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Short communication

Endogenous androgens, coronary atheroma and remodeling in women with suspected ischemic heart disease: A report from the Women's Ischemia Syndrome Evaluation (WISE) study

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ABSTRACT

Background: Women have smaller coronary size than men independent of body surface area. Female to male heart transplantation demonstrates coronary lumen enlargement.
Purpose: To investigate relationships between endogenous androgens and coronary luminal size in women with suspected ischemic heart disease (IHD).
Methods: We analyzed 69 women with available androgen levels.
Results: Group mean age was 54 ± 10 years with 64 % post-menopausal. Lumen cross-sectional area (CSA) and external elastic membrane (EEM) CSA positively correlated with free testosterone (FT) ($r = 0.29$, $p = 0.049$; r = 0.29, $p = 0.01$), respectively, and negatively correlated with SHBG ($r = -0.26$, $p = 0.03$; $r = -0.29$, $p = 0.02$), respectively. Atheroma CSA positively correlated with FT ($r = 0.24$. $p = 0.05$). These correlations became non-significant after adjusting for waist circumference.
Conclusions: In women with suspected ischemic heart disease, endogenous androgens, coronary atheroma and luminal size are related, and may be moderated by waist circumference.

1. Introduction

Ischemic Heart Disease (IHD) continues to be the leading cause of morbidity and mortality in women globally. The described differences in the pathophysiology of IHD between men and women have prompted research into potential contributing factors, including the impact of endogenous sex hormones. Data on the association of endogenous androgens in women with IHD, are not well understood. Notably, women have smaller coronary arteries size than men independent of body surface area, [1] and female to male heart transplantation demonstrates coronary lumen enlargement [2]. We sought to investigate relationships between endogenous androgens, coronary atheroma burden, and luminal size in women to understand potential mechanistic IHD pathways and treatment targets.

2. Methods

The NHLBI-WISE enrolled 936 women referred for clinically indicated angiography to further evaluate signs and symptoms suggestive of ischemic heart disease. The women underwent an initial evaluation that included demographic, medical history, psychosocial, symptom, and physical activity data, including menopausal status, and coronary angiography, as previously described [3]. A subset of women, without angiographic evidence of obstructive coronary artery disease, underwent coronary function testing with intravascular ultrasound (IVUS) for measurement of coronary atheroma and luminal size at the time of coronary angiography for suspected ischemia, as previously described [4].

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2.1. Measurement of androgen levels

Serum studies androstenedione, total testosterone, free testosterone (FT), sex hormone binding globulin (SHBG), testosterone / estradiol ratio, and free testosterone / bioavailable estradiol ratio were measured by validated immunoassays in the WISE core laboratory as previously described [3].

2.2. Statistical analysis

Relationships between androgen levels, waist circumference and IVUS variables, including lumen cross- sectional area (CSA), external elastic membrane (EEM) CSA, and atheroma CSA (EEM CSA minus lumen CSA) were assessed by Pearson correlation. Multiple regression modeling was performed to adjust for age, body mass index (BMI), and waist circumference.

3. Results

3.1. Baseline characteristics

Average age of the women was 54 ± 10, 17 % were non-white, 81 % had a high school education, 21 % had diabetes, 39 % had a history of hypertension, 44 % had dyslipidemia, 45 % had a history of smoking, 12 % were current smokers, and 80 % were post-menopausal. Average body mass index (BMI) and waist circumference was 32.1 ± 8.5 and 37.6 ± 6.6 in., respectively.

3.2. Relationships between serum androgens, coronary artery composition, waist circumference and coronary atheroma burden

Lumen CSA and EEM CSA positively correlated with FT ($r = 0.29$), ($p = 0.049$) (Fig. 1A) and (r = 0.29, $p = 0.01$) (Fig. 1B), respectively. Lumen CSA and EEM CSA negatively correlated with SHBG ($r = -0.26$, $p = 0.03$) (Fig. 1C) and ($r = -0.29$, $p = 0.02$) (Fig. 1D), respectively. Furthermore, Atheroma CSA positively correlated with FT ($r = 0.24$, $p = 0.05$) (Fig. 2). There were no statistically significant correlations between other androgens (androstenedione, total testosterone, testosterone/estradiol ratio, or free testosterone/bioavailable estradiol ratio) and IVUS measures. Waist circumference further positively correlated with EEM CSA ($r = 0.34$, $p = 0.004$) and FT ($r = 0.39$, p = 0.004) and negatively correlated with SHBG ($r = -0.42$. $p = 0.002$).

Multiple regression modeling adjusted for age and BMI demonstrated

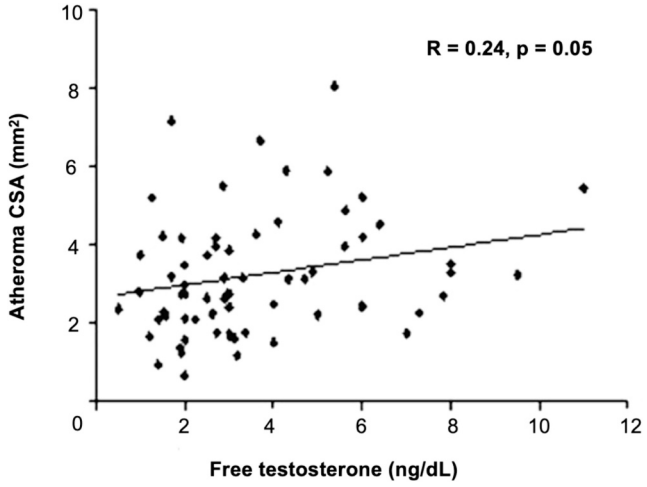

Fig. 2. Atheroma CSA correlation with Free Testosterone.

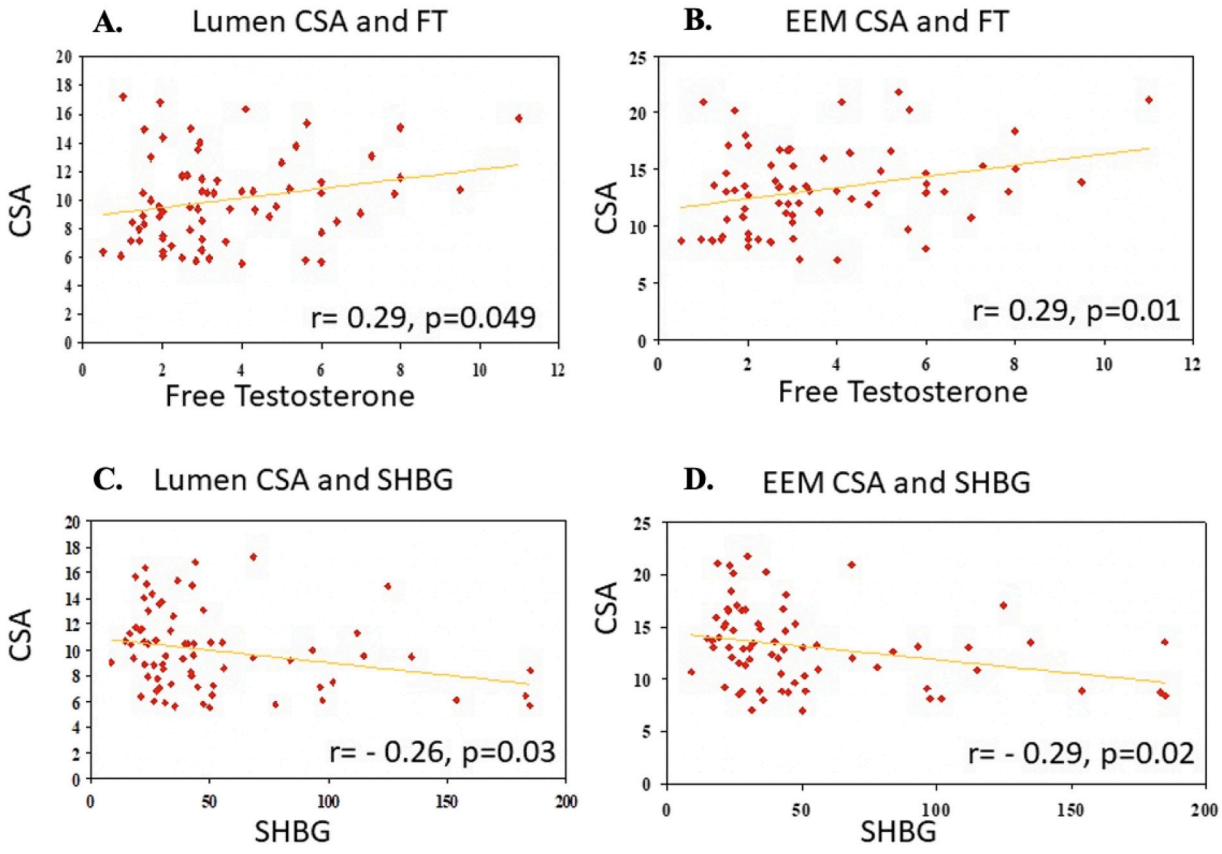

Fig. 1. Relationships between cross sectional area and free testosterone and sex hormone binding globulin (SHBG).

that the relationships between FT and SHBG and IVUS parameters remained unchanged. However, after adjusting for waist circumference, these relationships were no longer significant.

4. Discussion

In women with suspected IHD, free testosterone and SHBG are related to coronary lumen size and may be explained by associations between waist circumference with endogenous androgen levels. Furthermore, coronary atheroma burden positively correlated with free testosterone. These findings may offer insight into the potential mechanistic roles of endogenous androgens on lumen size via a direct pathway as previously described [2], and possibly via traditional coronary atherosclerosis pathways.

In addition to the prior work demonstrating women have smaller epicardial coronary arteries than men independent of differences in body surface area [1], and female to male post-transplant coronary size data [2], a male to female transition study demonstrated peripheral artery similar size to cis-gender women but smaller than cis-men, which the investigators speculated maybe due to androgen suppression [5]. In the early stages of atherosclerosis, the arterial wall undergoes compensatory outward enlargement to maintain the lumen area, a phenomenon known as Glagov phenomenon [6]. Therefore the proatherogenic nature of testosterone shown in our study may also suggest an indirect pathway affecting lumen size.

Other literature has demonstrated relationships between lumen area and major adverse cardiovascular events (MACE). A recent study that looked at IVUS measured minimum lumen area (MLA) and plaque burden found that the greater plaque burden and smaller MLA were associated with all-cause death [7], potentially contributing to relatively higher adverse IHD events in women. Indeed, women have more high-risk plaque features such as smaller MLA features compared with men adding to the attributable risk of MACE [8]. A 2018 study that looked at a cohort of post-menopausal women from the Multi-Ethnic Study of Atherosclerosis (MESA) found that a more androgenic sex hormone pattern was associated with increased rates of coronary heart disease, which persisted even after adjusting for known cardiac risk factors [9]. Furthermore, lower SHBG and higher free androgen index (ratio between free testosterone and SHBG) levels were observed among post-menopausal women with developed CVD events [10].

The current study identified direct relation between FT levels and coronary atheroma burden was no longer statistically significant after adjusting for waist circumference. Elevated endogenous androgen levels can be seen clinically in mid-life and postmenopausal women most often in polycystic ovary syndrome (PCOS) and obesity [11]. These results suggest potential mechanistic pathways for PCOS and obesity in women for coronary atherosclerosis. Furthermore, estradiol levels decrease during the menopausal transition while testosterone levels are relatively unchanged resulting in a relative androgen excess [12]. This relative androgen excess maybe an independent risk factor for cardiovascular disease that warrants further inquiry. Conducting additional longitudinal studies is needed to further understand these potential mechanisms.

5. Study limitations

This study has several limitations. First, it is an observational study and therefore may be affected by bias and confounding. Second, the study only included a subgroup of women undergoing IVUS with no obstructive CAD raising the possibility of referral bias. Third, the coronary IVUS imaging was limited to a single vessel, potentially underestimating the true prevalence and extent of atherosclerosis in these women. Last, our analysis did not include outcome data, and hence, we were not able to assess the associations between endogenous androgens, coronary size, MACE, and all-cause mortality.

6. Conclusions

Our study highlights a potentially significant relationship between free testosterone, SHBG, and coronary lumen size, which may be moderated by waist circumference in women presenting with suspected IHD. Furthermore, coronary atheroma is related to free testosterone, which similarly appears to be moderated by waist circumference in this population. These relationships between endogenous androgens, coronary atheroma, and luminal size highlight the need for further investigations to understand potential mechanistic IHD pathways and treatment targets in women.

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Ethical statement

The study was performed under an Institutional Review Board approved protocol in accordance with guidelines for human subjects in research. All patient subjects provided informed consent to participate in this study. All authors attest that this work is original and not under consideration for publication elsewhere.

CRediT authorship contribution statement

Sachini Ranasinghe: Writing – review & editing, Writing – original draft. **Ankur Jain:** Writing – review & editing, Writing – original draft. **Yasmeen Taha:** Writing – review & editing, Writing – original draft. **Eileen Handberg:** Writing – review & editing. **B. Delia Johnson:** Writing – review & editing. **Vera Bittner:** Writing – review & editing. **George Sopko:** Writing – review & editing. **Carl J. Pepine:** Conceptualization. **R. David Anderson:** Writing – review & editing. **C. Noel Bairey Merz:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

CNBM receives consulting fees from SHL Telemedicine, and consulting and stocks from iRhythm. CJP serves as the Editor-in-Chief of AHJO.

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