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The Association between Inflammation, Testosterone and SHBG in men: a cross-sectional Multi-Ethnic Study of Atherosclerosis

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Abstract

Context: Earlier studies have investigated the role of obesity-related inflammation and endogenous sex hormones in men. The role of interleukin-6 (IL-6) and C-Reactive Protein (CRP) with testosterone and sex hormone binding globulin (SHBG) levels in men is still debated.

Objective: To investigate the independent association between levels of high sensitivity CRP (hsCRP) and IL-6 with endogenous sex hormones in men.

Design: Cross sectional observational study using data from the Multi-Ethnic Study of Atherosclerosis.

Patients or Other Participants: A community-based sample of 3212 men aged 45–84 years was included. After exclusions, 3041 men remained for the analyses.

Main Outcome Measure(s): Serum concentrations of testosterone, SHBG, hsCRP, IL-6 and sTNFR were measured from the baseline exam. Multivariable linear regressions were used to examine the association of inflammatory markers with sex hormones.

Results: An inverse association was found between levels of hsCRP and levels of testosterone and SHBG, even after adjustment for confounders and IL-6 (Total Testosterone; B= −0.14, Bioavailable Testosterone; B= −0.06, and SHBG; B= −0.66). Similar results were found for IL-6, although a positive association was found for SHBG (B= 0.95). Notably, an inverse association was found for IL-6 with bioavailable testosterone in African Americans and Hispanic Americans aged 45–54 years. No associations were found for sTNFR and endogenous sex hormones.

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Conflict of interests

The authors declare no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Disclosure statement: The authors have nothing to disclose.

Conclusion: Our results indicate that inflammatory markers have independent associations with levels of testosterone (*total and bioavailable*) and furthermore, appear to associate differently with SHBG levels.

Keywords

hsCRP; Inflammation; Cytokines; Sex Hormones; Testosterone; Bioavailable Testosterone; Sex-Hormone Binding Globulin

INTRODUCTION

Late-onset hypogonadism (LOH) is a functional disorder of low testosterone levels in middle-aged and older men. The main causes are increasing age, obesity and co-morbidities including metabolic syndrome/type 2 diabetes mellitus (T2DM).[1] Indeed, an inverse relationship between obesity and endogenous sex hormones (total and free testosterone levels) and sex-hormone binding globulin (SHBG) has been described in men.[2] Notably, visceral fat has been shown to have a negative association with testosterone suggesting a role in the secretion of inflammatory cytokines in men and among different race/ethnic groups.[3, 4] As surrogates for visceral adiposity, the waist-hip ratio (WHR) and waist circumference (WC) have shown to most accurately be associated with the risk of developing cardiometabolic disorders.[5]

It is hypothesized that abdominal obesity results in alterations in the hypothalamic-pituitary-gonadal axis (HPG-axis), which, in turn, may result in a decline in testosterone concentrations in men.[6] Earlier studies have found that adipocyte-related cytokines (interleukin 1-beta (IL-1B), tumor necrosis factor-alpha (TNF-a)), insulin and leptin resistance are associated with different levels of testosterone by binding to the kisspeptin-neuron in the hypothalamus causing a decrease in secretion of luteinizing hormone and testosterone production.[6, 7] Moreover, soluble tumor necrosis factor – alpha receptors (sTNFR) have been described to reduce cellular response to TNF-a.[8] However, no studies have examined the possible associations between sTNFR and testosterone levels in a large study.

Sex-hormone binding globulin (SHBG) is a protein carrier with potential biologic anti-inflammatory function, regulating concentrations of testosterone.[9] Low levels of SHBG have been related to increased risk for insulin resistance, obesity, T2DM and metabolic syndrome in men.[10] However, the association between obesity and levels of SHBG seems to be bidirectional, as some studies have found adipocytokines such as TNF-a to decrease production of SHBG.[11] An inverse association between SHBG and high sensitivity CRP (hsCRP) in men has been demonstrated but the association with IL-6 remains uncertain.[12, 13] Of note, Tsigos and colleagues, injected recombinant IL-6 in men resulting in a decline in testosterone but no changes in levels of SHBG.[14]

The aim of this study was to investigate whether hsCRP and IL-6, independent of each other, are associated with levels of testosterone and SHBG in men and whether these associations vary by race/ethnic groups.

MATERIAL AND METHODS

Study Design and Study Population

Between 2000 and 2002, the Multi-Ethnic Study of Atherosclerosis (MESA) recruited 6814 adult men and women, between 45–84 years that were free of clinical cardiovascular disease. Participants were enrolled from six US communities (New York [NY], Baltimore [MD], Chicago [IL], Los Angeles [CA], Twin Cities [MI] and Winston-Salem [NC]). Approximately 38% were Non-Hispanic White, 28% African American, 23 % Hispanic American, and 11 % Asian American, with the latter be predominantly of Chinese descent. Follow-up visits have been conducted five times since baseline.

Participants with missing data on anthropometric measurements, inflammatory markers, testosterone, SHBG, lifestyle factors, co-morbidities and medication use were excluded from the study. Those with hsCRP levels above 10 mg/dL were also excluded in line with recommendations from the American Heart Association.[15] At baseline, there were a total of 3212 men with measured levels of testosterone, of whom 3041 had IL-6, 2919 had hsCRP and 1313 had sTNFR measurements (Table 1).

Data collection

Bild and colleagues have published details of the MESA study methods and further information is available on the study website (https://www.mesa-nhlbi.org).[16] Briefly, trained staff performed specimen phlebotomy and processing of venous blood samples, blood pressure measurements and all interviews of study participants. Fasting blood samples were drawn, processed, and stored using standardized procedures at −80°C.[17]

Information on lifestyle factors, medications and co-morbidities were gathered using validated questionnaires. Race/ethnicity was self-reported at baseline of MESA exam according to 2000 US Census criteria. Physical activity was measured by using a comprehensive, semiquantitative questionnaire.[18]

Current medication use was assessed according to standardized questionnaires.[19] Hypertension was confined as a systolic blood pressure above 140 mmHg and a diastolic above 90 mmHg or taking a blood pressure medication, while diabetes was defined as fasting glucose >=126 mg/dL or use of glucose lowering medications, respectively.[20, 21]

Assessment of androgen hormones

Measurement of endogenous sex hormone concentrations was done as part of an ancillary MESA study and have previously been described.[22] In brief, fasting serum samples were drawn in the morning at the baseline exam, between 07:30 AM and 10:30 AM and stored at −70°C.

Biochemical analyses were performed at the University of Massachusetts Medical Center Sex Hormone Laboratory (Worcester, MA). Total testosterone was measured using radioimmunoassay kits. Chemiluminescent enzyme immunometric assay (Immulite kits, Diagnostic Products Corporation, Los Angeles, CA) was used to assess concentrations of SHBG. Bioavailable testosterone (defined as sum of SHBG-free and albumin-bound

testosterone) and free testosterone (reported as a percent of total testosterone) were calculated according to the method of Södergård. A ~10% blind pool was obtained to assess quality control serum. The coefficients of variation for total testosterone and SHBG were 12.3% and 9.0%, respectively. Estradiol was measured using an ultra-sensitive radioimmunoassay kit (Diagnostic System Laboratories, Webster, TX).

Assessment of inflammatory markers

All plasma biomarkers were assessed in the Laboratory for Clinical Biochemistry Research at University of Vermont (Burlington, VT) at baseline. Measurement of IL-6, hsCRP and sTNFR have previously been described.[23, 24] HsCRP concentrations were quantified using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, IL) with an assay range of 0.175 – 1100 mg/L. Intra-assay CVs was assessed, ranging from 2.3 – 4.4% with inter-assay CVs range of 2.1 – 5.7%, respectively. IL-6 measurement was determined by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN), quantified in pg/mL with a lower detection limit of <0.0.094 pg/mL and a detection range of 0.156–10.0 pg/mL. Concentrations of sTNFR-1 were analyzed using an ultrasensitive ELISA assay (Quantikine Human sTNFR-I Immunoassay; R&D Systems, Minneapolis, MN). Analytical CV for sTNFR is 5%.

Statistical analysis

We performed a cross-sectional analysis using data from the baseline exam of MESA. Continuous variables were reported with means and standard deviations (SD), while categorical variables were shown as frequencies and percentages. The magnitudes of the associations were quantified as a one-unit increment of the distribution of hsCRP, IL-6 and sTNFR. Continuous testosterone (total, bioavailable and free) and SHBG were the outcome variables.

Linear regression models were used to assess the relationship between each inflammatory-specific markers with testosterone and SHBG, separately. The initial model showed the unadjusted association for inflammatory makers with sex hormones and SHBG. The second model was adjusted for age, race/ethnicity and WHR. Similar models were constructed for BMI and WC, separately. In the third model, further adjustment included SHBG or total testosterone (depending on the outcome variable), estradiol, hypertension, diabetes mellitus, alcohol consumption, smoking, use of non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, cholesterol medications and physical activity. When testosterone was the dependent variable, SHBG was included as a covariate and vice versa. In the final, fully adjusted model, the exposure variables, hsCRP and IL-6 were both included in the same model.

Tests for interaction were conducted for stratified BMI categories, age and race/ethnicity with p-value set as <0.2. Data were processed using SPSS Statistics, version 28.

Ethical Considerations

The MESA study protocol was approved by the institutional review boards (IRB) at the above-mentioned field centers. Written informed consent was given by all participants.[16]

RESULTS

Baseline characteristics of the study population are presented in Table 1. The mean age of the study population was 62.1 ± 10.2 with mean levels of testosterone and SHBG being 14.91 ± 5.52 and 44.34 ± 19.17, respectively. There were small, non-significant differences by age, anthropometrics, endogenous sex hormones and levels of inflammatory markers in the subsamples. Self-reported diabetes was highest in Hispanic Americans (17.6 %) followed by African Americans (17.0 %), Chinese Americans (11%) and non-Hispanic Whites (6.4 %).

Association for IL-6 with Endogenous Sex-Hormones in Men

There was a non-significant trend for the inverse association between IL-6 and *total testosterone* seen in both unadjusted model (Model 1) and after adjusting for age, race/ethnicity and the WHR (Model 2) (Table 2). When additionally adjusting for SHBG, estradiol and lifestyle factors (Model 3), as well as for hsCRP (Model 4), the association was statistically significant (B = −0.24, 95 % CI −0.38, −0.10, p = < 0.001, Model 4; B = −0.27, 95 % CI −0.41, −0.12, p < 0.001). When the outcome was *bioavailable testosterone*, significant inverse associations were found in all four models for IL6 (Table 2). There was a significant association between IL-6 and *SHBG* in Model 1. However, the association was non-significant after additional adjustment (Table 2). No associations were found between IL-6 and *free testosterone* (data not shown) Similar results were found when BMI and WC, separately, replaced WHR (data now shown).

The test for interaction was significant by age category for IL-6 with *bioavailable testosterone* (p = 0.12). More specifically, the association was significant in the fully adjusted model for age group 45–54 (B = −0.14, 95 % CI −0,26, −0.02, p = 0.024) but not for the groups 55–64 (p = 0.24), 65–74 (p = 0.08) and 75–84 (p = 0.67). Test for interaction was not significant for race/ethnicity and IL-6 with *bioavailable testosterone* (p = 0.79). However, a test for interaction was done for race/ethnicity in the different age groups, presenting significance for men aged 45–54 (p = 0.006), but not for men aged 55–64 (p = 0.27), 65–74 (p = 0.36), and 75–84 (p = 0.64). In the age category 45–54 years, a significant association was found in fully adjusted models in Hispanic Americans and African American men (Model 4; B = −0.20, 95 % CI −0.38, −0.01, p = 0.035, B = −0.30, 95 % CI −0.53, −0.01, p = 0.009, respectively) but not for non-Hispanic Whites and Chinese American men (p = 0.59 and p =0.57, respectively). No associations were found for IL-6 with other sex hormones (data not shown).

Association for hsCRP with Endogenous Sex-Hormones in Men

hsCRP was significantly and inversely associated with *total testosterone* in all the models (Table 3). Similar results were found with *bioavailable testosterone* (Table 3). However, hsCRP was significantly associated with *free testosterone* only in Model 2 (B = 0.02, 95 % CI 0.01, 0.03, p < 0.001). hsCRP was significantly and inversely associated with *SHBG* in all models (Table 3). Interestingly, and when adjusting for BMI in Model 3, no association was found for hsCRP with total testosterone (B = −0.07, 95 % CI −0.17, 0.02, p = 0.13).

The test for interaction between hsCRP and total testosterone by BMI groups was significant (p = 0.04). Specifically, the association was significant for BMI ≥ 30 kg/m2 in Model 3 (B = −0.15, 95 % CI −0.29, −0.02, p = 0.027) but not for BMI groups 18.5–24.9 kg/m2 or 25–29.9 kg/m2 (p=0.63, p= 0.55, respectively). Test for interaction showed no association for hsCRP with testosterone by racial/ethnic groups (p = 0.677).

Association for sTNFR with Endogenous Sex-Hormones in Men

The association between sTNFR and *SHBG* was only significant in the unadjusted model (B = 0.003, p = 0.006, 95 % CI 0.00, - 0.01). Similarly, we found no significant associations between sTNFR and *total*, *bioavailable*, and free *testosterone* (B = −7.585E-6, 95 % CI 0.00, - 0.00, p = 0.783, B = −7.209E-6, 95 % CI 0.00, 0.00, p = 0.582). There was no significant interaction for sTNFR with testosterone by race/ethnic group (p = 0.21) or for sTNFR with age categories (p= 0.30).

DISCUSSION

In this cross-sectional analysis of adult men from multiple race/ethnic groups, we found inverse independent associations between both IL-6 and hsCRP with *total* and *bioavailable* testosterone levels. To our knowledge, no earlier observational study has confirmed the hypothesis of a significant inverse relationship for IL-6 with testosterone in men, even after adjustment for hsCRP and estrogen. We also found a positive significant association of IL-6 with levels of *SHBG*.

Our results confirm existing studies finding an inverse significant association for hsCRP with SHBG levels. For example, Kupelian and Colleagues presented a significant inverse association for testosterone (total and free) and SHBG with hsCRP (n=1559) in men with urologic symptoms, including hypogonadism.[12] Similar results have been found in men with metabolic syndrome and T2DM.[13] Our results show a stronger association for hsCRP with SHBG when adjusted by IL-6, which suggests a negative confounding.

Our report showed a significant inverse association between hsCRP and testosterone, independent of IL-6 and estrogen levels. In an earlier study, we found a longitudinal inverse effect for hsCRP with bioavailable testosterone levels in men with increased risk of developing biochemical hypogonadism.[25] It has been hypothesized that hsCRP itself may contribute to decreased production of LH by suppressing the HPG axis in men with T2DM.[26] However, no adjustments were made for other inflammatory markers.

Thirdly, our study provides support of earlier hypotheses on an inverse association between IL-6 and levels of testosterone in a large healthy community-based study in men. In this regard, animal studies showed an inverse effect of IL-6 with decreased production of testosterone, negatively affecting both central and peripheral parts of the HPG-axis but, the results are discrepant.[7, 27] Findings have also showed an inverse relationship for TNF-a and IL-1B with levels of testosterone in men.[28] Moreover, findings from our study imply that the association for IL-6, when fully adjusted, show a stronger inverse association with levels of total testosterone, i.e., there is negative confounding. Earlier studies have described

pro-inflammatory properties of hsCRP which indirectly cause an increase in levels of IL-6 and IL-1B.[29]

Although non-significant, an inverse relationship was found for both IL-6 and CRP with free testosterone which has been presented in other studies.[12] However, results have not always been consistent. In a study by Van Pottelbergh and Colleagues, no associations were found for CRP with free testosterone.[30] Similarly, sTNFR was non-significantly associated with testosterone. Similar to our results, no correlation was found for sTNFR with low levels of testosterone in a study on men with COPD.[31]

We found a positive association between IL-6 and SHBG in men. To date, no study has found similar associations and is in contrary to other studies on inflammatory markers (TNF-a, IL-1), reporting a decrease in production of SHBG.[32] However, the association between inflammatory markers and SHBG is complex and still not fully understood. These differing results may warrant further discussion, as studies on SHBG have shown an association with higher risk of osteoarthritis and rheumatoid arthritis.[33] Furthermore, a positive association has been presented between IL-6 and rheumatoid arthritis.[34] This could indicate pleiotropic characteristics of SHBG dependent on its association with different inflammatory markers which encourages further studies investigating the association between IL-6 and SHBG.[33] In older men with hypogonadism, levels of total testosterone could be in normal range due to increased SHBG however, at the cost of low levels of free testosterone.[35]

An independent negative association for IL-6 with bioavailable testosterone in Hispanic Americans and African American men in the age group 44–54 years was found in the current report. A possible explanation could be that in our study prevalence of self-reported diabetes was highest in Hispanic Americans followed by African American men. Previous studies have shown that diabetes mellitus negatively influences levels of testosterone.[36] Certain ethnicities/races have been presented to be more prone to develop T2DM.[37] Further studies are required to confirm this relationship.

STRENGTHS AND LIMITATIONS

The detailed sampling of information using validated instruments permitted adjustment for important variables. Another strength was the standardized sampling of blood specimens in the morning after fasting accordingly to the international guidelines, avoiding diurnal changes in the levels of sex hormones.[38]

Radioimmunoassay technique (RIAs) has earlier been described as a less reliable method of measuring testosterone concentrations compared to mass spectrometry, especially at lower levels.[39] Furthermore, the interassay CV for total testosterone was 12 % (with a minimal detectable limit of 0.04 ng/mL). Earlier studies have shown that the median value of quality control sample among laboratories using the same method or instrument presented a coefficient of variation ranged between 5.1–22.7 % and could potentially result in difficulties in distinguishing eugonadal from mildy hypogonadal men.[40] Another limitation is the use of anthropometric measurements for body composition instead of radiological

techniques which have a more precise estimation of visceral adiposity. However, earlier studies have found a strong correlation between visceral fat measured by WHR.[5] Due to the observational nature of the study and cross-sectional design, residual confounding and temporal and selection biases cannot be excluded as well as cause-effect relationship.

CONCLUSION

This study presents new information on the association between pro-inflammatory cytokines and testosterone and SHBG in a large community-based study on men, independent of confounders and other measures of inflammation. Whilst the results indicate an inverse relationship between inflammatory markers (IL-6 and CRP) and testosterone, our results imply a stronger association between inflammation and bioavailable testosterone in African American and Hispanic American middle-aged men. Furthermore, our results present distinct associations for inflammation with levels of SHBG, independent of one another. This could indicate that inflammatory markers and SHBG interact differently with each other. Further studies are needed with adjustment for additional adipocytokines, as well as longitudinal studies to improve inferences for causality.

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Table 1.

Characteristics of men in MESA at baseline examination (2000–2002).

	IL-6 (N=3041)	hsCRP (N=2919)	sTNFR (N=1313)
	Mean ± SD/N (%)	**Mean ± SD/N (%)**	**Mean ± SD/N (%)**
Age (years)	62.0 ± 10.2	61.9 ± 10.2	61.5 ± 10.3
SBP (mmHg)	125.7 ± 19.5	125.5 ± 19.5	125.4 ± 19.0
DBP (mmHg)	74.8 ± 9.6	74.8 ± 9.5	74.8 ± 9.3
BMI (kg/m2)	28.0 ± 4.4	27.9 ± 4.3	27.6 ± 4.6
Waist Circumference	99.7±12.0	99.4 ± 11.8	98.4 ± 12.5
Waist-Hip-Ratio	0.96 ± 0.07	0.96 ± 0.07	0.96 ± 0.06
IL-6 (pg/mL)	1.5 ± 1.2	1.4 ± 1.1	1.5 ± 1.2
hsCRP (mg/L)	2.7 ± 4.4	2.0 ± 1.8	2.7 ± 4.3
TT (nmol/L)	14.9 ± 5.5	15.0 ± 5.5	15.0 ± 5.5
Bio T (nmol/L)	5.5 ± 2.2	5.5 ± 2.2	5.6 ± 1.9
Free Testosterone (%)	2.0± 0.5	2.0 ± 0.5	2.0 ± 0.5
SHBG (nmol/L)	44.2 ± 19.3	44.3 ± 19.3	43.3 ± 19.3
Estradiol (nmol/L)	0.12 ± 0.05	0.12 ± 0.05	0.12 ± 0.05
Race/Ethnicity			
White	1147 (41.7%)	1112 (42.1%)	317 (27.9%)
Chinese	252 (9.2%)	248 (9.4%)	229 (20.0%)
Black	710 (25.8%)	671 (25.4%)	285 (25.0%)
Hispanic/Latino	640 (23.3%)	611 (23.1%)	308 (27.5%)
Level of physical activity			
Poor	567 (20.6%)	550 (20.8%)	244 (21.4%)
Intermediate	414 (15.1%)	398 (15.1%)	171 (15.0%)
Ideal	1768 (64.3%)	1694 (63.1%)	724 (63.6%)
Smokers	396 (14.3%)	381 (14.4%)	187 (16.4%)
Current drinkers	1908 (69.4%)	1847 (69.9%)	771 (67.6%)
Diabetes Mellitus	325 (11.8%)	312 (11.8%)	142 (12.5%)
Hypertension	1170 (42.7%)	1114 (42.3%)	456 (40%)
B. Hypogonadism	175 (6.4%)	162 (6.1%)	60 (5.2%)
OS	25 (0.94%)	24 (0.95 %)	7 (0.61%)
Use NSAIDs	373 (13.6%)	362 (10.0%)	141 (12.4%)
Cholesterol medication	440 (16.0%)	432 (16.3%)	167 (14.6%)

SBP (systolic blood pressure), DBP (diastolic blood pressure), BMI (body mass index), hsCRP (high sensitivity c-reactive protein), SHBG (sex-hormone binding globulin), NSAIDS (non-steroidal anti-inflammatory drugs), Bioavailable Testosterone (Bio T), Total Testosterone (TT), Biochemical Hypogonadism (Hypogonadism), Oral Steroids (OS)

Table 2.

Association between Interleukin-6, Testosterone and Sex-Hormone Binding Globulin in Men.

	TOTAL TESTOSTERONE			BIOAVAILABLE TESTOSTERONE			SHBG		
	β	95% CI	*P*	β	95% CI	*P*	β	95% CI	*P*
MODEL 1	−0.42	−0.52, −0.32	<0.001	−0.07	−0.11, −0.03	<0.001	−1.21	−1.57, −0.84	<0.001
MODEL 2	−0.31	−0.41, −0.20	<0.001	−0.04	−0.08, −0.00	0.029	−0.97	−1.32, −0.62	<0.001
MODEL 3	−0.17	−0.25, −0.08	<0.001	−0.07	−0.11, −0.03	<0.001	−0.40	−0.69, −0.11	0.007
MODEL 4	−0.14	−0.23, −0.04	0.004	−0.06	−0.10, −0.02	0.005	−0.66	−0.97, −0.34	<0.001

Linear regression analyses were computed. Model 1 presents the unadjusted association for IL-6 with testosterone and SHBG. In Model 2 adjustment is made for age, WHR and race/ethnicity, Model 3 includes Model 2 and further adjustments for smoking, DM, HTN, alcohol usage, physical activity, SHBG/TT, estradiol, cholesterol medicine use, oral steroid use and NSAID use, and Model 4 include Model 3 and further adjustment for hsCRP. Waist-to-hip ratio (WHR), Diabetes Mellitus (DM), Hypertension (HTN), Sex hormone binding globulin (SHBG), Total Testosterone (TT), Non-steroidal anti-inflammatory drugs (NSAIDs), β (unstandardized coefficient of the association), 95 % CI (95 % Confidence Interval), p (significance).

Table 3.

Association between High Sensitivity C-Reactive Protein, Testosterone and Sex-Hormone Binding Globulin in Men.

	TOTAL TESTOSTERONE			BIOAVAILABLE TESTOSTERONE			SHBG		
	β	**95% CI**	***P***	**β**	**95% CI**	***P***	**β**	**95% CI**	***P***
MODEL 1	−0.35	−0.52, −0.19	<0.001	−0.20	−0.26, −0.14	<0.001	0.60	0.04, 1.16	0.037
MODEL 2	−0.15	−0.31, −0.02	0.082	−0.08	−0.14, −0.02	0.008	0.26	−0.28, 0.80	0.346
MODEL 3	−0.24	−0.38, −0.10	<0.001	−0.09	−0.17, −0.04	0.002	0.71	0.24, 1.19	0.003
MODEL 4	−0.27	−0.41, −0, 12	<0.001	−0.10	−0.17, −0.04	0.001	0.95	0.45, 1.45	<0.001

Linear regression analyses were computed. Model 1 presents the unadjusted association for hsCRP with testosterone and SHBG. In Model 2 adjustment is made for age, WHR and race/ethnicity, Model 3 includes Model 2 and further adjustments for smoking, DM, HTN, alcohol usage, physical activity, SHBG/TT, estradiol, cholesterol medicine use, oral steroid use and NSAID use, and Model 4 include Model 3 and further adjustment for IL-6. Waist-to-hip ratio (WHR), Diabetes Mellitus (DM), Hypertension (HTN), Sex hormone binding globulin (SHBG), Total Testosterone (TT), Non-steroidal anti-inflammatory drugs (NSAIDs), β (unstandardized coefficient of the association), 95 % CI (95 % Confidence Interval), p (significance).