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Serum androgen concentrations and subclinical measures of cardiovascular disease in men and women

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ABSTRACT

Objectives: Most of the observed associations of androgens and sex hormone-binding globulin (SHBG) with subclinical cardiovascular disease (CVD) stem from selected study samples with immunoassay-based hormone measurements. Thus, we used a large population-based sample with total testosterone (TT) and androstenedione (ASD) concentrations measured by liquid chromatography-tandem mass spectrometry.

Design: Data of 2140 individuals (mean age: 60,8 years) from the cohort Study of Health in Pomerania were assessed at baseline and 5-year follow-up.

Methods: Multivariable regression models were implemented to assess cross-sectional and longitudinal associations of TT, free testosterone (fT), ASD, SHBG and dehydroepiandrosterone-sulphate (DHEAS) with measures of subclinical CVD including intima media thickness (IMT), carotid plaques, left ventricular mass (LVM), fractional shortening (FS), relative wall thickness (RWT), and left ventricular geometry.

Results: Cross-sectional analyses yielded an association of TT with IMT in women (β-coefficient per log unit increase: 0.02; 95% CI: 0.007; 0.45) and ASD with FS in both sexes (men: β-coefficient: −2.94; 95% CI: −4.75; −1.12; women: β-coefficient: 1.64; 95% CI: 0.55; 2.73). In longitudinal analyses, DHEAS was positively associated with FS change (β-coefficient: 2.34; 95% CI: -0.59; 4.08). In women, SHBG was positively associated with incident plaques (Q1 vs. Q3 (Ref.): β-coefficient: 1.35; 95% CI: 1.04; 1.74). In both sexes, longitudinal analyses showed no consistent association of TT with subclinical CVD.

Conclusions: Despite several sex-specific associations of androgens and SHBG with subclinical CVD, the present representative study for the age group ≥45 years among men and women from the general population detected no consistent associations in longitudinal analyses.

1. Introduction

Cardiac remodeling describes a physiological process of incremental alterations in the heart's structure and function over the life course [1], characterized by changes in several echocardiographic indices including changes in left ventricular mass (LVM), LV wall thickening, and geometrical LV adaptations. Contemporary echocardiography and ultrasound techniques allow an early and non-invasive assessment of these subclinical measures of cardiovascular disease (CVD), including left ventricular hypertrophy (LVH), a structural adaptation of the heart to an increased blood pressure [2], changes in carotid intima media thickness (IMT), and modifications on the mesenchyme cells in vessel walls, called plaques [3]. Observational research provides solid evidence for a strong link of these measures with CVD onset and progression, as well as an increased mortality risk [4]. The potential link between androgens and subclinical CVD refers to animal models and observational research [3,4], suggesting sex-specific differences in CVD onset and progression [5]. Previous observational studies

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among men showed that total testosterone (TT), free testosterone (fT), dehydroepiandrosterone-sulphate (DHEAS), and sex hormone-binding globulin (SHBG) concentrations are inversely associated with carotid plaques, LVM [6,7] and IMT, partially mediated by obesity [3,7,8]. Studies among women reported that TT and fT were positively and SHBG inversely associated with IMT [3,9], whereas menopausal women showed no association of TT with IMT progression or subclinical atherosclerosis [10].

However, population-based analyses of longitudinal associations between endogenous androgens and SHBG and change in subclinical CVD among both sexes are scarce. Particularly immunoassay-based measurements of androgens are a common limiting factor in previous studies, especially among women [11]. Thus, the aim of the present study was to investigate cross-sectional and longitudinal associations between androgen and SHBG concentrations measured by liquid chromatography mass-spectrometry (LC-MS) and subclinical CVD in middle-aged men and women from a population-based cohort.

2. Methods

2.1. Study population

The population-based Study of Health in Pomerania (SHIP) is a cohort study, established in West-Pomerania, a region in north-eastern Germany. Details of the study design, procedures, and recruitment were published previously [12]. The target population was 6265 eligible individuals with German citizenship and main residency in the study area, selected from the population registration offices. 4308 individuals (2192 women) aged 20–80 years lastly participated between 1997 and 2001 in the baseline study (SHIP-0, response rate: 68.8%), after written informed consent was obtained from each participant. Five-year follow-up examinations were conducted between 2002 and 2006 (SHIP-1), involving 3300 individuals (1711 women, total response rate: 83.6%). The study was reviewed by the local ethical committee of the University Greifswald and is consistent with the principles of the Declaration of Helsinki. Echocardiography was performed in individuals aged 45 years or older. From these 2550 participants, 410 were excluded due to (overlap exists): self-reported hysterectomy (N = 31 women) or bilateral oophorectomy, medication use in the last seven days (based on the Anatomical Therapeutic Chemical classification index) including sex hormone antagonists (N = two women, 135 men), antiandrogens (N = seven women), and natural opium alkaloids (N = 23 women, 14 men). Furthermore, we excluded participants with prevalent or incident myocardial infarction (N = 45 women, 107 men) and aortic stenosis (N = 20 women, 25 men). None of the women were pregnant at baseline or follow-up. Altogether, the final baseline study population comprised 1145 women and 995 men (see flow chart in Supplementary Fig. 1).

2.2. Measures

Information on sociodemographic and behavioral characteristics, as well as medical history, including information about sex, age, physical inactivity, smoking habits, pregnancy, medical procedures, and medication use were collected, using a computer-assisted personal interview. As to smoking habits, participants were divided into three categories (current, former, and never-smokers). Women were stratified into pre- and post-menopausal, using a previously published categorization [13]. The use of hormone therapy (G03C, G03D, or G03F) and oral contraceptive (G03A) was assessed based on ATC codes. Weight was measured utilizing standard digital scales (to the nearest 0.1 kg). Body mass index (BMI) was calculated from the body weight in kilogram and height in meters [BMI = kg/m^2]. Systolic (SBP) and diastolic blood pressure (DBP) were measured after a resting period of at least five minutes and an interval between the three readings of three minutes, using an oscillometric digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan). For the present analyses the mean of the second and third measurements was used. Hypertension was defined as use of antihypertensive medication or systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg. Diabetes was defined as HbA1c $\geq$ 6.5, glucose $\geq$11.1 mmol/L or self-reported use of insulin or oral antidiabetic medications.

All hormone concentrations were measured at baseline and were previously described in detail [14]. Briefly, between 8:00 a.m. and 7:00 p.m. non-fasting serum samples were taken and stored at −80 °C until measurement by LC-MS [15]. The lower limit of quantitation was 0.25 nmol/L and intra- and inter-assay coefficients of variation were <10% for both TT and ASD over the range 0.3–35 nmol/L. SHBG concentrations were measured from frozen serum aliquots using a chemiluminescent enzyme immunoassay Advia Centaur (Siemens, Eschborn, Germany) with an inter-assay coefficient of variation of 6.6% at the 27.1 nmol/L level, 7.6% at the 48.2 nmol/L level, and 7.7% at the 52.3 nmol/L level. DHEAS was measured only in men, using a competitive chemiluminescent enzyme immunoassay on an Immulite 2500 analyzer (DPC Biermann GmbH, Bad Nauheim, Germany). FT was calculated from measured TT and SHBG concentrations for a standard average albumin concentration of 4.3 g/dL (equations (1)–(4)) [16].

$$\mathrm{fT[nmol/L]} = \left(\left(-a + \sqrt{b}\right)/c\right)/10^{-9} \quad (1)$$

$$a = \mathrm{SHBG[nmol/L]} - \mathrm{TT[nmol/L]} + 23.43 \quad (2)$$

$$b = a^2 + (4 \cdot 23.43 \cdot \mathrm{TT[nmol/L]}) \quad (3)$$

$$c = 2 \cdot 23.43 \cdot 10^9 \quad (4)$$

Carotid far-wall IMT scans were digitized through the axis of the distal straight portion (1 cm in length) of both common carotid arteries and recorded for subsequent offline analysis. Mean IMT was calculated by averaging the 10 consecutive measurement points (in 1 mm steps) from both sides. IMT was defined as the distance between the characteristic echoes from the lumen-intima and media-adventitia interfaces. Plaques were determined with sonography of the carotid artery. Echocardiography (two-dimensional and M-mode) was performed by certified physicians using a Vingmed CFM800A system (GE Medical Systems, Waukesha, Wisconsin, USA). M-mode images of the left ventricle were recorded at the papillary level. The leading-edge convention was used to measure left ventricular dimensions (posterior wall thickness (LVPWD), interventricular septum thickness (IVS), left ventricular end-diastolic (LVDD), and systolic (LVDS) diameter). LVM was calculated according to the following formula: LVM = 0.80 × (1.04 × [[LVDD + IVS + LVPWD]^3–LVDD^3]) + 0.60/height$^{2.7}$. LVH was defined by a LVM > 44 g/m$^{2.7}$ in women and a LVM >48 g/m$^{2.7}$ in men [17]. RWT was calculated according to the following formula: RWT = (2 × LVPWD)/LVDD. Categories of left ventricular geometry were defined for normal geometry (no LVH, and RWT of <0.42), concentric remodeling (no LVH and RWT >0.42), eccentric hypertrophy (LVH and RWT of <0.42), and concentric hypertrophy (LVH and RWT >0.42) [18]. Fractional shortening (FS) was defined as ([LVDD − LVDS]/LVDD) × 100. Progression of LVM, RWT, FS, and IMT was measured as difference between follow-up and baseline values.