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Plasma total testosterone and risk of incident atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) Study

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

The institutional review boards of each participating university approved the ARIC protocol, and participants provided informed consent at each ARIC examination.

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There are no linked research data sets for this submission. The authors are unable or have chosen not to specify which data set has been used.

Abstract

Objective: Whether endogenous testosterone concentrations are associated with atrial fibrillation (AF) development is not well established. We assessed the association between plasma total testosterone concentrations and incident AF in a population-based longitudinal study.

Study design: Using data from the prospective Atherosclerosis Risk in Communities (ARIC) study, we identified incident AF among 9,282 participants who had plasma total testosterone measured by liquid chromatography tandem mass spectrometry at Visit 4 (1996-1998).

Main outcome measures: AF cases were identified by electrocardiograms performed during study visits, hospital records/discharge codes, and death certificates through 2013. We estimated hazard ratios (HRs) and 95% confidence intervals (95% CIs) for incident AF across quartiles of plasma total testosterone, stratified by sex, with multivariable Cox models.

Results: The mean age of the participant sample at ARIC Visit 4 was 63 years (range 52-75); 54.5% were women. Mean (SD) plasma total testosterone levels were 537 ng/dL (213) for men and 27.6 ng/dL (34.7) for women. Over a mean of 13.7 years of follow-up, 1664 incident cases of AF were identified. Comparing those in the highest quartile of plasma total testosterone concentration to those in the lowest quartile and after adjustment for potential confounding variables, there was a positive association between plasma total testosterone and incident AF in men (HR 1.33, 95% CI 1.07, 1.66), but no such association in women (HR 0.99, 95% CI 0.80, 1.22).

Conclusion: A higher plasma total testosterone concentration was associated with a modestly greater incidence rate of AF in men.

Keywords

Testosterone; Atrial fibrillation; Epidemiology; ARIC study

1. Introduction

Atrial fibrillation (AF) is one of the most commonly observed chronic cardiac arrhythmias in the United States [1]. Lifetime risks for AF are high (1 in 6), even in the absence of antecedent congestive heart failure or myocardial infarction [2]. Despite advancements in treatment, rates of AF, and the associated morbidity and mortality, continue to increase over time [3]. AF prevalence tends to increase with age and is higher in men than in women [4]. The underlying mechanisms of these age and sex differences have not been fully elucidated [5, 6]. Besides age and sex, other major risk factors for AF include hypertension and other cardiac diseases like coronary heart disease (CHD) and heart failure (HF). Type 2 diabetes, obesity, and cigarette smoking are also considered other risk factors [7]. Testosterone is a hormone that has many different effects on the human body, including muscle growth and maintenance, bone development while inhibiting bone reabsorption, stimulating the production of red blood cells, libido, enhanced mood and cognition, erectile function and lipolysis, among others [8]. Testosterone levels tend to decrease with age, particularly in men [9]. The age related decline in testosterone levels has been implicated as a possible explanation for the age related increase in risk of coronary artery disease, hypertension and

heart failure, which are predisposing factors for the future development of AF [5, 10]. However, potential physiologic pathways from reduced testosterone to AF incidence are unknown and, if causal, are likely heterogeneous and multifactorial [11]. Existing data on testosterone concentrations in humans is limited mostly to men, and there often is not comparable research on women [3]. Due to its large amount of data on both sexes, the Atherosclerosis Risk in Communities (ARIC) study gives the opportunity to better analyze the possible role of endogenous testosterone in the pathogenesis of AF in men and women. Investigations on this potential association may be relevant to the ongoing debate about whether testosterone replacement therapy is an appropriate cardiovascular disease preventive strategy for those with low testosterone levels. We explored the association of concentrations of plasma total testosterone with the incidence of newly diagnosed AF. Based on similar patterns of association between testosterone and diabetes [12, 13], we hypothesized that testosterone concentration would be inversely associated with AF risk in men, but positively associated in women.

2. Materials and methods

2.1. Study population

The ARIC study is a prospective epidemiologic cohort study designed to investigate and identify natural history, etiology, and risk factors for atherosclerosis and other cardiovascular diseases [14]. A total of 15,792 men and women were recruited from four communities in the United States in 1987-1989. The institutional review boards of each participating university approved the ARIC protocol, and participants provided informed consent at each ARIC examination. Participants were invited for reexamination in 1990-1992 (Visit 2), 1993-1995 (Visit 3), 1996-1998 (Visit 4), 2011-2013 (Visit 5), and 2016-2017 (Visit 6). Follow up phone calls were performed annually through 2012 and semi-annually starting in 2012 to maintain contact, assess the health status of participants, and discover any new hospitalizations since the last contact. Visit 4 serves as baseline for the present study because plasma total testosterone was measured in the whole ARIC cohort at Visit 4.

2.2. Testosterone measurements

Morning blood samples were obtained from participants at Visit 4 (1996–1998) and the plasma was stored at -80°C . Plasma total testosterone was measured by liquid chromatography tandem mass spectrometry in 2012. Sex hormone-binding globulin (SHBG) was measured from the same plasma samples. The reliability coefficient from 398 pairs of plasma total testosterone samples from the same blood draw was 0.96; this value was 0.90 for 390 pairs of SHBG samples. There was no information collected at Visit 4 on plasma albumin levels, so bioavailable testosterone could not be calculated.

2.3. Atrial fibrillation ascertainment

AF cases were identified through 2013 by three methods: 12-lead electrocardiograms (ECGs) performed during study visits, hospital records/discharge codes, and death certificates. The presence of AF or other heart rhythm disorders on ARIC visit ECGs was identified by a computer algorithm, and AF was confirmed by a cardiologist [15]. Hospitalizations throughout follow up were identified through yearly phone calls to

participants and surveillance of surrounding hospitals; however, specific questions about AF were not asked of the participants. AF was considered to be present if the ICD-9-CM codes 427.31 (AF) or 427.32 (atrial flutter) were listed in any given hospitalization. Lastly, AF was defined from death certificates if ICD codes of interest were listed as any cause of death (ICD-9 427.3 or ICD-10 I48). AF cases associated with open cardiac surgery were excluded. Prior analyses to determine the validity of hospital discharge diagnoses for AF reported 84% sensitivity and 98% specificity within the ARIC cohort [16]. For this analysis, 96% of incident AF events were identified by hospital discharge codes, 4% more from ARIC visit ECGs, and 0.1 more from death certificate codes.

2.4. Measurement of other covariates

Potential confounding variables were measured at ARIC Visit 4. Blood pressure was measured twice with a random-zero sphygmomanometer, with the mean of the two measurements used to define systolic blood pressure (SBP). Height and weight were measured while the participant was wearing light clothes. Body mass index (BMI) was defined as weight (kilograms) divided by squared height (m^2). Participants were asked to bring currently used medications to the exam, including antihypertensives, testosterone replacement therapy, testosterone inhibiting medications, and hormone replacement therapy (HRT). The use of hormonal supplementation was also determined via self-reporting. Diabetes was defined by fasting blood glucose ≥ 126 mg/dL, non-fasting blood glucose ≥ 200 mg/dL, the use of antihyperglycemic medications, or self-reported physician diagnosis of diabetes. Information on smoking status (never, former, or current) was self-reported. Glomerular filtration rate was estimated from serum creatinine using the CKD Epidemiology Collaboration creatinine equation (eGFR) [17]. Prevalent CHD and HF were based on self-reported information at previous study visits and on adjudicated events before Visit 4.

2.5. Statistical analysis

Out of 11,656 ARIC participants at Visit 4, we excluded 298 for having prevalent AF at Visit 4; 7 for having no follow up; 37 African Americans from Minneapolis or Washington County, 24 Asians, 7 American Indians (due to small sample sizes that were not comparable to other racial groups within the ARIC study); and 219 with unreadable ECGs at Visit 4. Also excluded were 539 pre-menopausal women and 58 participants taking androgen supplementation or androgen inhibiting medication. The analysis included 9,282 (4,224 men and 5,058 women) after further exclusion of any missing covariates of interest, including testosterone measurements (Figure 1). Follow up was defined as the amount of time from Visit 4 (baseline) to incident AF, loss to follow up, death, or administrative censoring on December 31, 2013, whichever came first. Testosterone levels were split into sex-specific quartiles due to the non-linear nature of the association of AF and testosterone concentrations. Crude proportions and mean values were used to describe demographics, health behaviors, risk factors, and comorbid conditions by testosterone concentration quartiles (Tables 1 and 2). Poisson regression was used to calculate sex-specific incidence rates of AF by testosterone concentration quartiles. Cox regression models were used to calculate sex-specific hazard ratios (HRs) and 95% confidence intervals (CIs) of incident AF by testosterone concentration quartiles. Participants in the lowest testosterone concentration

quartiles were used as the reference category to keep analysis consistent, despite the hypothesis posing differing directions of the association between testosterone and incident AF among men and women.

The initial model adjusted for race, and age. Model 2 also adjusted for other main AF risk factors, which included BMI, SBP, use of antihypertensive medications, smoking status, eGFR, diabetes, prevalent CHD, and prevalent HF. Supplemental models also adjusted for sex hormone-binding globulin to estimate how much testosterone is un-bound to SHBG. The sample size of this supplemental model decreased because there were 70 participants without SHBG measurement. We verified there was no violation of the proportional hazards assumption by testing interactions of testosterone by time, within sex and HRT groups. Analyses were conducted in SAS 9.4 (SAS, Inc., Cary, NC).

3. Results

Tables 1 and 2 show baseline characteristics by sex and plasma total testosterone concentration quartiles. Men with lower testosterone levels had higher average BMIs, were less likely to currently smoke, more likely to take antihypertensive medications, and more likely to have prevalent diabetes, CHD, and HF. Women with lower testosterone levels had lower average BMIs, were more likely to use HRT, less likely to currently smoke, less likely to take antihypertensive medications, and less likely to have prevalent diabetes, CHD, or HF.

Over a mean of 13.7 years of follow up, 1664 incident cases of AF were identified. The crude incidence of AF was 117.2 cases per 10,000 person-years. Crude incidence rates of AF for men and women were 138.8 and 100.4 cases per 10,000 person-years, respectively. As shown in Table 3, men in quartile 4 of total testosterone, compared to those in quartile 1, had a nonsignificant 7% lower risk of AF in models adjusted for age and race (Model 1 HR 0.93, 95% CI 0.76, 1.14, Table 3). This relation is depicted more fully in Supplemental Figure 1. The relation reverted to a modest but statistically significant positive association after adjustment for potential confounding variables (Model 2 HR 1.33, 95% CI 1.07, 1.66, Table 3).

As depicted in Supplemental Figure 2, there was little association of total testosterone with AF among all post-menopausal women. Women in quartile 4, compared to those in quartile 1, had a nominal 1% lower adjusted rate of AF, after adjusting for potential confounding variables (Model 2 HR 0.99, 95% CI 0.80, 1.22, Table 4). Results were similar for women stratified by HRT use (Supplemental Table 1).

4. Discussion

Contrary to our hypothesis, this prospective population-based cohort study found a modest positive association between plasma total testosterone concentrations and AF incidence in men. We found no material association in women. There are few studies of testosterone and AF, and findings are inconsistent [11, 18–20]. A case-control study from China concluded there was a crude difference in mean total testosterone concentrations between men with lone AF and their matched controls (476 ng/dl versus 514 ng/dl, $p = 0.005$); however, this difference was eliminated after adjusting for estradiol concentrations, age, BMI, SBP, and

diastolic blood pressure [18]. The prospective Framingham Heart Study identified a significant interaction between age and testosterone in men and stratified men by age. In men aged 55-69 years and 80+ years, each 1-standard deviation lower testosterone concentration was associated with an HR of 1.30 (95% CI 1.07, 1.59) and 3.53 (95% CI 1.96, 6.37) for AF risk, respectively, after adjustment for smoking status, BMI, SBP, hypertension treatment, diabetes, PR interval, significant murmur and prevalent HF [11]. They also observed a nominal association between testosterone concentration and AF in men aged 70 to 79 years, but that was statistically not significant (HR 1.14, 95% CI 0.91, 1.44). The racial composition of the population from the Framingham Heart Study was less diverse than that of the ARIC study. The Multi-Ethnic Study of Atherosclerosis found that total testosterone was not associated with AF in men (HR 1.20, 95% CI 0.93, 1.55) or women (HR 0.96, 95% CI 0.70, 1.32), after adjusting 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 [19]. The Cardiovascular Health Study found no association in men of total or free testosterone with AF, but low concentrations of the metabolite dihydrotestosterone were associated with modestly elevated AF incidence [20]. A study from the US Veterans Health Administration (VHA) found that normalization of testosterone levels by testosterone replacement therapy was significantly associated with lower incidence of AF in men with low initial total testosterone concentrations compared with a matched group of participants who did not receive testosterone replacement therapy (HR 0.79, 95% CI 0.70, 0.89, $P=0.0001$) [21]. All in all, our findings, together with the general inconsistency of existing observational evidence, suggest that endogenous testosterone is not an important determinant of AF risk.

4.1. Study limitations

Many aspects of the ARIC study strengthened our results - there was a relatively large number of AF cases and information on many potential confounding variables. Further, results from the ARIC study are quite generalizable, because the cohort was initially quite representative of the underlying populations [16]. However, there were some limitations to our study. The first is in the method of AF ascertainment. Some AF cases would have been missed if they were asymptomatic, did not require hospitalization, were identified in an outpatient setting, or omitted from death certificates. This would result in differential bias if those with AF identified had different testosterone levels than those missed. However, this seems unlikely.

A major limitation is the use of a single total testosterone measurement over time. The prospective Nurses' Health Study found total testosterone to have a three-year intraclass correlation coefficient (ICC) of 0.88 (0.84, 0.93), suggesting a single measurement can reliably categorize average levels over at least a three-year period in postmenopausal women [22]. However, the Breakthrough Generations Study from the United Kingdom found the ICC for total testosterone in women to be 0.59 (0.47, 0.72) over 5 years [23]. We found no similar data on men, but other sources have discussed poor reliability of testosterone measurements in the clinical laboratory setting [24, 25]. Although the measurement of testosterone used was found to be reliable, a single measurement may not be an appropriate representation of testosterone levels over time. Another limitation to our study is that only

total testosterone was measured. Total testosterone includes free testosterone plus albumin- and SHBG-bound testosterone. Free testosterone is the testosterone not bound to proteins. Free testosterone is useful when there is a reason to suspect that the SHBG level is abnormally decreased, leading to potentially falsely low total testosterone readings, which can occur in older or obese populations [26]. We were unable to create models using free testosterone because plasma albumin was not measured in this cohort during the time frame of interest. We adjusted for SHBG in supplementary models (Supplemental Table 2), but this method could be incomplete and may not be an appropriate way to estimate free testosterone levels. It is possible there could be a difference between total testosterone and free testosterone in their association with AF incidence, a finding that was noted in The Multi-Ethnic Study of Atherosclerosis [19].

4.2. Conclusion

Our study suggests a modest positive association between plasma total testosterone concentrations and AF incidence in men, after adjusting for potential confounding variables. No association was found in women, in both crude models and those adjusting for potential confounding variables. The totality of evidence suggests that endogenous testosterone is not a major determinant of AF risk, although the relation between free testosterone and AF incidence is something that deserves further research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AF	atrial fibrillation
ARIC	Atherosclerosis Risk in Communities
BMI	body mass index
CHD	coronary heart disease
CI	confidence interval
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate

HF	heart failure
HR	hazard ratio
HRT	hormone replacement therapy
ICC	intraclass correlation coefficient
SD	standard deviation
SBP	systolic blood pressure
SHBG	sex hormone-binding globulin
VHA	Veterans Health Administration

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Highlights

- We prospectively assessed the relationship between atrial fibrillation and plasma testosterone.
- We followed 9,282 participants; 1,664 developed atrial fibrillation.
- Higher testosterone levels were associated with a higher incidence of atrial fibrillation in men.
- There was no such association in women.

Figure 1.
Participant selection process used for analysis, ARIC study visit 4, 1996-1998.
ARIC = Atherosclerosis Risk in Communities; ECG = electrocardiogram; HRT = hormone replacement therapy

Table 1

Selected baseline characteristics of men by plasma total testosterone concentration quartiles, ARIC study, 1996-1998.

	Men				
	388.62 ng/dL	388.63-511.23 ng/dL	511.24-659.25 ng/dL	>659.25 ng/dL	All
Total Testosterone Quartiles					
N	1061	1061	1062	1061	4224
Race (% African Americans)	18	15	16	20	17
Age (years)	63 (5.6)	63 (5.8)	63 (5.7)	63 (5.6)	63 (5.7)
BMI (kg/m ²)	31 (4.9)	29 (4.3)	28 (3.7)	26 (3.7)	28 (4.5)
Current Smoker (%)	10	12	15	23	15
eGFR (mL/min/1.73 m ²)	85 (16)	85 (16)	85 (15)	85 (15)	85 (15)
Mean Systolic BP (mmHg)	128 (18)	128 (18)	126 (18)	124 (18)	127 (18)
Antihypertensive medications (%)	50	44	39	36	42
Diabetes (%)	28	17	14	11	17
Prevalent CHD (%)	17	14	14	11	14
Prevalent HF (%)	6.3	3.8	2.9	2.8	4.0
SHBG (nmol/L)	23 (11)	29 (9)	36(11)	50(17)	34(16)

ARIC = Atherosclerosis Risk in Communities; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; eGFR = estimated glomerular filtration rate; HF = heart failure; SHBG = sex hormone-binding globulin.

Values correspond to mean (standard deviation) or percentage, unless otherwise stated.

Table 2

Selected baseline characteristics of women by plasma total testosterone concentration quartiles, ARIC study, 1996-1998.

	Post-Menopausal Women				
	17.20 ng/dL	17.21-23.17 ng/dL	23.18-31.55 ng/dL	>31.55 ng/dL	All
Total Testosterone Quartiles					
N	1272	1273	1273	1273	5058
HRT users (%)	39	32	27	24	30
Race (% African Americans)	24	26	24	28	26
Age (years)	63 (5.4)	63 (5.4)	63 (5.4)	64 (5.5)	63 (5.4)
BMI (kg/m ²)	28 (5.7)	29 (6.0)	29 (6.5)	30 (6.6)	29 (6.2)
Current Smoker (%)	11	14	16	17	14
eGFR (mL/min/1.73 m ²)	87 (17)	87 (16)	87 (16)	86 (17)	87 (16)
Mean Systolic BP (mmHg)	127 (19)	128 (19)	129 (20)	130 (20)	128 (20)
Antihypertensive medications (%)	42	44	43	49	45
Diabetes (%)	12	16	17	18	16
Prevalent CHD (%)	3.7	3.7	4.0	5.5	4.3
Prevalent HF (%)	4.7	5.4	5.7	7.2	5.7
SHBG (nmol/L)	59 (46)	54 (43)	54 (40)	56 (42)	56 (43)

ARIC = Atherosclerosis Risk in Communities; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; eGFR = estimated glomerular filtration rate; HF = heart failure; HRT = hormone replacement therapy; SHBG = sex hormone-binding globulin.

Values correspond to mean (standard deviation) or percentage, unless otherwise stated.

Table 3

Association of plasma total testosterone with incidence of AF in men, ARIC study, 1996–2013.

Men					
Total Testosterone Quartiles	387.82 ng/dL	387.83–510.83 ng/dL	510.84–659.19 ng/dL	>659.19 ng/dL	
AF cases	189	202	192	189	
Person-years	13630	13937	14085	13986	
Incidence Rate ^{a,b}	131	137	123	125	
Hazard Ratio ^b (95% CI)	1 (ref)	1.03 (0.85, 1.26)	0.91 (0.74, 1.10)	0.93 (0.76, 1.14)	
Hazard Ratio ^c (95% CI)	1 (ref)	1.21 (0.99, 1.48)	1.17 (0.95, 1.45)	1.33 (1.07, 1.66)	

AF = atrial fibrillation; ARIC = Atherosclerosis Risk in Communities; BMI = body mass index; CHD = coronary heart disease; CI = confidence interval; eGFR = estimated glomerular filtration rate; HF = heart failure; SBP = systolic blood pressure.

^a per 10,000 person-years.

^b Model 1: race and age adjusted.

^c Model 2: model 1 and adjusted for BMI, smoking status, eGFR, SBP, antihypertensive medication use, diabetes, prevalent CHD, and prevalent HF.

Table 4

Association of plasma total testosterone with incidence of AF in women, ARIC study, 1996-2013.

All Post-Menopausal Women				
Total Testosterone Quartiles	17.20 ng/dL	17.21-23.17 ng/dL	23.18-31.55 ng/dL	>31.55 ng/dL
AF cases	160	183	186	189
Person-Years	17984	18326	17722	17492
Incidence Rate ^{a,b}	81	91	95	92
Hazard Ratio (95% CI)	1 (ref)	1.11 (0.90, 1.37)	1.17 (0.95, 1.45)	1.15 (0.93, 1.42)
Hazard Ratio ^c (95% CI)	1 (ref)	1.04 (0.84, 1.29)	1.07 (0.87, 1.33)	0.99 (0.80, 1.22)

AF = atrial fibrillation; ARIC = Atherosclerosis Risk in Communities; BMI = body mass index; CHD = coronary heart disease; CI = confidence interval; eGFR = estimated glomerular filtration rate; HF = heart failure; HRT = hormone replacement therapy; SBP = systolic blood pressure.

^a per 10,000 person-years.

^b Model 1: race and age adjusted.

^c Model 2: model 1 and adjusted for BMI, smoking status, eGFR, SBP, antihypertensive medication use, diabetes, prevalent CHD, and prevalent HF.