# Association Between Endogenous Sex Hormones and Liver Fat in a Multiethnic Study of Atherosclerosis

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Q5 **BACKGROUND & AIMS:** **Levels of circulating of sex hormones are associated with glucose metabolism and adiposity, but little is known about their association with ectopic fat. We aimed to characterize the association between circulating sex hormones and liver fat.**

**METHODS:** **We conducted a cross-sectional analysis by using data from the Multiethnic Study of Atherosclerosis to assess the association of the circulating levels of bioavailable testosterone, estradiol, dehydroepiandrosterone, and sex hormone binding globulin (SHBG) with fatty liver. Fatty liver was defined as a reduction of ≤40 Hounsfield units, measured by computed tomography, in 2835 postmenopausal women and 2899 men (45–84 years old; white, black, Hispanic, or Chinese) at 6 centers in the United States.**

**RESULTS:** **Women in the highest tertile of bioavailable testosterone were significantly more likely to have fatty liver than women in the lowest tertile (odds ratio, 1.77; 95% confidence interval, 1.07–2.92). We found an even greater difference for level of estradiol (odds ratio, 2.49; 95% confidence interval, 1.41–4.39) after adjusting for age, race/ethnicity, waist-to-hip ratio, hypertension, total and high-density lipoprotein cholesterol, smoking, insulin sensitivity, and hormone replacement therapy use. Men in the highest tertile of estradiol level were significantly more likely to have fatty liver than men in the lowest tertile (odds ratio, 2.10; 95% confidence level, 1.29–3.40). Men in the highest tertile of SHBG were less likely to have fatty liver than those in the lowest tertile (odds ratio, 0.46; 95% confidence interval, 0.27–0.77). Other associations between hormone levels and fatty liver were not statistically significant.**

**CONCLUSIONS:** **On the basis of a cross-sectional study, postmenopausal women with high levels of bioavailable testosterone are at greater risk for fatty liver. In men, higher levels of SHBG are associated with reduced risk for fatty liver. Higher levels of estradiol are associated with fatty liver in both sexes. This pattern is consistent with the sex-specific associations of sex hormones with other cardiometabolic risk factors.**

*Keywords:* MESA; Testosterone; SHBG; Estradiol; Epidemiology; NAFLD.

Ectopic deposition of fat in the liver in the absence of significant alcohol consumption is the early stage of nonalcoholic fatty liver disease (NAFLD), one of the most common chronic liver conditions that may progress to more serious clinical consequences including nonalcoholic steatohepatitis, fibrosis, liver failure, and hepatocellular carcinoma.[1–4] Metabolic abnormalities are major drivers of NAFLD and include overweight and obesity,[5,6] metabolic syndrome,[7,8] and insulin resistance.[6] Because the population prevalence of overweight and obesity is increasing in the general U.S. population, the prevalence of NAFLD is also reaching epidemic proportions.[9,10] Circulating levels of endogenous sex hormones are associated with these metabolic abnormalities; higher levels of testosterone are associated with lower levels of central obesity cross-sectionally and

***Abbreviations used in this paper:*** **Bio-T, bioavailable testosterone; CT, computed tomography; DHEA, dehydroepiandrosterone; $E_2$, estradiol; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; HU, Hounsfield units; MESA, Multiethnic Study of Atherosclerosis; NAFLD, nonalcoholic fatty liver disease; QUICKI, quantitative insulin sensitivity check index; SHBG, sex hormone binding globulin.**


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longitudinally[11–13] and with lower prevalence and incidence of diabetes in men but not in postmenopausal women.[14–16] Higher levels of estradiol and lower levels of sex hormone binding globulin (SHBG) are associated with greater central obesity, metabolic syndrome, diabetes, and atherogenic lipid profile in both men and postmenopausal women.[17]

Reports of studies in small samples suggest that lower levels of SHBG are associated with increased NAFLD in men and menopausal women.[18–20] Another study reported an association between low levels of dehydroepiandrosterone (DHEA) and NAFLD.[21] However, no associations with estradiol or testosterone have been reported in U.S., multiracial, population-based studies.

The aim of this study was to determine the cross-sectional associations of liver fat with circulating sex hormones in a large multiethnic U.S. population sample and examine whether this association is independent of cardiometabolic profile.

## Materials and Methods

More detailed methods are described in the Supplementary Material.

### Sample Population

This analysis was performed by using data from sex hormone ancillary study of the baseline examination of the Multiethnic Study of Atherosclerosis (MESA), which included 3009 postmenopausal women and 3164 men. Liver fat measurements derived from abdominal computed tomography (CT) scans were available in 2835 women and 2899 men who were included in the current analysis. All study participants gave informed consent, and the Institutional Review Boards of all participating centers oversaw the study.

### Sex Hormone Measurements

Blood drawn between 7:30 and 10:30 AM was used for the assays. Serum stored at −70°C was assayed at the University of Massachusetts Medical Center at Worcester, MA. Total testosterone and DHEA were measured directly by using radioimmunoassay kits, and SHBG was measured by chemiluminescent enzyme immunometric assay by using Immulite kits obtained from Diagnostic Products Corporation (Los Angeles, CA). Estradiol ($E_2$) was measured by use of an ultrasensitive radioimmunoassay kit from Diagnostic System Laboratories (Webster, TX). The intra-assay coefficients of variation for total testosterone, SHBG, DHEA, and $E_2$ were 12.3%, 9.0%, 11.2%, and 10.5%, respectively. Bioavailable testosterone (BioT) was calculated by using the method of Vermeulen et al.[22]

### Liver Fat Measurements

Images were acquired by using either electron beam tomography or 4-detector row CT scanners.[23,24] Examples of images from participants with high liver attenuation (ie, low liver fat content) and low liver attenuation (ie, high liver fat content) are shown in Figure 1*A* and *B*, respectively. Hepatic attenuation and splenic attenuation (when the spleen was in the field of view) were assessed from 3 regions of interest (>100 $mm^2$) in the liver and 1 in the spleen. We defined fatty liver as liver attenuation <40 Hounsfield units (HU) for the main analyses and

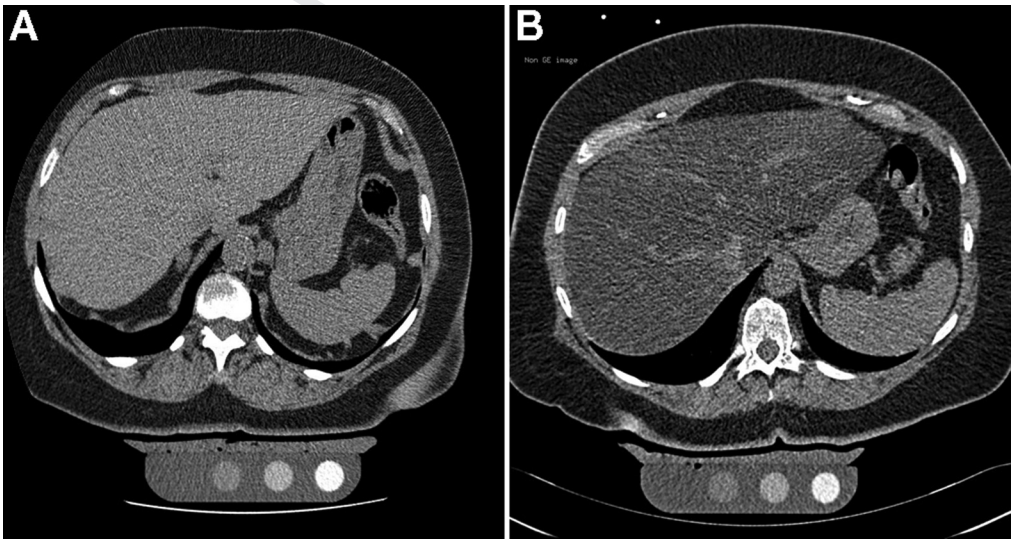


**Figure 1.** Examples of abdominal CT images showing the liver (L) and spleen (S) from persons with high liver attenuation, ie, low liver fat content (*A*) and one with low liver attenuation, ie, high liver fat content (*B*). Liver attenuation in HU was used as a quantitative variable and also to define fatty liver (attenuation <40 HU) in the main analysis. In images where spleen image was available, liver-to-spleen attenuation ratio was calculated, and ratio <1 was defined as fatty liver for Supplementary analysis.