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Full Length Article

# Sex hormone levels and change in left ventricular structure among men and post-menopausal women: The Multi-Ethnic Study of Atherosclerosis (MESA)

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ABSTRACT

*Objective:* Sex hormone (SH) levels may contribute to sex differences in the risk of heart failure with preserved ejection fraction (HFpEF). We examined the associations of SH levels with left ventricular mass (LVM) and mass (M):volume (V) ratio, which are risk markers for HFpEF.

*Study design:* We studied 1941 post-menopausal women and 2221 men, aged 45–84 years, participating in the Multi-Ethnic Study of Atherosclerosis (MESA). Serum SH levels, cardiac magnetic resonance imaging (MRI) and ejection fraction (EF) ≥50% had been recorded at baseline (2000–2002). Of these participants, 2810 underwent repeat MRI at Exam 5 (2010–2012). Stratified by sex, linear mixed-effect models were used to test associations between SH and sex hormone binding globulin (SHBG) level [per 1 SD greater log-transformed (SH)] with baseline and change in LV structure. Models were adjusted for age, race/ethnicity, center, height, weight, education, physical activity and smoking, and, in women, for hormone therapy and years since menopause.

*Main outcome measures:* LVM and M:V ratio.

*Results:* After a median of 9.1 years, higher free testosterone levels were independently associated with a modest increase in LVM (g/yr) in women [0.05 (95% CI 0.01, 0.10)] and men [0.16 (0.03, 0.28)], while higher SHBG levels were associated with less LVM change (g/yr) in women [−0.07 (−0.13, −0.01)] and men [−0.15 (−0.27, −0.02)]. In men, higher dehydroepiandrosterone and estradiol levels were associated with increased LVM. Among women, free testosterone levels were positively and SHBG levels inversely associated with change in M:V ratio.

*Conclusion:* A more androgenic profile (higher free testosterone and lower SHBG levels) is associated with a greater increase in LVM in men and women and greater increase in M:V ratio in women over the course of 9 years.

## 1. Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for half of all HF cases and is more prevalent among women [1]. Changes in left ventricular (LV) structure, such as LV hypertrophy and LV concentric remodeling [i.e. increased mass-to-volume (M:V) ratio], are risk markers for incident HFpEF [2]. Treatments that reduce LV mass (LVM) are associated with a decreased risk for incident cardiovascular disease (CVD) and HF [3]. Thus, imaging indices of LV structure are important prognostic risk markers [4].

*Abbreviations:* HFpEF, heart failure with preserved ejection fraction; CVD, cardiovascular disease; MRI, magnetic resonance imaging; RV, right ventricle; LV, left ventricle; LVM, left ventricular mass; LVEDV, left ventricular end diastolic volume; M:V ratio, left ventricular mass to volume ratio; SBP, systolic blood pressure; SH, sex hormones; T, Testosterone; E2, Estradiol; DHEA, dehydroepiandrosterone; SHBG, sex hormone binding globulin

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Sex differences in LV structure have been observed. Men have a greater LV end diastolic volume (LVEDV) and LVM, even after adjusting for differences in body size [5,6]. Sex hormones may influence LV structure differently in men vs. women. For example, a prior study in men found lower androgen levels [i.e. testosterone (T)] were associated with greater LVM [7]. However, the opposite pattern was seen in hypertensive peri-menopausal women, with higher androgen levels (free T) associated with LV diastolic dysfunction [8].

At the menopausal transition, women experience drastic changes in the levels of endogenous sex hormones with an abrupt decrease in estradiol (E2) and sex hormone binding globulin (SHBG), as well as a concommitant but more gradual decrease in total T. In women, a more androgenic pattern of sex hormones after menopause has been associated with elevated blood pressure (BP), insulin resistance, and other CVD risk factors [9,10]. Thus, a more androgenic profile may lead to adverse LV remodeling in post-menopausal women and potentially contribute to the female predominance of HFpEF risk at older ages.

Prior studies evaluating sex hormones and LV structure have been limited by cross-sectional designs and smaller sample sizes [7,8]. It is still uncertain how sex hormone levels may influence cardiac structure over time after accounting for changes in established CVD risk factors. Therefore, we studied the cross-sectional and longitudinal associations of sex hormone levels with LV structure in a multi-ethnic population without clinical CVD at baseline. We hypothesized that a more androgenic sex hormone profile at baseline (i.e. lower E2, higher free T, and lower SHBG) would be longitudinally associated with increased LVM and increased M:V ratio (i.e. concentric remodeling) among post-menopausal women but not men.

## 2. Methods

### 2.1. Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is an ongoing prospective cohort investigating subclinical CVD in a community-based sample of 6814 men and women aged between 45–84yrs at baseline. Participants were recruited from four race/ethnicities across six U.S. centers, as described previously [11]. MESA exclusion criteria included a history of clinical CVD or HF (assessed by self-reported questionnaire), weight > 300 lb, and any restriction to participation. For our analysis, we excluded pre-menopausal women, as sex hormone levels substantially change after menopause.

Our study had two components (Fig. 1): 1) cross-sectional analyses (N = 4162) of participants at baseline (2000–2002) who had available sex hormone and cardiac MRI data, and a preserved ejection fraction (EF ≥ 50%) and 2) longitudinal analyses (N = 2810) that included participants with an additional follow-up MRI at Exam 5 (2010–2012). The protocols of MESA were approved by the institutional review boards of all collaborating institutions; all participants provided written informed consent.

### 2.2. Exposure variables

Baseline serum sex hormones were measured from an early morning fasting blood sample and stored at −70 °C. Hormone assays were performed at the University of Massachusetts Medical Center in Worcester, MA. E2 was measured using an ultrasensitive radioimmunoassay kit (Diagnostic System Laboratories, Webster, TX). Total T and dehydroepiandrosterone (DHEA) were measured using radioimmunoassay kits, and SHBG was measured by chemiluminescence enzyme immunometric assay using Immulite kits (Diagnostic Products Corporation, Los Angeles, CA) [9]. Free T was calculated using the Sodergard method [12] and reported as percent of total T. The intra-assay coefficients of variation for total T, SHBG, DHEA, and E2 were 12.3%, 9.0%, 11.2%, and 10.5%, respectively.

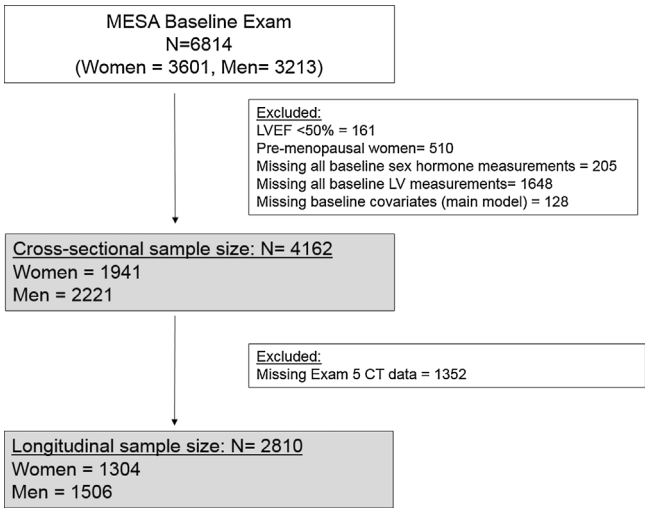


**Fig. 1.** Flowchart of study sample.

### 2.3. Outcome variables

LV parameters (LVM, LVEDV, and M:V ratio) were measured by cardiac MRI at baseline and Exam 5. Left atrial size parameters were not measured from the MRIs and thus not available for analysis. The cardiac MRI was performed using 1.5T magnets with a phased array surface coil placed both anteriorly and posteriorly with ECG gating. The MRI consisted of long and short axis images taken during short breath holding at resting lung volume. Further details of the MRI protocol have been described previously [6,13]. MRI images were analyzed at the central reading center at the Johns Hopkins Hospital, Baltimore, MD.

LVM was measured at end-diastole. Papillary muscles were included in the LVEDV measurement and excluded from LVM. Interventricular septum was included in the LVM. The intraclass correlation was 0.98 for LVM and 0.98 for LVEDV for baseline MRI data [13]. The overall interobserver intraclass correlation coefficients for LVM and LVEDV were 0.95 and 0.96 [6].

### 2.4. Covariates

Standard questionnaires assessed race/ethnicity, education level, smoking status, and physical activity (defined as intentional exercise in METS*min/week). Medications were determined by an inventory. Menopausal status was determined by an algorithm incorporating self-reported status, age, age at menopause/hysterectomy/ovariectomy, and hormone therapy (HT) use [14]. Only post-menopausal women were included.

Height and weight were measured per standardized procedures [11]. Resting BP was measured three times in the seated position using a Dinamap automated sphygmomanometer, and average of the 2nd and 3rd readings was used. Diabetes was determined by self-reported physician diagnosis, a fasting glucose level of ≥126 mg/dl, or the use of hypoglycemic medication. Covariates were assessed at Exams 1 and 5.

### 2.5. Statistical analysis

Baseline characteristics were stratified by sex and summarized using means (standard deviations (SD)), medians (interquartile interval), or percentages. The sex hormone levels were postively skewed and thus were logarithmically-transformed and analyzed per 1 SD of their natural log. LV measures were used as continuous variables.

To assess the longitudinal associations between baseline sex hormones and LV structure changes over time, we used multivariable-adjusted linear mixed effect models, and allowed for random variations in baseline sex hormones and longitudinal slopes of sex hormones across