872) and presented in Supplementary Table 2. The participant characteristics at Exam 5 are shown in Supplementary Table 3. After a 10-year follow-up, there were no changes in the differences in risk factors by sex but an increase in those taking antihypertensive medications.

Table 1. Characteristics of study participants (*N* = 2,877) at the MESA baseline exam (2000–2002)

Characteristic	Women (*N* = 1,345)	Men (*N* = 1,532)	*P* value
Demographic factors			
Age (years)	65.1 (8.9)	62.0 (10.2)	<0.001
Race/ethnicity			
White, Caucasian	35.7	35.7	0.9
Chinese American	16.3	16.6	
Black, African American	27.4	26.3	
Hispanic	20.6	21.4	
Education			
<High school	22.1	16.7	<0.001
High school	20.5	15.2	
<College	29.1	24.8	
≥College	28.3	43.3	
Lifestyle factors			
Physical activity (METS*min/wk)	3450 (1665, 6075)	4348 (2078, 8160)	<0.001
Smoking status			
Never	60.6	42.0	<0.001
Former	29.5	43.6	
Current	9.9	14.4	
Cardiovascular risk factors			
Heart rate (beats/min)	63.8 (9.0)	61.3 (9.6)	<0.001
Body mass index (kg/m^2)	27.7 (5.4)	27.1 (4.0)	<0.01
Systolic blood pressure (mm Hg)	129.0 (23.7)	125.8 (19.7)	<0.001
Diastolic blood pressure (mm Hg)	69.1 (10.5)	74.8 (9.5)	<0.001
Mean arterial pressure (mm Hg)	89.0 (13.5)	91.8 (11.8)	<0.001
Antihypertensive medication	43.4	35.3	<0.001
Total cholesterol (mg/dl)	200.7 (33.9)	188.2 (33.5)	<0.001
HDL cholesterol (mg/dl)	57.2 (15.4)	45.5 (11.7)	<0.001
Cholesterol lowering meds	21.1	14.7	<0.001
Diabetes mellitus			
Normal	75.8	71.3	<0.01
Impaired fasting glucose	11.8	16.5	
Diabetes mellitus	12.4	12.2	
Glomerular filtration rate	75.8 (15.6)	78.6 (15.8)	<0.001
Creatinine	0.8 (0.7, 0.9)	1.0 (0.9, 1.2)	<0.001
Current hormone therapy	33.3		
Sex hormones			
Total T (nmol/l)	0.87 (0.56, 1.28)	14.37 (11.66, 17.87)	<0.001
Free T (%)	1.29 (0.88, 1.68)	1.99 (1.65, 2.33)	<0.001
Estradiol (nmol/l)	0.07 (0.04, 0.15)	0.11 (0.09, 0.14)	0.002
DHEA (nmol/l)	10.06 (7.04, 14.44)	12.79 (9.23, 17.32)	<0.001
SHBG (nmol/l)	59.5 (41.2, 95)	40.8 (31.4, 53.0)	<0.001
Aortic parameters			
Ascending aortic distensibility (mm Hg^{-1} 10^{-3})	1.13 (0.73, 1.82)	1.27 (0.79, 2.16)	<0.001
Pulse wave velocity (m/s)	7.77 (5.93, 10.48)	7.44 (5.93, 10.48)	0.89
Ascending aortic strain	6.87 (4.55, 10.37)	6.77 (4.44, 10.62)	0.84

Data are mean (SD), for normally distributed variables, median (25th, 75th percentiles) for skewed variables, or (%) of subjects for categorical variables. *P* values were obtained using *t*-test or chi-square test. Abbreviations: DHEA, dehydroepiandrosterone; MESA, Multi-Ethnic Study of Atherosclerosis; HDL, high density lipoprotein; T, testosterone; SHBG, sex hormone binding globulin.

Cross-sectional analysis

The continuous associations of free testosterone and SHBG levels with average adjusted difference in AAD are shown in Figure 2 and 3, respectively. These generally show that, in women, higher free testosterone was associated with lower AAD and higher SHBG was associated with greater AAD, with the opposite trend in men.

Among women (N = 1,345), the highest tertile (compared to the lowest) of free testosterone was significantly associated with lower log-transformed AAD [−0.10 (−0.19, −0.01)] (Table 2, adjusted) and lower AAS [−0.10 (−0.19, −0.01)] (Supplementary Table 4, adjusted). The highest tertile of SHBG was associated with borderline greater AAD [0.09 (−0.00, 0.19), P = 0.05] and greater AAS [0.09 (0.00, 0.18)]. The association of higher free testosterone with lower AAS remained significant in sensitivity analyses excluding women on HT [−0.12 (−0.23, -0.01), N = 923). Among men (N = 1,532), the highest tertile estradiol was significantly associated with greater AAD [0.12 (0.04, 0.20)], Table 2] and AAS [0.10 (0.03, 0.18), Supplementary Table 4].

In unadjusted analyses, higher free testosterone was inversely, and higher SHBG was positively, associated with higher aortic arch PWV (i.e., stiffness) in both men and women, while in men, higher estradiol and DHEA were also inversely associated with higher PWV (Table 3). However, there were no significant associations between sex hormones and baseline aortic arch PWV in either women or men after adjustment for age and other risk factors.

Associations of sex hormones for AAD and PWV were generally similar after further adjustment for lipids, diabetes, and estimated glomerular filtration rate (Supplementary Table 5).

Longitudinal analysis

After an average follow-up time of 10 years, 1,005 participants (457 women and 548 men) underwent a repeat MRI of the thoracic aorta. There were no significant associations of sex hormones with adjusted longitudinal change in AAD (Table 2) or AAS (Supplementary Table 4) in either sex. In men, the middle tertile of total testosterone, but not the highest tertile, was borderline associated with change in PWV (Table 3). The borderline association of the 2nd tertile of total testosterone with PWV in men persisted after adjusted for additional CVD risk factors (Supplementary Table 5).

DISCUSSION

In this well-characterized community-based cohort of individuals free of clinical CVD at baseline, we found significant associations between sex hormone levels and prevalent measures of aortic distensibility, which differed by sex. Specifically, a less androgenic pattern of sex hormones (i.e., lower free testosterone and higher SHBG) in women, and higher estradiol in men, were cross-sectionally associated with greater AAD and AAS. We did not find any cross-sectional associations of sex hormones with aortic arch PWV after adjustment. In longitudinal analyses, we did not find any associations of sex hormones with change in AAD after a 10-year follow-up, albeit in a smaller sample size of women and men. There was no longitudinal association of sex hormones with change in PWV either, except a borderline association for the middle tertile of total testosterone in men, which may be spurious.

The discrepant results between our cross-sectional and longitudinal results may possibly be attributed to several reasons. First, the baseline mean age (years) was 65 in women and 62 in men; thus, it is possible that at the time of the cross-sectional study the maximal effect of the hormones on aortic stiffness may have already been exerted resulting in significant associations at baseline with little to no progression at follow-up. Cross-sectional measures may be more robust because they are representative of the cumulative exposure over time to that point in time and the methods are more standardized, while longitudinal measures may vary because personnel and equipment have changed over 10-years' time.

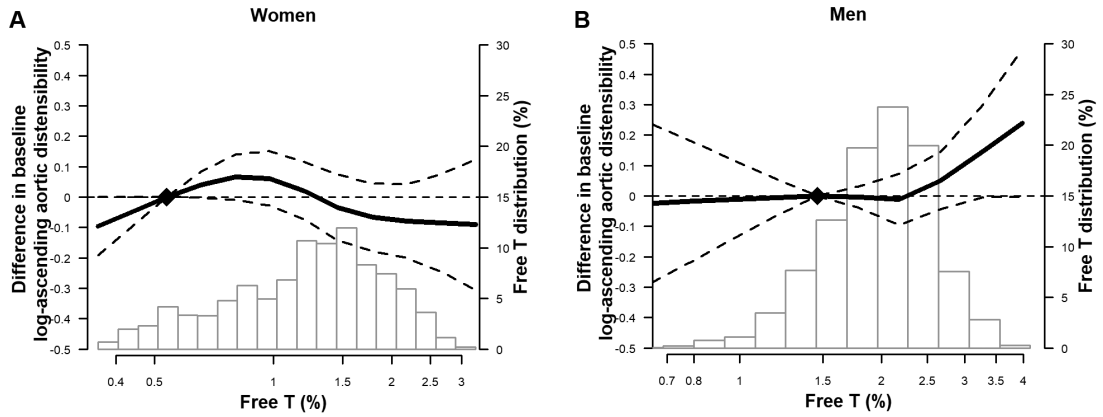

Figure 2. Adjusted differences of baseline ascending aortic distensibility in women (**a**) and men (**b**) associated with free testosterone levels (%) at baseline (MESA 2000–2002). Adjusted for age, race/ethnicity, study site, education, physical activity, smoking, height, weight, heart rate, mean arterial pressure, use of antihypertensive medications (women: additionally, adjusted for current hormone therapy, and years since menopause). Curves represent adjusted average difference (solid lines) and their 95% confidence intervals (dashed lines) of ascending aortic distensibility at baseline based on restricted cubic splines for free testosterone with knots at the 5th, 35th, 65th and 95th percentiles of their sample distributions. The reference values (diamond dots) were set at 10th percentile (women: 0.57%, men: 1.39% for free testosterone). Abbreviations: MESA, Multi-Ethnic Study of Atherosclerosis; T, testosterone.

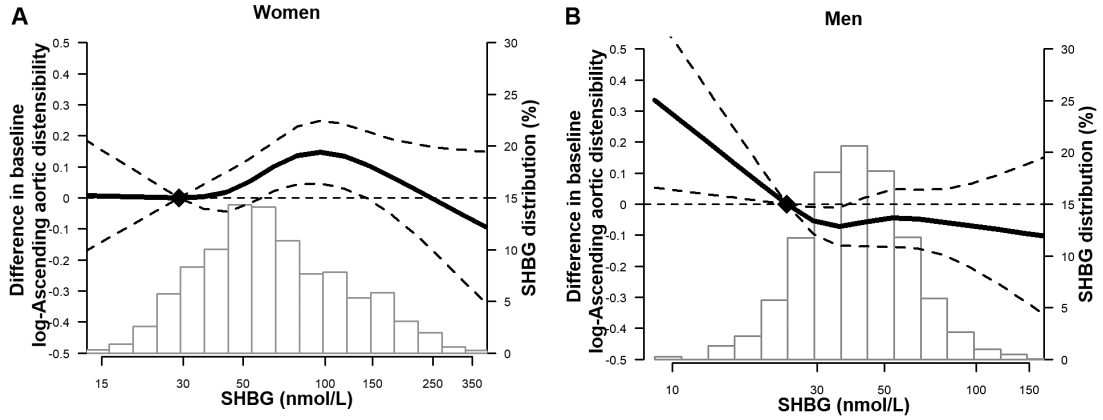

Figure 3. Adjusted differences of baseline ascending aortic distensibility in women (**a**) and men (**b**) associated with SHBG levels (nmol/l) at baseline (MESA 2000–2002). Adjusted age, race/ethnicity, study site, education, physical activity, smoking, height, weight, heart rate, mean arterial pressure, use of antihypertensive medications (women: additionally, adjusted for current hormone therapy and years since menopause). Curves represent adjusted average difference (solid lines) and their 95% confidence intervals (dashed lines) of ascending aortic distensibility at baseline based on restricted cubic splines for SHBG with knots at the 5th, 35th, 65th and 95th percentiles of their sample distributions. The reference values (diamond dots) were set at 10th percentile (women: 29.7 nmol/l, men: 24.2 nmol/l). Abbreviations: MESA, Multi-Ethnic Study of Atherosclerosis; SHBG, sex hormone binding globulin.

Additionally, the longitudinal sample (participants with a follow-up aortic MRI 10 years later) was half the size of the cross-sectional sample and may be underpowered, although coefficients were largely null. Nonetheless, our findings of the cross-sectional associations of sex hormone levels with prevalent measures of aortic distensibility in women and men may offer insight into mechanisms behind sex differences for HFpEF risk.

Sex hormones may play a role in aortic stiffness regulating the mechanical and elastic properties of arteries.[26] Sex hormone levels have been associated with traditional CVD risk factors such as blood pressure[27]; however, we found associations of lower free testosterone in women and higher estradiol in men to be cross-sectionally associated with aortic distensibility even after adjustment for mean arterial pressure, a potential mediating variable. Sex hormones may also influence aortic stiffness through their effects on the extracellular matrix components. Testosterone can promote the degradation of elastin and hence predisposes to stiffer arteries by increasing the amount of matrix metalloproteinase-3.[28] Estrogen may alter vascular endothelial cells to become spherical with a consequent increase in elasticity.[29]

Among men, prior work from the BLSA found that testosterone, free testosterone index, and DHEA were inversely associated, and SHBG positively associated, with stiffness of the large arteries, with total testosterone alone being significant after adjusting for age.[16] Similarly, among men in our study, we also found free testosterone and DHEA were inversely associated, and SHBG positively associated, with PWV in unadjusted data, but this did not persist after adjustment for age and other risk factors. Another study found these inverse associations were stronger among younger men with hypertension.[30] This may be due to microvascular dysfunction with worsening arterial stiffness in the presence of low testosterone.[31] However, a novel finding in our study was that higher estradiol levels in men were independently associated with greater AAD at baseline. Differences between these studies may be due to population characteristics or age-dependent effects of sex hormones on the aortic wall.[30]

Studies of postmenopausal women have found increased circulating levels of androgens are associated with increased measures of carotid arterial stiffness and carotid-femoral PWV.[15,32,33] Our study similarly found higher androgens (free testosterone) were also associated with lower baseline aortic distensibility assessed by aortic MRI in postmenopausal women, suggesting this may be a mechanism contributing to the increased risk of HFpEF in older women. Consistent with this, we previously found in this same cohort that a more androgenic sex hormone profile was associated with increased left ventricular mass in postmenopausal women.[19] We did not find an association of estradiol with aortic stiffness in women, but endogenous estradiol levels are low in women not on HT following the menopausal transition. Exogenous estrogen administration in the form of HT may have favorable effects on arterial stiffness.[34,35] The relation of sex hormones with CVD risk may differ among HT users and nonusers,[36] although we adjusted for HT use in our main models and excluded HT users in a sensitivity analysis.

Strengths of our study include conducting both cross-sectional and longitudinal analyses in a well-characterized cohort of women and men free of CVD at baseline, adjusted for important demographic, socioeconomic, and cardiovascular factors. We used MRI-derived aortic stiffness parameters. MRI is thought to reflect changes in the aorta more accurately, and the aorta contributes up to 50% of the total arterial compliance, which may not be captured by the measures of carotid arterial stiffness that has been done in the past.[3,37]

However, limitations include: (i) Sex hormones were measured only once at baseline, and therefore we could not assess for change in sex hormone levels. (ii) The coefficients of variation for the sex hormone assays are not negligible and could have led to misclassification. (iii) In the calculations of aortic distensibility, we used brachial PP as a surrogate for central PP. Per, the "amplification phenomenon" brachial PP

Table 2. Sex hormone levels with baseline and annual change in log-transformed ascending aortic distensibility over 10 years

		Ascending aortic distensibility (ΔlogAAD, units)			
		Cross sectional		Longitudinal	
	Sex hormones[a]	Unadjusted	Adjusted[b]	Unadjusted	Adjusted
Women	Total T_2	−0.08 (−0.17, 0.00)	−0.08 (−0.16, 0.00)	0.01 (−0.01, 0.03)	0.01 (−0.00, 0.03)
	Total T_3	−0.03 (−0.11, 0.06)	0.00 (−0.08, 0.08)	0.01 (−0.01, 0.02)	0.01 (−0.01, 0.02)
	E2_2	0.08 (−0.00, 0.17)	0.08 (−0.00, 0.16)	−0.00 (−0.02, 0.02)	−0.01 (−0.02, 0.01)
	E2_3	**0.10 (0.01, 0.18)**	0.03 (−0.08, 0.14)	−0.00 (−0.02, 0.01)	0.00 (−0.02, 0.02)
	DHEA_2	−0.02 (−0.11, 0.07)	−0.05 (−0.14, 0.03)	0.02 (−0.00, 0.03)	0.01 (−0.01, 0.03)
	DHEA_3	0.08 (−0.01, 0.17)	0.00 (−0.08, 0.09)	0.00 (−0.01, 0.02)	0.00 (−0.01, 0.02)
	Free T_2	−0.04 (−0.13, 0.05)	−0.03 (−0.12, 0.06)	0.00 (−0.02, 0.02)	0.00 (−0.01, 0.02)
	Free T_3	−0.07 (−0.15, 0.02)	**−0.10 (−0.19, −0.01)**	0.00 (−0.01, 0.02)	0.00 (−0.02, 0.02)
	SHBG_2	0.04 (−0.05, 0.13)	0.08 (−0.00, 0.16)	−0.00 (−0.02, 0.01)	−0.00 (−0.02, 0.02)
	SHBG_3	0.06 (−0.03, 0.15)	0.09 (−0.00, 0.19)	−0.00 (−0.02, 0.01)	−0.00 (−0.02, 0.02)
	(*N*)	1,345	1,345	457	457
Men	Total T_2	0.04 (−0.05, 0.13)	0.01 (−0.07, 0.09)	0.01 (−0.01, 0.02)	0.01 (−0.01, 0.02)
	Total T_3	−0.00 (−0.09, 0.09)	−0.04 (−0.12, 0.05)	−0.00 (−0.02, 0.01)	−0.00 (−0.02, 0.01)
	E2_2	0.08 (−0.01, 0.17)	0.04 (−0.04, 0.11)	−0.00 (−0.02, 0.01)	−0.00 (−0.02, 0.01)
	E2_3	**0.17 (0.08, 0.26)**	**0.12 (0.04, 0.20)**	−0.01 (−0.02, 0.01)	−0.01 (−0.02, 0.01)
	DHEA_2	0.07 (−0.02, 0.16)	−0.04 (−0.13, 0.04)	0.01 (−0.01, 0.02)	0.01 (−0.01, 0.02)
	DHEA_3	**0.23 (0.14, 0.31)**	0.02 (−0.07, 0.11)	−0.01 (−0.02, 0.01)	−0.01 (−0.02, 0.01)
	Free T_2	0.08 (−0.00, 0.17)	−0.03 (−0.11, 0.05)	−0.01 (−0.03, 0.01)	−0.01 (−0.03, 0.00)
	Free T_3	**0.25 (0.16, 0.34)**	0.03 (−0.06, 0.11)	−0.01 (−0.02, 0.01)	−0.01 (−0.03, 0.00)
	SHBG_2	**−0.16 (−0.25, −0.07)**	−0.07 (−0.15, 0.01)	0.00 (−0.01, 0.02)	0.00 (−0.01, 0.02)
	SHBG_3	**−0.23 (−0.32, −0.14)**	−0.02 (−0.11, 0.06)	0.01 (−0.01, 0.02)	0.01 (−0.00, 0.03)
	(*N*)	1532	1,532	548	548

Results reflect the associations [in β coefficients (95% CI)] of difference in baseline sex hormone levels (per tertile) with baseline (Exam 1, 2000–2002) and difference in annual change in log-transformed Ascending Aortic Distensibility (mm Hg^{-1} 10^{-3}) over a 10-year period (Exam 5, 2010–2012) among men and women in MESA. Tertile 1 of sex hormone serves as reference value. Statistically significant ($P < 0.05$) results are in bold. Abbreviations: AAD, ascending aorta distensibility; CI, confidence interval; DHEA, dehydroepiandrosterone; E2, estradiol; MESA, Multi-Ethnic Study of Atherosclerosis; T, testosterone; SHBG, sex hormone binding globulin.

[a]Range of sex hormone tertiles:•

Total T (nmol/l): (for men: tertile 1 ≤ 12.49, tertile 2 = 12.56–16.38, tertile 3 ≥ 16.41; for women: tertile 1 ≤ 0.66, tertile 2 = 0.69–1.11, tertile 3 ≥ 1.15).•

E2 (nmol/l): (for men: tertile 1 ≤ 0.095, tertile 2 = 0.099–0.128, tertile 3 ≥ 0.13; for women: tertile 1 ≤ 0.05, tertile 2 = 0.06–0.11, tertile 3 ≥ 0.11).•

DHEA (nmol/l): (for men: tertile 1 ≤ 10.27; tertile 2 = 10.31–15.75, tertile 3 ≥ 15.82; for women: tertile 1 ≤ 8.19, tertile 2 = 8.22–12.91, tertile 3 ≥ 12.94).•

Free T %: (for men: tertile 1 ≤ 1.80%, tertile 2 = 1.80–2.24%, tertile 3 ≥ 2.25%; for women: tertile 1 ≤ 1.03%, tertile 2 = 1.04–1.53 %, tertile 3 ≥ 1.54%).•

SHBG (nmol/l) (for men: tertile 1 ≤ 33.9, tertile 2 = 34.1–47.0, tertile 3 ≥ 47.1; for women: tertile 1 ≤ 47.2, tertile 2 = 47.6–79.6, tertile 3 ≥ 79.9).

[b]Model adjusts for age, race/ethnicity, site, education, baseline (cross sectional) and change (longitudinal) in physical activity, smoking, height, weight, heart rate, mean arterial pressure, use of antihypertensive medication (women: additionally, adjusted for current hormone therapy use, years since menopause).

may overestimate central PP in a younger population, but in an older population (as in MESA), it is more comparable.[38] (iv) Cross-sectional results are subject to temporal and selection bias while longitudinal results are subject to selection and survival bias. (v) Associations are modest (presented in ΔlogAAD units) but similar in magnitude with several traditional risk factors.[3] (vi) We performed multiple testing giving rise to the possibility that findings were obtained by chance, although results were generally consistent with the prior literature and with our *a priori* hypotheses. Our study was meant to be exploratory and could guide further testing in this area. (vii) Our cohort consisted of postmenopausal women, as HFpEF predominantly affects this age group; however, additional insight on the role of sex hormones at

Table 3. Sex hormone levels with baseline and annual change in log-transformed pulse wave velocity over 10 years

		Pulse wave velocity (ΔlogPWV, units)			
		Cross sectional		Longitudinal	
	Sex hormones[a]	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
Women	Total T_2	0.03 (−0.03, 0.08)	0.02 (−0.03, 0.07)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)
	Total T_3	0.03 (−0.03, 0.08)	0.01 (−0.04, 0.07)	−0.01 (−0.02, 0.01)	−0.00 (−0.01, 0.01)
	E2_2	−0.04 (−0.09, 0.02)	−0.01 (−0.06, 0.04)	−0.01 (−0.02, 0.00)	−0.01 (−0.02, 0.00)
	E2_3	−0.03 (−0.08, 0.03)	0.03 (−0.04, 0.10)	−0.01 (−0.02, 0.00)	−0.01 (−0.02, 0.00)
	DHEA_2	−0.01 (−0.06, 0.05)	0.01 (−0.04, 0.07)	0.01 (−0.00, 0.02)	0.01 (−0.00, 0.02)
	DHEA_3	0.00 (−0.06, 0.06)	0.05 (−0.01, 0.10)	−0.00 (−0.01, 0.01)	−0.01 (−0.02, 0.01)
	Free T_2	−0.01 (−0.07, 0.04)	−0.03 (−0.08, 0.03)	0.01 (−0.00, 0.02)	0.01 (−0.00, 0.02)
	Free T_3	**−0.06 (−0.12, −0.01)**	−0.04 (−0.10, 0.02)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)
	SHBG_2	0.05 (−0.01, 0.10)	0.01 (−0.04, 0.07)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)
	SHBG_3	**0.07 (0.01, 0.12)**	0.04 (−0.02, 0.11)	−0.01 (−0.02, 0.01)	−0.00 (−0.01, 0.01)
	(*N*)	1,345	1,345	457	457
Men	Total T_2	−0.05 (−0.11, 0.00)	−0.04 (−0.09, 0.01)	**0.01 (0.00, 0.02)**	**0.01 (0.00, 0.02)**
	Total T_3	−0.00 (−0.06, 0.05)	−0.00 (−0.05, 0.05)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)
	E2_2	**−0.07 (−0.13, −0.02)**	−0.03 (−0.08, 0.02)	0.01 (−0.00, 0.01)	0.00 (−0.01, 0.01)
	E2_3	**−0.10 (−0.16, −0.05)**	−0.03 (−0.08, 0.02)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)
	DHEA_2	**−0.11 (−0.17, −0.06)**	−0.02 (−0.07, 0.03)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)
	DHEA_3	**−0.16 (−0.22, −0.11)**	0.01 (−0.05, 0.07)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)
	Free T_2	**−0.13 (−0.18, −0.07)**	−0.03 (−0.08, 0.02)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)
	Free T_3	**−0.19 (−0.25, −0.14)**	−0.00 (−0.06, 0.05)	0.00 (−0.01, 0.01)	0.00 (−0.01, 0.01)
	SHBG_2	**0.08 (0.02, 0.13)**	−0.01 (−0.06, 0.05)	−0.00 (−0.01, 0.01)	−0.00 (−0.01, 0.01)
	SHBG_3	**0.20 (0.14, 0.25)**	0.02 (−0.03, 0.08)	−0.00 (−0.01, 0.01)	−0.00 (−0.01, 0.01)
	(*N*)	1,532	1,532	548	548

Results reflect the associations [in β coefficients (95% CI)] of difference in baseline sex hormone levels (per tertile) with baseline (Exam 1, 2000–2002) and difference in annual change in log-transformed Pulse Wave Velocity over a 10-year period (Exam 5, 2010–2012) among men and women in MESA. Tertile 1 of sex hormones serves as reference value. Statistically significant ($P < 0.05$) results are in bold. Abbreviations: CI, confidence interval; DHEA, dehydroepiandrosterone; E2, estradiol; MESA, Multi-Ethnic Study of Atherosclerosis; T, testosterone; SHBG, sex hormone binding globulin; PWV, pulse wave velocity.

[a]For range of sex hormone tertiles, please see footnote to Table 2.

[b]Model adjusts for adjusts for age, race/ethnicity, site, education, baseline (cross sectional) and change (longitudinal) in physical activity, smoking, height, weight, heart rate, mean arterial pressure, use of antihypertensive medication (women: additionally, adjusted for current hormone therapy use, years since menopause).

the menopausal transition could be obtained in future work by studying a perimenopausal age group.

CONCLUSIONS

In summary, our study was focused on gaining a better understanding of the potential contribution of sex hormone levels to arterial stiffness and HFpEF risk and the female preponderance for both. We found associations of sex hormone levels with prevalent measures of aortic stiffness, which differed by sex. As such, sex hormone levels may identify individuals at higher vascular risk that might benefit from other risk reducing strategies. Further experimental studies are needed to elucidate whether changes in sex hormone levels influence aortic stiffness over time.

SUPPLEMENTARY DATA

Supplementary materials are available at *American Journal of Hypertension* online.

ACKNOWLEDGMENTS

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org. Dr Subramanya's fellowship and this work was supported by the American Heart Association (AHA) Go Red for Women Strategic Focused

Research Network contract AHA 16SFRN27870000. Drs. Michos and Zhao were supported by the Blumenthal Scholars Fund for Preventive Cardiology Research. Dr Shah is supported by National Institutes of Health (NIH) National Heart, Lung, and Blood Institute grants R01 HL107577 and R01 HL127028, and by AHA grant #16SFRN28780016. The MESA study was supported by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the NIH National Heart, Lung, and Blood Institute, and by R01 HL074406 and R01 HL074338.

DISCLOSURE

Unrelated to this work, Dr Michos has received an honorarium from Siemens Healthcare Diagnostics for being a blinded medical events adjudicator for a clinical trial (in 2016). Dr Ouyang has research grant support from Cordex Systems. Other authors declared no conflict of interest.

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