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Sex Hormones and the Risk of Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis (MESA)

Wesley T. O'Neal, MD, MPH[1], **Saman Nazarian, MD, PhD**[2], **Alvaro Alonso, MD, PhD**[3], **Susan R. Heckbert, MD, PhD**[4,5], **Viola Vaccarino, MD, PhD**[1,3], and **Elsayed Z. Soliman, MD, MSc, MS**[6,7]

[1]Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA

[2]Department of Medicine, Division of Cardiology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

[3]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA

[4]Cardiovascular Health Research Unit, University of Washington, Seattle, WA, USA

[5]Department of Epidemiology, University of Washington, Seattle, WA, USA

[6]Department of Internal Medicine, Section on Cardiology, Wake Forest School of Medicine, Winston-Salem, NC, USA

[7]Epidemiological Cardiology Research Center (EPICARE), Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, NC, USA

Abstract

Purpose—Atrial fibrillation (AF) is more prevalent in men than women. Due to these sex differences in AF susceptibility, we examined whether sex hormones have differing associations with AF risk in men and women.

Methods—This analysis included 4,883 (mean age=63±10 years; 39% women; 64% non-white) participants from the Multi-Ethnic Study of Atherosclerosis. Sex hormones (total testosterone, bioavailable testosterone, estradiol, and sex hormone binding globulin (SHBG)) were measured at baseline (2000–2002) for all male and all postmenopausal female participants. AF was ascertained by hospital discharge records, Medicare claims data, and study electrocardiograms through December 31, 2012.

Results—Over a median follow-up of 10.9 years, a total of 613 (13%) AF cases were detected. A higher incidence rate of AF was observed for males (n=385, age-standardized incidence rate per

Corresponding Author: Wesley T. O'Neal, MD, Department of Medicine, Division of Cardiology, 101 Woodruff Circle, Woodruff Memorial Building, Atlanta GA 30322 USA, wesley.oneal@emory.edu.

COMPLIANCE WITH ETHICAL STANDARDS

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

1000 person-years=12.3, 95%CI=11.1, 13.6) than females (n=228, age-standardized incidence rate per 1000 person-years=9.0, 95%CI=7.9, 10.3). In men, higher bioavailable testosterone levels were associated with increased AF risk (HR=1.32, 95%CI=1.01, 1.74; p=0.044; comparing 3rd to 1st tertile), while an association in the opposite direction was observed for women (HR=0.81, 95%CI=0.58, 1.13; p=0.22; comparing 3rd to 1st tertile). Other hormones were not associated with AF in men or women.

Conclusion—Higher levels of endogenous bioavailable testosterone contribute to AF development in men. The combination of endogenous bioavailable testosterone and other risk factors potentially are important for AF development in men.

Keywords

sex hormones; atrial fibrillation; epidemiology; risk

INTRODUCTION

Atrial fibrillation (AF) is more prevalent in men compared with women, but the reasons for these sex differences remain unclear [1,2]. Prior reports have demonstrated sex differences in the prevalence of AF risk factors [3,4], suggesting that men and women have different predisposing factors to AF development. Additionally, women who have AF have a higher risk of adverse events compared with their male counterparts [5–9].

Sex hormone levels have been associated with well-known AF risk factors, such as increased adiposity [10], hypertension [11], and diabetes [12]. Additionally, a report from the Framingham Heart Study has demonstrated that lower levels of total testosterone and estradiol were associated with an increased risk of AF in Caucasian men [13]. Therefore, it is plausible sex hormones have differing associations with AF risk in men and women. Accordingly, the purpose of this analysis was to examine the prospective association of endogenous sex hormones with incident AF by sex in the Multi-Ethnic Study of Atherosclerosis (MESA).

METHODS

Study Population

Details of MESA have been reported previously [14]. Briefly, between July 2000 and September 2002, a total of 6,814 persons were recruited at 6 field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota). Participants were required to be between 45 and 84 years of age and to have no clinical cardiovascular disease at baseline. All participants provided informed consent and the study protocol was approved by the Institutional Review Boards at each participating institution. For the purpose of this analysis, participants were excluded if baseline AF was present, or the following were missing: sex hormone measurements, baseline characteristics, or follow-up AF data. The analysis also was limited to postmenopausal women who did not report the current use of hormone replacement therapy at baseline, and men without reported testosterone replacement therapy. Women

were considered postmenopausal if they reported prior menopause at the time of sex hormone measurements.

Baseline Characteristics

Participant characteristics were collected during the initial MESA visit. Age, sex, race/ethnicity, income, and education were self-reported. Annual income was categorized as < $25,000, $25,000–$49,999, $50,000–$74,999 or ≥$75,000, and education was categorized as "high school or less," "some college," or "college or more." Smoking was defined as the current use of cigarettes. Blood samples were obtained after a 12-hour fast and plasma glucose was measured. Diabetes was defined as fasting glucose values ≥126 mg/dL or a history of diabetes medication use. Blood pressure was measured for each participant after 5 minutes in the seated position. Systolic measurements were recorded 3 separate times and the mean of the last 2 values was used. Aspirin, antihypertensive, and lipid-lowering medication use were self-reported and confirmed by pill bottle review. Body mass index was computed as the weight in kilograms divided by the square of the height in meters. Left ventricular hypertrophy was defined by the Cornell criteria (R wave amplitude AV_L plus S wave amplitude V_3 ≥2.8 mV in males and ≥2.0 mV in females) using baseline electrocardiogram data [15].

Sex Hormones

Sex hormones were measured at baseline for all male and all postmenopausal female participants from blood samples, and the methodology for serum hormone measurements have been reported previously [16]. Sex hormone measurements for total testosterone, bioavailable testosterone, estradiol, and sex hormone binding globulin (SHBG) were used in this analysis. Bioavailable testosterone was determined as total testosterone minus SHBG-bound testosterone. Reference ranges for the sex hormones examined in this analysis are shown in Supplemental Table 1. Of note, higher estradiol levels were observed in men compared with the postmenopausal women in this analysis. This was expected due to the lack of gonadal estradiol synthesis after menopause [17].

Atrial Fibrillation

Incident AF events were ascertained through December 31, 2012. Study participants were contacted by telephone every 9–12 months during follow-up and were asked to report all hospitalizations. Medical records, including discharge diagnoses, were obtained for each hospitalization. Additionally, for participants 65 years or older enrolled in fee-for-service Medicare, Medicare claims data were used to identify AF diagnoses in the inpatient and outpatient settings. Incident AF was defined by International Classification of Diseases Ninth Revision codes 427.31 or 427.32. Electrocardiograms from study visit 5 also were used to ascertain incident AF.

Statistical analysis

Baseline characteristics were compared between men and women. Categorical variables were reported as frequency and percentage, while continuous variables were recorded as mean ± standard deviation. Statistical significance for categorical variables was tested using

the chi-square method, and for continuous variables using the student's t-test. We examined the association of each sex hormone with incident AF in men and women, separately. Participants entered the analysis at the initial study visit and were followed until one of the following: diagnosis of AF, death, loss to follow-up, or end of follow-up (December 31, 2012). Age-standardized cumulative incidence estimates were computed for AF in men and women, separately. Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between each hormone using tertiles (tertile 1=referent) and incident AF. Multivariable models were adjusted for the following covariates: age, race, education, income, current smoking, study site, diabetes, systolic blood pressure, height, body mass index, aspirin, antihypertensive medications, lipid-lowering therapies, and left ventricular hypertrophy. Due to the expected decline in testosterone levels with advanced age, we tested for interactions with age in the associations of total testosterone and bioavailable testosterone with AF, separately. However, they were not significant (total testosterone: p=0.81; bioavailable testosterone: p=0.30) and thus the analyses for total testosterone and bioavailable testosterone were not stratified by age. Interaction terms also were computed by sex across sex-specific tertiles of sex hormone levels for each sex hormone. The proportional hazards assumption was not violated in our analyses. Statistical significance was defined as $p < 0.05$. SAS Version 9.4 (Cary, NC) was used for all analyses.

RESULTS

A total of 4,883 (mean age= 63±10 years; 39% women; 36% white; 13% Chinese-American; 27% Black; 24% Hispanic) participants were included in the final analysis. Baseline characteristics stratified by sex are shown in Table 1. The distributions of sex hormones in men and women are shown in Table 2.

Over a median follow-up of 10.9 years (25th–75th percentiles=10.2, 11.6), a total of 613 (13%) cases of incident AF were detected. A higher incidence rate of AF was observed for males (n=385, age-standardized incidence rate per 1000 person-years=12.3, 95%CI=11.1, 13.6) than females (n=228, age-standardized incidence rate per 1000 person-years=9.0, 95%CI=7.9, 10.3).

The associations between each sex hormone and AF are shown in Table 3. Of the sex hormones examined, higher bioavailable testosterone levels were associated with AF risk in men (HR=1.32, 95%CI=1.01, 1.74; p=0.044; comparing 3rd to 1st tertile), and the association for bioavailable testosterone in women was in the opposite direction (HR=0.81, 95%CI=0.58, 1.13; p=0.22; comparing 3rd to 1st tertile; p-interaction=0.15). Other hormones examined were not associated with AF in men or women.

DISCUSSION

In this analysis from MESA, we examined whether sex hormones had differing associations with AF risk in men and women. Higher circulating levels of bioavailable testosterone were associated with an increased risk for AF in men. The other sex hormones examined were not associated with AF in men or women.

It is well-documented that men are more likely to develop AF compared with women [1,2]. Sex differences in height have been reported as a possible explanation for the predilection for AF in men compared with women [18], presumably due to variation in atrial dimensions. This is supported by data demonstrating that women have smaller left atria compared with men [19]. Other reports have suggested differences in atrial electrophysiology by sex. Advanced interatrial block more commonly develops in men than women, and this electrocardiographic phenotype precedes AF development [20]. Furthermore, sex differences in P-wave indices have been reported, providing support that atrial conduction varies between men and women [21]. Overall, these reports provide evidence that women are less likely to develop AF than men, and this phenomenon possibly is related to differences in adverse atrial remodeling.

The findings of the current analysis suggest that men are more likely to develop AF with higher levels of bioavailable testosterone. Similar findings were not observed with the other sex hormones in men or women. Possibly, higher levels of bioavailable testosterone are associated with adverse atrial remodeling in which AF is likely to develop in men. Accordingly, the combination of increased levels of bioavailable testosterone and other well-known risk factors possibly are important in AF development in men.

To our knowledge, only one study has examined the influence of sex hormones on AF development. A report of 1,251 men from the Framingham Heart Study showed that lower levels of total testosterone and estradiol were associated with a higher risk of AF [13]. In contrast, total testosterone and estradiol were not associated with incident AF in the current analysis. However, we have demonstrated that higher levels of bioavailable testosterone are associated with a higher risk of AF in men. Differences between the findings from the Framingham Heart Study and the current report possibly are related to variation in the study populations examined, as the men in the Framingham Heart Study were largely Caucasian and older compared with the male participants in MESA. Additionally, we were able to examine the relationship between bioavailable testosterone and AF, and this was not done in the Framingham Heart Study. Possibly, bioavailable testosterone reflects a more accurate measurement of this sex hormone with regard to AF risk.

Our results should be interpreted in the context of certain limitations. Sex hormones were measured at baseline and it is possible that the risk of AF varies with fluctuations in the level of each hormone. Incident AF was ascertained from hospitalization discharge records and Medicare claims using International Classification of Diseases codes, which possibly resulted in misclassification. However, these codes have adequate positive predictive value for the identification of AF events [22]. We did not have data on other important AF risk factors, such as left atrial diameter, and the results possibly vary when accounting for this factor. Additionally, data on thyroid function were not available and this factor potentially influenced our findings. Furthermore, we included several covariates in our multivariable models, but we acknowledge that residual confounding remains a possibility.

In conclusion, the findings in this analysis suggest that bioavailable testosterone contributes to the risk of AF in men. Potentially, the combination of endogenous bioavailable testosterone and other risk factors are important in AF development in men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline Characteristics (N=4,883)

Characteristic	Men (n=3,003)	Women (n=1,880)	P-value
Age, mean ± SD, years	62 ± 10	65 ± 9.2	<0.001
Race/ethnicity			
White (%)	1,184 (40)	574 (31)	
Chinese-American (%)	387 (13)	265 (14)	
Black (%)	730 (24)	561 (30)	
Hispanic (%)	702 (23)	480 (25)	<0.001
Education			
High school or less (%)	926 (31)	891 (47)	
Some college (%)	817 (27)	540 (29)	
College or more (%)	1,260 (42)	449 (24)	<0.001
Annual income			
< $25,000 (%)	770 (26)	876 (47)	
$25,000 to $49,999 (%)	820 (27)	548 (29)	
$50,000 to $74,999 (%)	570 (19)	234 (12)	
≥ $75,000 (%)	843 (28)	222 (12)	<0.001
Current smoker (%)	430 (14)	197 (10)	<0.001
Diabetes (%)	453 (15)	286 (15)	0.90
Height, mean ± SD, cm	174 ± 7.6	159 ± 7.3	<0.001
Body mass index, mean ± SD, kg/m^2	28 ± 4.4	29 ± 6.1	<0.001
Systolic blood pressure, mean ± SD, mm Hg	126 ± 19	130 ± 24	<0.001
Antihypertensive medication use (%)	1,041 (35)	747 (40)	<0.001
Aspirin use (%)	821 (27)	407 (22)	<0.001
Lipid lowering medication use (%)	482 (16)	353 (19)	0.014
Left ventricular hypertrophy (%)	50 (1.7)	142 (7.6)	<0.001

*Statistical significance for continuous data was tested using the student's t-test procedure and for categorical data the chi-square test was used.

SD=standard deviation.

Table 2

Distributions of Sex Hormones (N=4,883)

Sex Hormone	Men (n=3,003)	Women (n=1,880)
Total testosterone (nmol/L)		
mean ± SD	14.9 ± 5.5	1.1 ± 0.87
median	14.2	0.94
Quartile 1, 3	12.3. 16.4	0.73, 1.2
Bioavailable testosterone (nmol/L)		
mean ± SD	5.5 ± 2.1	0.32 ± 0.30
median	5.2	0.24
Quartile 1, 3	4.6, 6.0	0.17, 0.35
Estradiol (nmol/L)		
mean ± SD	0.12 ± 0.05	0.075 ± 0.078
median	0.11	0.059
Quartile 1, 3	0.10, 0.13	0.05, 0.07
SHBG (nmol/L)		
mean ± SD	44.2 ± 19.3	57.2 ± 30.7
median	40.6	50.1
Quartile 1, 3	34.1, 48.1	40.9, 62.2

SHBG=sex hormone binding globulin; SD=standard deviation.

Table 3

Risk of AF associated with Sex Hormones in Men and Women

Sex Hormone	AF Cases	Men (N=3,003)		Women (N=1,880)		P-interaction
		HR* (95%CI)	P-value	HR* (95%CI)	P-value	
Total testosterone						
Tertile 1	210	Ref	-	Ref	-	
Tertile 2	197	1.12 (0.87, 1.45)	0.36	0.99 (0.72, 1.38)	0.98	0.61
Tertile 3	206	1.20 (0.93, 1.55)	0.16	0.96 (0.70, 1.32)	0.80	
Bioavailable testosterone						
Tertile 1	254	Ref	-	Ref	-	
Tertile 2	195	0.96 (0.75, 1.74)	0.71	0.96 (0.69, 1.32)	0.79	0.15
Tertile 3	164	1.32 (1.01, 1.74)	0.044	0.81 (0.58, 1.13)	0.22	
Estradiol						
Tertile 1	240	Ref	-	Ref	-	
Tertile 2	180	0.85 (0.66, 1.09)	0.19	0.89 (0.64, 1.23)	0.47	0.47
Tertile 3	193	1.09 (0.84, 1.40)	0.51	0.84 (0.60, 1.16)	0.28	
SHBG						
Tertile 1	143	Ref	-	Ref	-	
Tertile 2	209	1.05 (0.79, 1.39)	0.73	1.34 (0.94, 1.91)	0.10	0.83
Tertile 3	261	1.04 (0.78, 1.39)	0.77	1.39 (0.96, 1.99)	0.079	

*Adjusted for age, race, education, income, current smoking, study site, diabetes, systolic blood pressure, height, body mass index, aspirin, antihypertensive medications, lipid-lowering therapies, and left ventricular hypertrophy.

AF=atrial fibrillation; CI=confidence interval; HR=hazard ratio; SHBG=sex hormone binding globulin.