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Publication Date

2023-06-01

DOI

10.1016/j.ajpc.2023.100479

Peer reviewed

American Journal of Preventive Cardiology 14 (2023) 100479

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

The association of sex-specific hormones with coronary artery plaque characteristics from Miami Heart (MiHeart) study

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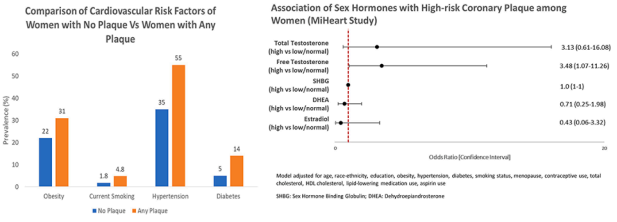
GRAPHICAL ABSTRACT

Central Illustration : Comparison of Cardiovascular Risk Factors of Women with no Plaque vs Women with any Plaque and The Association of Sex Hormones with High-Risk Coronary Plaque Among Women (Miheart Study).



Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CT, computed tomography; CVD, cardiovascular disease; DHEA, dehydroepiandrosterone; HRP, high-risk plaque; MiHeart, Miami heart study; SHBG, sex hormone binding globulin.

Funding Support and Author Disclosures: The Miami Heart Study was funded by Baptist Health South Florida.Dr Sharma is supported by the Blumenthal Scholarship in Preventive Cardiology at the Ciccarone Center for the Prevention of Cardiovascular Disease at Johns Hopkins University School of Medicine and AHA grant 979,462.Dr. Blankstein has received research support from Amgen Inc and Novartis Inc and is a consultant to Caristo Diagnostics, Silence Therapeutics and Roivant Science Inc.Dr. Shapiro has served on Scientific Advisory Boards with Amgen, Novartis, and Novo Nordisk and as a consultant for Regeneron.Dr. Cury is a consultant to GE Healthcare, Covera Health and Cleerly.Dr. Nasir is on the advisory board of Amgen, Novartis, Novo Nordisk, his research is partly supported by the Jerold B. Katz Academy of Translational Research and is a member of the Steering Committee of the PAK-SEHAT study which is partly funded by an unrestricted research grant from Getz Pharma.Dr. Cainzos-Achirica is also a member of the Steering Committee of the PAK-SEHAT study.

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https://doi.org/10.1016/j.ajpc.2023.100479
Received 15 November 2022; Received in revised form 1 February 2023; Accepted 25 February 2023
Available online 2 March 2023

ARTICLE INFO

Keywords:
Sex hormones
Plaque
Coronary artery disease
Testosterone

ABSTRACT

Objective: The association of sex-specific hormones with coronary computed tomography angiography(CCTA)-based plaque characteristics in women without cardiovascular disease is not well understood. We investigated the association of sex-specific hormones with coronary artery plaque characteristics in a contemporary multi-racial cohort with no clinical coronary artery disease (CAD).

Methods: In this cross-sectional analysis, we utilized data from 2,325 individuals with no clinical CAD from the Miami Heart (MiHeart) study. Multivariable logistic regression models were used to investigate the association of sex hormones: sex hormone binding globulin (SHBG), dehydroepiandrosterone (DHEA), free and total testosterone, estradiol, with plaque characteristics among women and men.

Results: Of the 1,155 women, 34.2% had any plaque and 3.4% had any high-risk plaque features (HRP) while among men (n = 1170), 63.1% had any plaque and 10.4% had HRP. Among women, estradiol and SHBG were associated with lower odds of any plaque after adjusting for age and race-ethnicity (estradiol OR per SD increase: 0.87, 95%CI: 0.76–0.98; SHBG OR per SD increase: 0.82, 95%CI: 0.72–0.93) but the significance did not persist after adjustment of cardiovascular risk factors. High free testosterone was associated with higher odds of HRP (aOR:3.48, 95%CI:1.07–11.26) but null associations for the other sex hormones with HRP, in the context of limited sample size. Among men, there were no significant associations between sex-specific hormones and plaque or HRP.

Conclusion: Among young to middle-aged women with no clinical CAD, increasing estradiol and SHBG were associated with lower odds of any plaque and higher free testosterone was associated with HRP. Larger cohorts may be needed to validate this.

1. Introduction

Atherosclerotic cardiovascular disease (CVD) is the leading cause of death in both women and men globally [1]. Our understanding of sex differences in subclinical atherosclerosis and plaque composition and characteristics have greatly improved with the use of coronary computed tomography (CCTA) as it has emerged as an important tool to understand the role of non-obstructive atherosclerosis as well as diffuse, high risk plaque (HRP) as precursors of acute cardiac events in women [2–4]. CCTA can be used to identify HRP features which are associated with higher event rates [4]. High-risk coronary atherosclerosis features evaluated CCTA is suggested to have a prognostic role but the association of sex hormones and HRP in young to middle aged women with no clinical coronary artery disease is understudied.

Beyond traditional risk factors, sex differences exist in the development and outcomes of CVD, suggesting the influence of sex hormones. Women develop coronary artery disease (CAD) almost a decade later than men [5–7]. It is also well documented that CAD manifests differently in women compared to men in terms of plaque composition, morphology and vulnerability [8–10]. A recent study on sex differences in CCTA-based plaque volume found low fibrofatty atheroma plaque volume in women compared to men [10]. Historically, the primary male sex hormone has been considered pro-atherogenic and pro-inflammatory but there is growing evidence that lower endogenous levels are associated with CAD [11–13], while the primary female sex hormone exerts a cardioprotective effect by promoting nitric oxide mediated vascular relaxation, proliferation, and angiogenesis [14,15].

Among women, data on association of endogenous androgens with CAD are inconsistent. Some studies report association of high androgens or low androgens with CAD or no associations [16,17]. Prior studies evaluating sex hormones with other CVD measures such as pro B-natriuretic peptide and left ventricular structure, have found associations with a high androgenic hormone profile in women [18,19] but data on the use of CCTA to assess plaque composition and vulnerability features, and its association with sex hormones particularly in young to middle aged women remain limited. In this analysis, we sought to evaluate the association of sex hormones (total testosterone, free testosterone, dehydroepiandrosterone, estradiol and sex hormone binding globulin) and the presence of subclinical atherosclerosis and HRP characteristics in a large cohort of young to middle-aged women and men.

2. Methods

In this cross-sectional analysis, we utilized baseline data from the ongoing Miami Heart (MiHeart) study. The MiHeart is a community based, prospective cohort study conducted and coordinated at Baptist Health South Florida with 2459 middled aged male and female participants. These participants, who were volunteers from the Greater Miami area were free of clinically overt cardiovascular disease and enrolled between May 2015 and September 2018. The original study focuses on the determinants and natural history of subclinical cardiovascular disease. A detailed description of the methods, inclusion, and exclusion criteria of the Miheart study is described elsewhere [20]. The original study protocol was approved by the institutional review board of Baptist Health South Florida. All participants provided written informed consent and those who could not do so, for whatever reason were excluded. This current study is within the scope of the IRB-approved research. Our current study focuses on a subset of 2325 individuals (1155 women and 1170 men) from the MiHeart study, with complete data on CCTA and sex hormones (Fig. 1).

Contrast-enhanced cardiac-gated CT scans were performed using a GE Revolution scanner. Prior to the scan, participants were given metoprolol to achieve a heart rate of ≤65 beats per minute. In addition, 0.4 mg sublingual nitroglycerine was given, and subsequently 60–80 ml of iodinated contrast was administered intravenously at a low rate of 5–7 ml/s before acquiring the angiographic image. Assessment of 18-segment plaque presence/burden and classification were performed at a central core imaging lab. Further details of the methods are described elsewhere [20]. For the purpose of this current study, our main outcomes of interest were the presence of any coronary plaque, and any HRP characteristics. HRP characteristics were defined as the presence of any one or more of the following plaque vulnerability features: positive remodeling (remodeling index >1.1), low attenuation plaque (mean CT number <30 Hounsfield Units), spotty calcification (calcification with length <3 mm and occupying ≤90° of the vessel arc) and/or napkin ring (presence of a ring-like peripheral higher attenuation with central low CT attenuation).

Endogenous sex hormones were measured by Quest diagnostic laboratories, Houston TX. Sex hormones studied included total testosterone (ng/dL), free testosterone (pg/mL), dehydroepiandrosterone (DHEA, ng/dL), estradiol (pg/mL) and sex hormone binding globulin (SHBG, nmol/L). In this study, sex hormones were explored as continuous variables, and binary variables (high vs low/normal). High total testosterone was defined as ≥60 ng/dL, high free testosterone ≥ 4.2 pg/mL,

high SHBG ≥ 144 nmol/l, high DHEA ≥370 ng/dL and high estradiol ≥ 400 pg/mL if premenopausal, or ≥30 pg/mL if postmenopausal, as per Quest Diagnostic laboratory standards [21].

Covariates were obtained from standardized questionnaires, physical examination, and laboratory measures. Self-reported sociodemographic characteristics included age, race-ethnicity (non-Hispanic white, Hispanic, other) and education (less than high school, high school, some college with no degree, bachelors, post graduate studies, unknown). Other covariates included body mass index (underweight: <18.5 kg/m^2 normal weight: 18.5–24.9 kg/m^2 overweight: 25–29.9 kg/m^2, obese: ≥30 kg/m^2), smoking status (never smoker, former smoker, current smoker), menopause (yes/no), contraceptive use (yes/no) and lipid lowering medication use (yes/no).

Hypertension was defined as either self-reported, systolic blood pressure ≥130 mmHg or diastolic ≥80 mmHg, as per the American College of Cardiology/American heart Association (ACC/AHA) guidelines [22] or blood pressure-lowering medication use. Diabetes was defined as either self-reported, fasting glucose levels ≥126 mg/dL, glycosylated hemoglobin ≥6.5%, or diabetes medication use.

Participant characteristics were stratified by the presence or absence of any coronary plaque and were explored using students t-tests for continuous variables, Pearson's chi squared/Fischer's exact tests for categorical variables and Wilcoxon rank sum test for variables that were not normally distributed. Using nested multivariable logistic regression models, we estimated the odds ratios and 95% confidence intervals (CI) for the association of sex hormones with the outcomes: any coronary plaque and any HRP characteristics among women and among men. Specifically, Model 1 was adjusted for age and race-ethnicity; Model 2 was additionally adjusted for education, obesity, hypertension, diabetes, smoking status, (menopause and contraceptive use in addition, for the analyses in women) and Model 3 was further adjusted for total cholesterol, HDL cholesterol, lipid-lowering medication use and statin use. Additionally, sex hormones were explored as continuous variables using multivariable logistic regression models adjusting for same. All reported p-values were two-sided, and $p < 0.05$ was used to determine statistical significance. All analyses were conducted in Stata version 16 (StataCorp, College Station, TX).

3. Results

Of the total 2325 study participants, 1155 were women and 1170 were men. Among the women, 34.2% had the presence of any coronary plaque. Women with the presence of any coronary plaque were older (57 vs 53 years, $p < 0.001$), obese (31% vs 22%, $p < 0.001$), current smokers (4.8% vs 1.8%, $p < 0.001$), hypertensive (55% vs 35%, $p < 0.001$) and diabetic (14% vs 5%, $p < 0.001$ compared with women with no plaque (Table 1). Total cholesterol and LDL-cholestero were higher while HDL-cholesterol was lower in women with any plaque compared to women with no plaque. Also, a higher proportion of women with any plaque used lipid lowering therapy (28% vs 10%), diabetes therapy (9.4% vs 3.0%), hypertension therapy (25% vs 15%) and aspirin therapy (24% vs 14%) (all $p < 0.001$) compared with women with no plaque. Women with any coronary plaque had lower median levels of DHEA [196 (IQR: 127, 311) vs 238 (IQR:155, 356) ng/dL] and estradiol [9 (IQR: 4, 20) vs 16 (IQR: 5, 73) pg/ml,] (all $p < 0.001$) compared with women without plaque (Table 1). About 60% of the women were postmenopausal. Baseline characteristics of women stratified by postmenopausal status and plaque status are described in Supplementary Table 1.

Overall, HRP was present in 3.4% of the women. The prevalence of any plaque and HRP by sex hormone levels (high vs low/normal) are shown in Table 2. The distribution of HRP features by sex hormone status are shown in Supplementary Table 2. Among men, 63.1% had the presence of any coronary plaque and 10.4% had HRP features. Men with any coronary plaque were older (54 vs 49 years, $p < 0.001$, current smokers (3.9% vs 1.9%, $p = 0.03$) and more likely to have hypertension (60% vs 42%, $p < 0.001$), and diabetes mellitus (9.6% vs 5.6%, $p = 0.02$) compared with men with no plaque (Table 1).

Among women, high levels of sex hormones were not significantly associated with the presence of any plaque compared with low/normal levels. (High total testosterone aOR:0.88, 95%CI: 0.35–2.23; high free testosterone aOR:0.77, 95%CI: 0.35–1.72; high SHBG aOR: 0.96, 95%CI: 0.45–2.04; high DHEA aOR:0.92, 95%CI: 0.65–1.31 and high estradiol aOR: 0.80, 95%CI: 0.65–1.31) (Table 3). Similarly, among men, there were no significant associations between high levels of sex-specific hormones and any plaque compared with low/normal levels [high total testosterone aOR:1.11, 95%CI: 0.23 – 5.23; high free testosterone aOR: 1.29, 95%CI:0.26–6.96), high DHEA aOR:1.10, 95%CI: 0.53–2.29).

When the sex hormones were explored as continuous variables, there were null associations of total testosterone, free testosterone, and DHEA with any plaque in women (Table 4). However, increasing SHBG was associated with lower odds of any plaque in women in the age-race-adjusted model (aOR per SD increase: 0.82, 95%CI:0.72–0.93) but the significance did not persist after further adjustment. Increasing estradiol

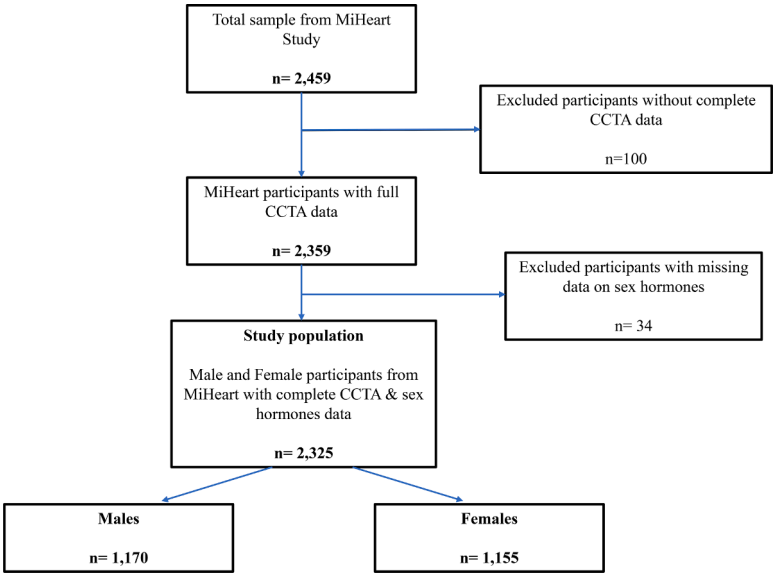

Fig. 1. Flow chart describing the selection of the analytical sample from the MiHeart cohort.

Table 1
Characteristics of female and male participants of the miami heart study according to plaque status.

Variables	Women $N = 1155$ No plaque[1] $N = 760$	Any plaque[1] $N = 395$	p-value	Men $N = 1170$ No plaque[1] $N = 431$	Any plaque[1] $N = 739$	p-value
Sociodemographics						
Age, years	53 (48, 58)	57 (52, 62)	<0.001	49 (45, 54)	54 (50, 59)	<0.001
Race/Ethnicity			0.3			<0.001
Non-Hispanic white	329 (43%)	170 (43%)		156 (36%)	348 (47%)	
Hispanic	360 (47%)	177 (45%)		223 (52%)	333 (45%)	
Other	71 (9.3%)	48 (12%)		52 (12%)	58 (7.8%)	
Education status			0.2			0.2
Less than high school	1 (0.1%)	2 (0.5%)		0 (0%)	5 (0.7%)	
High school	53 (7.0%)	37 (9.4%)		39 (9.0%)	64 (8.7%)	
Some college, no degree	84 (11%)	53 (13%)		51 (12%)	83 (11%)	
Bachelors	384 (51%)	189 (48%)		222 (52%)	353 (48%)	
Post-graduate studies	235 (31%)	111 (28%)		115 (27%)	232 (31%)	
Unknown/not disclosed	3 (0.4%)	3 (0.8%)		4 (0.9%)	2 (0.3%)	
Total Income, USD			0.14			0.6
< 25K	17 (2.2%)	12 (3.0%)		7 (1.6%)	11 (1.5%)	
25 K to 49K	64 (8.4%)	43 (11%)		23 (5.3%)	35 (4.7%)	
50 K to 74K	71 (9.3%)	47 (12%)		29 (6.7%)	49 (6.6%)	
75 K to 149K	265 (35%)	146 (37%)		153 (35%)	235 (32%)	
≥150K	259 (34%)	110 (28%)		177 (41%)	346 (47%)	
Not disclosed	84 (11%)	37 (9.4%)		42 (9.7%)	63 (8.5%)	
Cardiovascular Risk Factors						
BMI (kg/m2)	25.6 (22.8, 29.1)	27.4 (24.2, 32.0)	<0.001	28.6 (26.4, 31.7)	29.0 (26.7, 32.1)	0.12
Body mass index (categorical)			<0.001			0.5
Underweight	6 (0.8%)	3 (0.8%)		0 (0%)	1 (0.1%)	
Normal weight	338 (44%)	118 (30%)		55 (13%)	80 (11%)	
Overweight	251 (33%)	151 (38%)		213 (49%)	351 (47%)	
Obese	165 (22%)	123 (31%)		163 (38%)	307 (42%)	
Smoking status			0.002			0.034
Never smoker	557 (73%)	260 (66%)		338 (78%)	536 (73%)	
Former smoker	189 (25%)	116 (29%)		85 (20%)	174 (24%)	
Current smoker	14 (1.8%)	19 (4.8%)		8 (1.9%)	29 (3.9%)	
Mean Systolic blood pressure (mmHg)	118 (108, 128)	125 (114, 135)	<0.001	123 (114, 130)	126 (118, 136)	<0.001
Mean Diastolic blood pressure (mmHg)	75 (69, 81)	78 (72, 83)	<0.001	79 (74, 84)	81 (76, 86)	<0.001
Hypertension	266 (35%)	216 (55%)	<0.001	179 (42%)	443 (60%)	<0.001
Glucose (mg/dL)	91 (86, 96)	94 (88, 101)	<0.001	93 (87, 98)	95 (89, 102)	<0.001
HbA1c (%)	5.50 (5.30, 5.70)	5.70 (5.40, 5.90)	<0.001	5.50 (5.30, 5.70)	5.60 (5.30, 5.80)	<0.001
Diabetes mellitus	39 (5.1%)	57 (14%)	<0.001	24 (5.6%)	71 (9.6%)	0.015
Total cholesterol (mg/dL)	208 (187, 233)	214 (187, 241)	0.041	197 (171, 222)	194 (167, 225)	0.5
LDL cholesterol (mg/dL)	118 (98, 142)	127 (103, 151)	0.004	122 (101, 142)	118 (93, 148)	0.4
HDL cholesterol (mg/dL)	69 (56, 83)	63 (51, 76)	<0.001	49 (42, 59)	48 (40, 58)	0.1
Triglycerides (mg/dL)	82 (63, 112)	95 (68, 133)	<0.001	105 (72, 146)	109 (80, 151)	0.045
Medication use						
Lipid lowering therapy (any)	76 (10%)	111 (28%)	<0.001	74 (17%)	282 (38%)	<0.001
Lipid lowering therapy (statins)	71 (9.3%)	106 (27%)	<0.001	65 (15%)	275 (37%)	<0.001
Diabetes therapy	23 (3.0%)	37 (9.4%)	<0.001	19 (4.4%)	43 (5.8%)	0.3
Hypertensive therapy	113 (15%)	97 (25%)	<0.001	63 (15%)	185 (25%)	<0.001
Aspirin	103 (14%)	94 (24%)	<0.001	73 (17%)	268 (36%)	<0.001
Contraception use	170 (23%)	63 (16%)	0.009	5 (4.7%)	10 (6.8%)	0.5
Sex hormones						
Total Testosterone (ng/dL)	20 (13, 27)	18 (13, 26)	0.13	434 (332, 569)	440 (335, 559)	>0.9
Free Testosterone (pg/mL)	1.20 (0.80, 1.80)	1.30 (0.80, 1.90)	0.055	53 (41, 66)	49 (40, 63)	0.034
DHEA, unconjugated (ng/dL)	238 (155, 356)	196 (127, 311)	<0.001	264 (177, 368)	214 (141, 319)	<0.001
Estradiol, ultrasensitive (pg/mL)	16 (5, 73)	9 (4, 20)	<0.001	27 (21, 34)	27 (21, 35)	0.4

[1] Median (IQR); *n* (%)
BMI – Body Mass index
LDL – Low density lipoprotein
HDL – High density lipoprotein
DHEA - Dehydroepiandrosterone.

was also associated with lower odds of any plaque in women in the age-race-adjusted model (aOR per SD increase:0.87, 95%CI:0.76–0.98) but the significance did not persist after further adjustment. Among men, total testosterone, free testosterone, SHBG, estradiol and DHEA, when explored continuously, were not significantly associated with any plaque (Table 4).

Among women, high free testosterone was associated with three times higher odds of HRP (aOR: 3.48, 95%CI: 1.07–11.26) in the fully adjusted model, whereas high SHBG (aOR:1.00, 95%CI:1.00–1.00), high DHEA (aOR:0.71, 95%CI: 0.25–1.98) and high estradiol (aOR: 0.43, 95%CI:0.06–3.32) were not significantly associated with HRP (Table 5). When sex hormones were explored as continuous variables, SHBG was associated with lower odds of HRP in women in model 1 (OR per SD increase: 0.64, 95%CI:0.42–0.97) but the significance did not persist after adjustment. There were no significant associations with DHEA or estradiol with HRP.

4. Discussion

In this well characterized cohort of individuals, free of CVD at

Table 2
Frequency of any plaque and CCTA high-risk plaque characteristics among women and men, overall and by specific hormone-related exposures.

	Women Any Plaque	Any high-risk plaque feature	Men Any Plaque	Any High-Risk Plaque feature
	n (%)	n (%)	n (%)	n (%)
Overall	395 (34.2)	39 (3.4)	739 (63.1)	122 (10.4)
High total testosterone (≥ 60 ng/dL)				
Low/Normal	386 (97.7)	37 (94.9)	7 (0.9)	0 (0.0)
High	9 (2.3)	2 (5.1)	732 (99.1)	122 (100.0)
High free testosterone (≥ 4.2 pg/mL)				
Low/Normal	380 (96.2)	34 (87.2)	6 (0.8)	0 (0.0)
High	15 (3.8)	5 (12.8)	733 (99.2)	122 (100.0)
High SHBG (≥ 144 nmol/L)				
Low/Normal	384 (97.2)	39 (100.0)	739 (100.0)	122 (100.0)
High	11 (2.8)	0 (0.0)	0(0)	0(0)
High DHEA (≥ 370 ng/dL)				
Low/Normal	328 (83.0)	33 (84.6)	610 (82.5)	108 (88.5)
High	67 (17.0)	6 (15.4)	129 (17.5)	14 (11.5)
High estradiol (≥ 400 pg/mL if premenopausal; ≥ 30 pg/mL if postmenopausal)				
Low/Normal	372 (94.2)	38 (97.4)	739 (100.0)	122 (100.0)
High	23 (5.8)	1 (2.6)	0 (0)	0(0)

SHBG - sex hormone binding globulin.
DHEA - Dehydroepiandrosterone.

Table 3
The association between sex hormones (High vs Low/Normal) and presence of any plaque among women and men.

Any Plaque (vs No Plaque) Women Sex Hormones	Model 1 *OR (95% CI)*	Model 2 *OR (95% CI)*	Model 3 *OR (95% CI)*
High total testosterone (≥ 60 ng/dL)			
Low/Normal	Reference	Reference	Reference
High	0.96 (0.41, 2.25)	0.80 (0.32, 2.01)	0.88 (0.35, 2.23)
High free testosterone (≥ 4.2 pg/mL)			
Low/Normal	Reference	Reference	Reference
High	1.18 (0.59, 2.35)	0.88 (0.41, 1.88)	0.77 (0.35, 1.72)
High SHBG (≥ 144 nmol/L)			
Low/Normal	Reference	Reference	Reference
High	0.68 (0.34, 1.38)	0.81 (0.39, 1.71)	0.96 (0.45, 2.04)
High DHEA (≥ 370 ng/dL)			
Low/Normal	Reference	Reference	Reference
High	0.93 (0.67, 1.30)	0.93 (0.66, 1.31)	0.92 (0.65, 1.31)
High estradiol (≥ 400 pg/mL if premenopausal; ≥ 30 pg/mL if postmenopausal)			
Low/Normal	Reference	Reference	Reference
High	0.68 (0.41, 1.14)	0.79 (0.46, 1.35)	0.80 (0.46, 1.38)
Men Sex Hormones	Model 1 *OR (95% CI)*	Model 2 *OR (95% CI)*	Model 3 *OR (95% CI)*
High total testosterone (≥ 60 ng/dL)			
Low/Normal	Reference	Reference	Reference
High	2.98 (1.01, 8.93)	1.91 (0.47, 7.83)	1.11 (0.23, 5.23)
High free testosterone (≥ 4.2 pg/mL)			
Low/Normal	Reference	Reference	Reference
High	3.40 (1.09, 11.0)	2.25 (0.53,10.4)	1.29 (0.26,6.96)
High SHBG (≥ 144 nmol/L)			
Low/Normal	NA	NA	NA
High	NA	NA	NA
High DHEA (≥ 370 ng/dL)			
Low/Normal	Reference	Reference	Reference
High	1.06 (0.77, 1.46)	1.19 (0.60, 2.37)	1.10 (0.53, 2.29)
High estradiol (≥ 400 pg/mL if premenopausal; ≥ 30 pg/mL if postmenopausal)			
Low/Normal	NA	NA	NA
High	NA	NA	NA

Model 1: Adjusted for age and race/ethnicity.
Model 2: Adjusted for Model 1 + education, obesity, hypertension, diabetes, smoking status, (+ menopause and contraceptive use for women).
Model 3: Adjusted for Model 2 + total cholesterol, HDL cholesterol, lipid-lowering medication use, aspirin use.
Boldface indicates statistical significance ($p < 0.05$).
Abbreviations: DHEA- Dehydroepiandrosterone; SHBG -Sex Hormone Binding Globulin.

baseline, we found that subclinical coronary plaque was associated with cardiovascular risk factors such as obesity, hypertension, diabetes, dyslipidemia, and smoking. In multivariable analyses, increasing estradiol and SHBG levels in women were associated with lower odds of any coronary plaque after adjusting for age and race-ethnicity. We also found that higher androgenic hormone profile, i.e., higher serum free testosterone in women was associated with HRP after adjusting for CVD risk factors, lipid therapy, and aspirin use. There were however null associations between sex-specific hormones and any plaque or HRP among men. To our knowledge, this is the first study of a younger cohort that establishes the associations of sex hormones and HRP characteristics and subclinical atherosclerosis pathogenesis in middle-aged asymptomatic individuals.

Women tend to be older when presenting with CAD [5–7,23], have lower rates of obstructive disease but higher risk of major adverse cardiac events compared to men [24,25]. These differences might be due to plaque characteristics and sex and gender disparities in the recognition, management and follow up. Our understanding of the pathophysiology of myocardial infarction in women has improved and we know that plaque erosion and plaque rupture can both contribute to myocardial infarction in non-obstructive coronary arteries [26]. Recently, a study on sex differences in coronary plaque in a low-to-intermediate risk population of stable CAD patients found no significant sex differences in total percentage atheroma volume increase over time [10]. In the same study, fibro-fatty plaque was lower in women at any age and women under 55 years demonstrated significantly greater reduction in fibrous and non-calcified percentage atheroma volume over time compared to age-matched men [10]. The data on plaque characteristics and outcomes has also improved recently. In an analysis of 522 patients (mean follow-up 37 ± 10 months), increased total plaque volume, plaque volume <150 Hounsfield units, and plaque volume <30 Hounsfield units were each associated with higher rates of acute coronary syndrome, cardiac death, or late revascularization [27]. This study established the prognostic value of atherosclerosis assessment beyond just luminal stenosis. Our study adds to the literature on using CCTA to

Table 4
Association between sex hormones (continuous) and presence of Any plaque among women and men.

Any Plaque (vs No Plaque) Women Variables	*Model 1 OR (95% CI)*	*Model 2 OR (95% CI)*	*Model 3 OR (95% CI)*
Total Testosterone (ng/dL) (Per SD increase)	1.03 (0.33, 3.25)	1.09 (0.30, 3.93)	1.23 (0.34, 4.39)
Free Testosterone (pg/mL) (Per SD increase)	2.43 (0.35, 16.79)	1.61 (0.18, 14.46)	1.13 (0.13, 10.15)
Sex Hormone Binding Globulin (nmol/L) (Per SD increase)	**0.82 (0.72, 0.93)**	0.91 (0.79, 1.04)	1.02 (0.89, 1.17)
DHEA, unconjugated (ng/dL) (Per SD increase)	0.97 (0.86, 1.10)	0.99 (0.87, 1.13)	0.99 (0.87, 1.13)
Estradiol, ultrasensitive (pg/mL) (Per SD increase)	**0.87 (0.76, 0.98)**	0.90 (0.78, 1.03)	0.91 (0.79, 1.04)
Men			
	Model 1 OR (95% CI)	*Model 2 OR (95% CI)*	*Model 3 OR (95% CI)*
Total Testosterone (ng/dL) (Per SD increase)	1.043 (0.904, 1.204)	0.735 (0.354, 1.529)	0.730 (0.334, 1.598)
Free Testosterone (pg/mL) (Per SD increase)	1.098 (0.969, 1.244)	0.751 (0.265, 2.131)	0.626 (0.207, 1.898)
Sex Hormone Binding Globulin (nmol/L) (Per SD increase)	0.781 (0.587, 1.038)	0.855 (0.304, 2.409)	1.225 (0.385, 3.894)
DHEA, unconjugated (ng/dL) (Per SD increase)	0.887 (0.765, 1.028)	1.093 (0.658, 1.815)	1.066 (0.618, 1.836)
Estradiol, ultrasensitive (pg/mL) (Per SD increase)	1.450 (0.874, 2.405)	1.769 (0.511, 6.122)	3.104 (0.925, 10.417)

Model 1: Adjusted for age and race/ethnicity.
Model 2: Adjusted for Model 1 + education, obesity, hypertension, diabetes, smoking status, (+ menopause and contraceptive use for women).
Model 3: Adjusted for Model 2 + total cholesterol, HDL cholesterol, lipid-lowering medication use, aspirin use.
High Risk plaque includes any vulnerable plaque features such as positive remodeling, low attenuation plaque, spotty calcification.
and/or napkin ring.
Boldface indicates statistical significance ($p < 0.05$).
Abbreviations: DHEA- Dehydroepiandrosterone; SD- standard deviation.

Table 5
Association between Sex Hormones (High vs Low/Normal) and Presence of Any High-risk plaque characteristics among women and men.

Any High-risk plaque characteristics (vs None) Women Sex Hormones	*Model 1*	*Model 2*	*Model 3*
High total testosterone (≥ 60 ng/dL)			
Low/Normal	Reference	Reference	Reference
High	2.60 (0.57, 11.88)	2.54 (0.51, 12.56)	3.13 (0.61, 16.08)
High free testosterone (≥ 4.2 pg/mL)			
Low/Normal	Reference	Reference	Reference
High	**4.98 (1.76, 14.03)**	**3.85 (1.25, 11.86)**	**3.48 (1.07, 11.26)**
High SHBG (≥ 144 nmol/L)			
Low/Normal	Reference	Reference	Reference
High	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
High DHEA (≥ 370 ng/dL)			
Low/Normal	Reference	Reference	Reference
High	1.01 (0.41, 2.53)	0.91 (0.35, 2.33)	0.71 (0.25, 1.98)
High estradiol (≥ 400 pg/mL if premenopausal; ≥ 30 pg/mL if postmenopausal)			
Low/Normal	Reference	Reference	Reference
High	0.33 (0.04, 2.41)	0.42 (0.06, 3.20)	0.43 (0.06, 3.32)
Men			
Sex Hormones	**Model 1**	**Model 2**	**Model 3**
High total testosterone (≥ 60 ng/dL)			
Low/Normal	Reference	Reference	Reference
High	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
High free testosterone (≥ 4.2 pg/mL)			
Low/Normal	Reference	Reference	Reference
High	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
High SHBG (≥ 144 nmol/L)			
Low/Normal	NA	NA	NA
High	NA	NA	NA
High DHEA (≥ 370 ng/dL)			
Low/Normal	**Reference**		
High	0.6 (0.31, 1.05)	0.17 (0.01,0.90)	0.15 (0.01, 0.87)
High estradiol (≥ 400 pg/mL if premenopausal; ≥ 30 pg/mL if postmenopausal)			
Low/Normal	NA	NA	NA
High	NA	NA	NA

SHBG - sex hormone binding globulin; DHEA - Dehydroepiandrosterone.
Model 1: Adjusted for age and race/ethnicity.
Model 2: Adjusted for Model 1 + education, obesity, hypertension, diabetes, smoking status, (+ menopause and contraceptive use for women).
Model 3: Adjusted for Model 2 + total cholesterol, HDL cholesterol, lipid-lowering medication use, aspirin use.
High Risk plaque includes any vulnerable plaque features such as positive remodeling, low attenuation plaque, spotty calcification.
and/or napkin ring.
Boldface indicates statistical significance ($p < 0.05$).
Abbreviations: DHEA- Dehydroepiandrosterone; SD- standard deviation.

assess HRP features beyond coronary artery calcium, and while this is a cross-sectional analysis with no outcomes, future prospective analyses will allow for better understanding of CVD outcomes in this middle-aged population.

In this present study, we found that increasing estradiol and SHBG were associated with lower odds of any plaque among women. However, this association did not persist after controlling for cardiovascular risk profile, and other clinical variables such as medication use for hypertension, statin therapy and aspirin use. Additionally, we found that high free testosterone in women was associated with 3 times higher odds of the presence of HRP characteristics whereas high SHBG, high DHEA and high estradiol were not. Though underpowered, our findings point in the same direction as findings of prior studies. Prior evidence suggests excess androgenic sex hormones in young to middle-aged women are associated with increased risk of traditional cardiometabolic risk factors [28], and with a variety of subclinical CVD measurements including greater left ventricular concentric remodeling, aortic stiffness, and carotid intimal thickness [29]. We explored the association of sex hormones with plaque characteristics in our present study as well as data on SHBG. One study found that SHBG was inversely associated with the presence of CAC (OR 0.59; 95% CI (0.40–0.87); $P = 0.008$) and the highest quartile of carotid-intimal thickness (OR 0.56; 95% CI (0.37–0.84); $P = 0.005$) [29].

A more androgenic sex hormone profile is independently associated with increased risk of incident CVD, CHD, and heart failure clinical events in post-menopausal women [18,19,30]. This supports the hypothesis that testosterone is especially atherogenic in the presence of low estrogen. Prior studies have shown that in older men with symptomatic hypogonadism, treatment with testosterone gel for 1 year compared with placebo was associated with a significantly greater increase in coronary artery noncalcified plaque volume [31]. These findings in women should be taken into context for those who have primary

ovarian failure and polycystic ovarian syndromes, and conditions associated with androgenic excess in women. Additionally, our findings suggest that subclinical coronary plaque and high-risk plaque features may be an intermediate step linking excess androgens with CVD risk in young to middle-aged women.

Atherosclerotic CVD is the leading cause of morbidity and mortality in women in the United States and worldwide [1,32,33], and a better understanding of the role of sex hormones in CCTA-based plaque characteristics in women with subclinical atherosclerosis is needed and may help predict future CV events, particularly in the younger to middle age group. Sex hormones induce various changes on the heart, endothelium, and vascular tone. Endogenous estrogen has been shown to be cardioprotective and has been established to increase HDL-cholesterol with a significant decrease in LDL-cholesterol. It is also known to enhance vasodilation through increased release of nitric oxide and prostaglandin production, and additional long-term effects of changes in gene and protein expression in modulating response to atherosclerosis [34]. Due to the vasoprotective effects of circulating endogenous estrogen, women tend to develop CVD later than men and substantial evidence suggests premenopausal women are protected from cardiovascular disease compared to age-matched men [35]. In our study, we found women with any plaque were more likely to be older compared to those without.

The role of androgens in the pathogenesis of atherosclerotic CVD tends to differ in both sexes. A small fraction of testosterone exists in the free form and the rest are bound to SHBG. Men with lower levels of circulating testosterone have higher risk of atherosclerotic CVD [11–13]. However, in women, a high free testosterone and low SHBG, are associated with higher risk of atherosclerotic CVD [36,37]. CCTA has proven to be a useful tool in identifying subclinical atherosclerosis non-invasively. In this younger asymptomatic population, our findings set the stage for future larger longitudinal studies to better understand the association of sex-hormones with subclinical atherosclerosis. If further confirmed, a higher androgenic burden in young women may be considered as a risk enhancing factor for plaque and HRP and may highlight the need for awareness among clinicians to warrant further screening and close monitoring of such patients for subclinical atherosclerosis.

Our study had several strengths. We had a well-characterized multiracial cohort of individuals free of clinical coronary artery disease at baseline. We adjusted for relevant sociodemographic characteristics, cardiovascular risk factors, menopause, and medication use. Our study should also be considered in the context of some limitations. Subgroup analyses with HRP had greatly reduced sample sizes and so we were unable to stratify by menopausal status. There was missing data on hormone replacement status in post-menopausal women. Additionally, we did not have data available on certain medical conditions that may affect sex hormones such as polycystic ovarian syndrome, thyroid disorders, etc. Data on reproductive history such as early menopause, menarche, multiparity, adverse pregnancy outcomes were also not available and hence could not be explored. Sex hormones and coronary plaque were measured only at a single time-point, so we were unable to evaluate the association between change in sex hormones levels. Lastly, our study is a cross-sectional analysis, and we do not have any longitudinal analysis at this time to understand the progression over time.

To summarize, our study concentrated on exploring the association of sex hormones with the presence of any coronary plaque and HRP features in an asymptomatic multi-ethnic cohort of younger individuals with CVD risk factors but no overt CAD. Our study suggests that an androgenic hormone milieu in younger women predisposes to high-risk plaque. Understanding the androgenic sex-hormone profile might be of interest to clinicians while addressing subclinical coronary atherosclerosis in women. Future larger longitudinal studies may be needed to better explore these associations.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Garima Sharma reports a relationship with American Heart Association Inc that includes: funding grants. Ron Blankstein reports a relationship with Amgen Inc that includes: consulting or advisory. Ron Blankstein reports a relationship with Norvatis Inc that includes: consulting or advisory. Ron Blankstein reports a relationship with Caristo Diagnostics that includes: consulting or advisory. Ron Blankstein reports a relationship with Silence Therapeutics that includes: consulting or advisory. Ron Blankstein reports a relationship with Roivant Sciences Inc that includes: consulting or advisory. Michael Shapiro reports a relationship with Amgen Inc that includes: consulting or advisory. Michael Shapiro reports a relationship with Norvatis that includes: consulting or advisory. Michael Shapiro reports a relationship with Novo Nordisk Inc that includes: consulting or advisory. Michael Shapiro reports a relationship with Regeneron Pharmaceuticals Inc that includes: consulting or advisory. Ricardo Cury reports a relationship with GE Healthcare that includes: consulting or advisory. Ricardo Cury reports a relationship with Covera Health that includes: consulting or advisory. Ricardo Cury reports a relationship with Cleerly Inc that includes: consulting or advisory. Khurram Nasir reports a relationship with Amgen Inc that includes: consulting or advisory. Khurram Nasir reports a relationship with Novartis that includes: consulting or advisory. Khurram Nasir reports a relationship with Novo Nordisk Inc that includes:. Khurram Nasir reports a relationship with Jerold B Katz Academy of Translational Research that includes: funding grants. Khurram Nasir reports a relationship with Getz Pharma that includes: funding grants.

Acknowledgments

NA.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2023.100479.

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