Hormones
https://doi.org/10.1007/s42000-023-00507-w

ORIGINAL ARTICLE

# The effect of testosterone level on metabolic syndrome: a cross-sectional study

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Received: 14 February 2023 / Accepted: 7 November 2023


## Abstract

**Background** Metabolic syndrome (MS) may reduce circulating testosterone and, at the same time, low testosterone levels may lead to MS. Thus, identifying problems regarding sex hormones and examining their effects on the pathogenesis of MS is important to prevent serious complications of the condition, such as diabetes or cardiovascular diseases.

**Aims** This study aimed to investigate the correlations between MS-related parameters and androgen levels.

**Methods** A total of 108 males [median age 48.5 years (min/max = 21/77 years)] were included in the study. Blood pressure and anthropometric measurements (body mass index, waist circumference, hip circumference, thigh circumference, neck circumference, and length of index and ring finger) were performed. Biochemical analysis was assessed. Additionally, total testosterone, free testosterone, and sex hormone binding globulin levels were investigated.

**Results** Weak negative correlations were observed between testosterone levels and several anthropometric measures/glucose metabolisms ($p < 0.05$). The highest correlation was between total testosterone levels and body mass index (rho= −0.390, $p < 0.001$)

**Conclusion** According to our results, controlling weight, one of the preventable risk factors, can have a positive effect on testosterone levels and, therefore, on the cardiovascular system through different mechanisms.

**Keywords** Metabolic syndrome · Testosterone · Sex hormones

## Introduction

Metabolic syndrome (MS) represents a cluster of metabolic abnormalities, such as increased blood pressure, high blood sugar levels, excess body fat particularly around the waist, and high cholesterol/triglyceride levels. The prevalence of MS is rising due to decreased physical activity levels and increased obesity rates. MS increases the risk of coronary arterial disease, stroke, type 2 diabetes, and mortality [1]. Possible new treatment approaches have been sought based on previously determined MS markers, androgens being today one of the investigated parameters.

Testosterone plays a number of key roles in the building of bone and muscle mass, erythropoiesis, and homeostasis of glucose and lipid metabolism [2, 3]. While higher levels of testosterone were previously thought to be a risk factor for MS due to higher incidence of cardiovascular diseases in males, lower levels of testosterone were also found to be related to MS and higher cardiovascular risk [4]. Moreover, lower testosterone levels were reported in patients with MS [4]. Furthermore, systematic screening of comorbidities

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Published online: 20 November 2023

including MS was recommended in patients with hypogonadism [5]. On the other hand, testosterone replacement therapy was not shown to be effective for glycemic control, thus demonstrating the glucometabolic safety of the method [6].

An extensive cross-sectional study from Korea on 6967 adult men revealed that testosterone levels were inversely correlated with hyperglycemia, triglyceride levels, decreased high-density lipoprotein cholesterol (HLD) levels, and blood pressure [7]. Moreover, testosterone levels were found to be related to waist circumference, dyslipidemia, and insulin resistance based on fasting plasma glucose levels in Japanese men [8]. A study from Finland reported that when men had lower testosterone levels, the risk of MS might increase up to 2.7 times [9].

Based on the literature, determining any possible problems related to testosterone prior to occurrence of MS and cardiovascular disease appears to be of importance. However, to the best of our knowledge, the relationships between testosterone and MS have not to date been investigated in detail in Turkish males. Therefore, the aim of the present study was to investigate the possible relationships between testosterone levels and MS in Turkish males with MS.

## Methods

This cross-sectional study was approved by the Ankara Training and Research Hospital Ethical Committee (number: 0345). Written informed consent was obtained from the participants prior to their participation.

## Patients

All male patients with MS who were followed by the Ministry of Health, Ankara Training and Research Hospital, Internal Medicine Clinic-I, were invited to enroll in the study between November 2009 and January 2010. As the clinic is an adult clinic only, adult patients (>18 years old) were included in the study. Patients were excluded if they had a general medical condition, cirrhosis, nephrotic syndrome, hypogonadism, hypopituitarism, adrenal tumor, orchiectomy, testosterone replacement therapy, hyperthyroidism, and/or alcoholism.

## Procedures

Patients were questioned regarding exercise habits. Blood pressure and anthropometric measurements (body mass index, waist circumference, hip circumference, thigh circumference, neck circumference, and length of index and ring finger) were performed. Biochemical analysis related to fasting glucose, fasting insulin, uric acid, high-sensitivity C-reactive protein (Hs-CRP), albumin, thyroid-stimulating hormone (TSH), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels was assessed. Additionally, total testosterone, free testosterone, and sex hormone binding globulin (SHBG) levels were investigated.

## Outcome measures

### Body mass index

Body weight and height measurements were performed with the subjects barefoot wearing light clothes. Height was recorded in centimeter and body weight recorded in kilogram (with one decimal). Body mass index (BMI) was calculated by using the formula: $kg/m^2$.

### Anthropometric measures

Waist circumference was measured in a position parallel to the ground, in the standing position, and at the end of the expiration, from the middle of the lowest rib and spina iliaca anterior superior. Hip circumference was measured at the widest point. Thigh circumference was measured in a position parallel to the ground and in the standing position at the widest point of the thigh (just below the hip). Neck circumference was measured in a position parallel to the ground just below the cricoid cartilage with the patient's arms resting at his side and his face towards the assessor.

Length of the index finger and ring finger were measured with the palm up and the fingers extended, from the tip to the base of the finger.

### Biochemical analysis

Biochemical analysis was performed in the central biochemistry laboratories of Ankara Training and Research Hospital. Blood samples were collected in the morning between 9 a.m. and 11 a.m. following 12-h fasting. Fasting plasma glucose, fasting insulin, uric acid, Hs-CRP, total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels were analyzed from the fasting blood. Glucose, total cholesterol, HDL cholesterol, and triglyceride levels were assessed with the Roche Modular DP analyzer with original Roche Diagnostics kits. LDL cholesterol was calculated by using the Friedewald formula (LDL = total cholesterol – triglyceride/5-HDL). Insulin levels were analyzed using DRG Diagnostics (DRG instruments GmbH, Germany) ELISA kits. To assess insulin sensitivity, the HOMA-IR (homeostatic model assessment of insulin resistance) method

was calculated using the following formula: (fasting serum insulin (μIU/ml) × fasting plasma glucose (mmol)/22.5). Blood samples were used in an Advia Centaur XP device, and total testosterone was assessed by using the chemiluminescent method. Free testosterone was measured by using radioactive immune assay (RIA) method, and SHBG was evaluated with the chemiluminescent method.

## MS diagnosis

The patients were assessed regarding metabolic analysis using the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) and International Diabetes Federation (IDF) criteria (Table 1). Any patient fulfilling either of these two criteria was included in the study.

## Statistical analysis

Data analysis was performed by using SPSS for Windows 11.5. Normal distribution of the data was examined with the Kolmogorov-Smirnov test. Data were expressed as mean ± standard deviations and minimum/maximum values or median and minimum/maximum values. Possible correlations were investigated with Spearman's rank correlation coefficient due to the heterogeneity of the data. $p < 0.05$ was accepted as statistically significant.

# Results

A total of 108 male patients were included in the study. The median age of the patients was 48.5 (min/max = 21/77) years. Concerning exercise habits, patients described themselves as sedentary ($n = 3$, 2.8%), minimally active ($n = 35$, 32.7%), and moderately active ($n = 69$, 64.5%). No patients reported that they had high-levels of exercise habits. Androgen levels, anthropometric measures, glucose metabolism levels, and blood lipid levels are presented in Table 2.

**Table 2** Androgen levels, anthropometric measures, glucose metabolism, and blood lipid levels

| ($n = 108$) | Mean ± standard deviation | Minimum/Maximum |
|---|---|---|
| Androgen levels | | |
| Total testosterone | 443.0 ± 212.3 | 18.3/1626.1 |
| Free testosterone | 11.76 ± 4.44 | 0.80/34.70 |
| Free/total testosterone ratio | 0.304 ± 0.143 | 0.103/1.195 |
| Sex hormone binding globulin | 24.87 ± 13.18 | 5.24/82.00 |
| Anthropometric measures | | |
| Body mass index (kg/m$^2$) | 26.7 ± 3.8 | 18.8/38.9 |
| Neck circumference (cm) | 38.4 ± 2.3 | 34.0/45.0 |
| Waist circumference (cm) | 96.5 ± 10.6 | 72.0/120.0 |
| Hip circumference (cm) | 94.7 ± 7.6 | 76.0/120.0 |
| Waist/hip ratio | 1.01 ± 0.06 | 0.87/1.2 |
| Thigh circumference (cm) | 52.4 ± 3.6 | 43.0/63.0 |
| Waist/thigh ratio | 8.2 ± 0.2 | 1.5/2.2 |
| Glucose metabolism | | |
| Fasting blood glucose | 96.8 ± 14.3 | 64.0/155.0 |
| Postprandial glucose | 120.3 ± 29.8 | 63.0/251.0 |
| Insulin | 13.3 ± 12.6 | 2.1/87.0 |
| Homeostatic model assessment of insulin resistance | 3.3 ± 3.3 | 0.5/21.9 |
| Blood lipid levels | | |
| Total cholesterol | 202.7 ± 46.4 | 110.0/369.0 |
| Light-density lipoprotein | 124.9 ± 38.9 | 45.0/292.0 |
| High-density lipoprotein | 43.0 ± 9.8 | 26.0/82.0 |
| Non-high-density lipoprotein | 159.7 ± 45.0 | 68.0/326.0 |
| Triglycerides | 186.9 ± 145.9 | 44.0/1050.0 |
| Other parameters | | |
| Uric acid | 5.1 ± 1.1 | 0.1/7.6 |
| High-sensitivity CRP | 6.1 ± 8.6 | 0.20/54.0 |

**Table 1** MS diagnosis criteria

| NCEP-ATP III criteria [10] | IDF criteria [11] |
|---|---|
| 1. Waist circumference >102 in males, >88 in females | 1. Triglyceride >150 mg/dl or being treated medically due to high triglyceride levels |
| 2. Triglyceride level ≥150 mg/dl | 2. HDL cholesterol <40 mg/dl in males, <50 mg/dl in females or being treated due to low HDL levels |
| 3. HDL cholesterol level <40 mg/dl in males, <50 mg/dl in females | 3. Systolic blood pressure >130 mm/Hg or diastolic blood pressure >85 mm/Hg or being treated due to high blood pressure |
| 4. Blood pressure ≥130/85 mmHg | 4. Fasting blood glucose >100 mg/dl or previously diagnosed with diabetes mellitus. |
| 5. Fasting glucose ≥100 mg/dl | Oral glucose tolerance test is recommended for patients with high fasting blood glucose, but it is not obligatory |
| **Diagnosis:** Fulfilling three of the five criteria | **Diagnosis:** Having a waist circumference of >94 cm in males, >80 cm in females + fulfilling two of the four criteria |

The highest significant correlations were between total testosterone levels and BMI (rho = −0.390, $p < 0.001$), free testosterone levels and postprandial glucose (rho = −0.381, $p < 0.001$), free/total testosterone ratio and insulin (rho = 0.309, $p = 0.001$); SHBG and BMI (rho = −0.360, $p < 0.001$), and SHBG and uric acid (rho = −0.360, $p < 0.001$). The correlations between androgens and other parameters are presented in Table 3.

## Discussion

The present study was conducted to investigate the relationships between androgens and MS markers. Negative relationships were detected between testosterone levels and some anthropometric measures and glucose metabolisms. However, all the relationships were at a poor level.

**Table 3** The relationships between androgens and other parameters

| Parameters | Total testosterone | Free testosterone | Free/total testosterone ratio | Sex hormone binding globulin |
|---|---|---|---|---|
| Age (year) | rho: −0.049<br>*p*: 0.455 | **rho: −0.168**<br>***p*: 0.011** | **rho: −0.118**<br>***p*: 0.011** | rho: 0.040<br>*p*: 0.543 |
| Anthropometric measures | | | | |
| Body mass index (kg/m$^2$) | **rho: −0.390**<br>***p* < 0.001** | **rho: −0.229**<br>***p*: 0.017** | rho: 0.085<br>*p*: 0.384 | **rho: −0.360**<br>***p* < 0.001** |
| Neck circumference (cm) | **rho: −0.274**<br>***p*: 0.004** | rho: −0.096<br>*p*: 0.323 | **rho: 0.211**<br>***p*: 0.028** | rho: −0.167<br>*p*: 0.084 |
| Waist circumference (cm) | **rho: −0.367**<br>***p* < 0.001** | rho: −0.147<br>*p*: 0.128 | rho: 0.120<br>*p*: 0.217 | **rho: −0.302**<br>***p*: 0.001** |
| Hip circumference (cm) | **rho: −0.263**<br>***p*: 0.006** | rho: −0.157<br>*p*: 0.104 | rho: 0.167<br>*p*: 0.084 | rho: −0.186<br>*p*: 0.054 |
| Waist/hip ratio | **rho: −0.286**<br>***p*: 0.003** | rho: −0.133<br>*p*: 0.172 | rho: 0.123<br>*p*: 0.203 | **rho: −0.259**<br>***p*: 0.007** |
| Thigh circumference (cm) | **rho: −0.366**<br>***p* < 0.001** | **rho: −0.209**<br>***p*: 0.030** | **rho: 0.275**<br>**p: 0.004** | **rho: -0.277**<br>**p: 0.004** |
| Waist/thigh ratio | rho: −0.180<br>*p*: 0.063 | rho: −0.100<br>*p*: 0.305 | rho: 0.013<br>*p*: 0.895 | rho: −0.106<br>*p*: 0.275 |
| Glucose metabolism | | | | |
| Fasting blood glucose | **rho: −0.204**<br>***p*: 0.034** | **rho: −0.334**<br>***p* < 0.001** | rho: −0.032<br>*p*: 0.746 | rho: −0.134<br>*p*: 0.167 |
| Postprandial glucose | rho: −0.135<br>*p*: 0.163 | **rho: −0.381**<br>***p* < 0.001** | rho: −0.138<br>*p*: 0.155 | rho: −0.133<br>*p*: 0.171 |
| Insulin | **rho: −0.346**<br>***p* < 0.001** | rho: −0.171<br>*p*: 0.078 | **rho: 0.309**<br>***p*: 0.001** | rho: −0.155<br>*p*: 0.109 |
| Homeostatic model assessment of insulin resistance | **rho: −0.356**<br>***p* < 0.001** | **rho: −0.220**<br>***p*: 0.022** | **rho: 0.278**<br>***p*: 0.004** | rho: −0.166<br>*p*: 0.086 |
| Blood lipid levels | | | | |
| Total cholesterol | rho: 0.023<br>*p*: 0.812 | rho: 0.103<br>*p*: 0.293 | rho: 0.085<br>*p*: 0.510 | rho: −0.126<br>*p*: 0.197 |
| Light-density lipoprotein | rho: 0.068<br>*p*: 0.490 | rho: 0.107<br>*p*: 0.276 | rho: 0.023<br>*p*: 0.818 | rho: −0.129<br>*p*: 0.187 |
| High-density lipoprotein | rho: 0.076<br>*p*: 0.441 | rho: 0.113<br>*p*: 0.248 | rho: 0.006<br>*p*: 0.948 | rho: 0.090<br>*p*: 0.357 |
| Non-high-density lipoprotein | rho: −0.053<br>*p*: 0.593 | rho: 0.130<br>*p*: 0.184 | rho: 0.041<br>*p*: 0.678 | **rho: −0.219**<br>***p*: 0.024** |
| Triglycerides | rho: −0.187<br>*p*: 0.055 | rho: −0.133<br>*p*: 0.175 | rho: 0.112<br>*p*: 0.254 | rho: −0.143<br>*p*: 0.145 |
| Other parameters | | | | |
| Uric acid | **rho: −0.248**<br>***p*: 0.010** | rho: 0.019<br>*p*: 0.846 | **rho: 0.290**<br>***p*: 0.002** | **rho: −0.360**<br>***p* < 0.001** |
| High-sensitivity CRP | rho: −0.114<br>*p*: 0.238 | rho: −0.133<br>*p*: 0.170 | rho: 0.024<br>*p*: 0.806 | rho: −0.141<br>*p*: 0.146 |

rho: Spearman's rank correlation coefficient, $p < 0.05$

In general, a negative relationship is reported between androgens and obesity in the literature; however, it is not clear whether this relationship may be associated with central adiposity or with general adiposity. Some studies have reported that total testosterone level is more closely related to waist circumference than to BMI [12–15]. However, we determined that there was a slightly closer relationship between total testosterone and BMI, than between total testosterone and waist circumference (−0.390 vs. −0.366). Similar to our results, Kaplan et al. determined that testosterone levels decrease due to increased BMI in males both with and without MS [16]. In another study, using quantitative computerized tomography, an increase in subcutaneous fat was observed in hypogonadal men. The same study proposed that androgens may be responsible for inhibition of adipogenesis, and for increasing lipolysis [17].

In some studies, low levels of SHBG were found to be related to obesity and hyperinsulinemia in obese men [17, 18], while in others, higher insulin levels in obesity were observed to be related to depression of hepatic SHBG synthesis [19, 20]. In the present study, both central obesity markers (waist circumference, waist/hip ratio, and neck circumference) and peripheral obesity markers (BMI, hip circumference, and thigh circumference) showed negative relationships with total testosterone and SHBG.

Insulin resistance was shown to be related to low levels of testosterone and SHBG [21–25]. Testosterone has a role in the pathogenesis of insulin resistance by inhibiting lipoprotein lipase activity [26]. Decreased testosterone and SHBG levels were reported to be related to diabetes risk [15, 27]. Similar relationships were detected between HOMA-IR and androgens in the present study. These negative relationships may be explained by reduced testosterone secretion due to hyperinsulinemia [26], higher levels of interleukin-1B (IL-1B), IL-6, tumor necrosis alpha (TNF-α) [28–30], oxidative processes [31], and the effects of androgens on glucose transport [32, 33].

Lower levels of testosterone were found to be associated with an atherogenic lipid profile, including increased LDL and triglyceride levels [34]. However, in the present study, we noted only a weak correlation between non-HDL cholesterol and SHBG.

Higher triglyceride levels were observed to be related to lower level of testosterone [13, 24, 35]. On the other hand, testosterone replacement did not lead to a desirable effect on lipid profile. Total cholesterol, triglycerides, and LDL levels were altered minimally following testosterone replacement, while significant changes were detected in LDL particle size [36, 37]. No significant correlations were detected between blood lipids and androgens in the present study.

Higher uric acid levels were reported to be a risk factor for cardiovascular diseases in epidemiologic studies [38, 39]. On the other hand, uric acid is not an individual risk factor for atherosclerosis, but a marker of MS when it is clustered with other factors such as insulin resistance [40, 41]. Negative correlations have previously been detected between uric acid and testosterone [42, 43]. Similarly, we noted similar correlations between uric acid and total testosterone and SHBG.

Hs-CRP is a marker of low-level inflammation and an independent predictor of myocardial infarct, stroke, and peripheral arterial disease in individuals without cardiovascular disease [44, 45]. While some authors have reported a number of negative correlations between Hs-CRP and androgens [46, 47], others report no correlations between these two parameters [48, 49]. In the current study, we observed no correlations between Hs-CRP and androgens.

Both NCEP-ATP III and IDF criteria were used to define MS in the present study. As both criteria are widely accepted, this approach was chosen to increase the generalizability of the results.

Our study has some limitations. We did not evaluate steatosis, which is frequently associated with MS. We also did not investigate erectile dysfunction or any other types of sexual problems. Finally, since no systematic approach was used to capture the physical activity levels of the participants, the subjects were questioned subjectively.

## Conclusion

While the roles of testosterone in the male productive system and sexual functions are well-known, its effects on glucose metabolism, lipid metabolism, and cardiometabolic functions only today are being gradually understood. Some low-level negative relationships were detected between androgens and MS markers in the present study, most probably due to a cause-and-effect relation between these parameters. However, regardless of whether their actions are due to cause or to effect, androgens seem to have other roles than merely sexual functions. Moreover, preventable risk factors such as weight gain and obesity may help to optimize testosterone levels and cardiovascular health.

## Declarations

**Ethics approval** The study was approved by the Ankara Training and Research Hospital Ethical Committee (number: 0345). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Conflict of interest** The authors declare no competing interests.

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