

Original Research

Serum Testosterone and Metabolic Syndrome in Old-Aged Males: Preliminary Findings of the AHAP Cohort Study

Aylar Khalilipour¹, Nazila Malekian¹, Haleh Esmaili², Seyed Reza Hosseini², Mohammadali Bayani³, Ali Bijani², Fatemeh Izadpanah¹, Reza Ghadimi^{2*}

¹ Student Research Committee, Babol University of Medical Sciences, Babol, Iran

² Social Determinants of Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

³ Department of Internal Medicine, Babol University of Medical Sciences, Babol, Iran

*Correspondence to: Reza Ghadimi, Social Medicine, Babol University of Medical Sciences, 47176-47745, Ganjafrooz Street, Babol, Mazandaran, Iran. E-mail: rezaghadimi@yahoo.com. Phone: +98 11 321190557; Fax: +98 11 32190557

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Abstract

Introduction: Metabolic syndrome (MetS) is one of the critical health concerns. The relationship between low total testosterone and MetS was reported in some studies. However, the association independent of other related components is not fully known. This study was performed to evaluate the prevalence rates of MetS among older men with and without hypogonadism and the related association. **Material and Methods:** This cross-sectional study was conducted on 800 male subjects aged 60 years and older. Anthropometric indices, blood pressure, total serum testosterone, and serum lipid profile were determined. The Iranian National Committee of Obesity criteria were used to define metabolic syndrome. **Results:** The mean total testosterone in the MetS group was significantly lower compared to the non-MetS group. Total testosterone showed significant inverse associations with triglycerides and waist circumference. The crude odds ratio for MetS between the low and high total testosterone groups was 1.43, which remained statistically significant after adjustments, while total testosterone levels showed no significant association with MetS after adjusting by BMI. **Conclusion:** Testosterone is negatively and independently associated with MetS regarding age, smoking status and alcohol intake in Iranian men. Therefore, the early diagnosis and treatment of hypogonadism should be considered in MetS prevention.

Keywords: Metabolic syndrome, testosterone, aged.

Introduction

Metabolic syndrome (MetS), as a cluster of medical conditions, is one of the most important health concerns and includes obesity, high blood pressure, high fasting plasma glucose and serum triglyceride, and low high-density lipoprotein (HDL) levels [1]. In the last decade, the prevalence of MetS is increasing in the world, varying between races and populations [2]. The prevalence of MetS in the United States of America, Asian Pacific, and East and Southeast Asia is increased, reaching a value of around 25% [3, 4]. Iran, as an Asian country, is not an exception. The

results of two meta-analysis studies have shown a higher prevalence of MetS in males (about 26%) [5, 6]. Although only a partial mechanism of the MetS pathway is known, it is clear that food habits, sedentary lifestyle, stress, and other environmental factors have crucial roles [7].

Furthermore, the inverse relationship between total testosterone (TT) and sex hormone-binding globulin (SHBG) levels with MetS has been illustrated [8]. Therefore, low sex hormone levels (total testosterone and SHBG) may be a risk factor for MetS, just like increased insulin resistance and adipose tissue [9, 10]. Hence, a low testosterone level is one of the possible



risk factors for MetS. It is not clear whether the relationship of low TT to MetS is independent of BMI and waist circumference or not [11, 12]. Besides, the relationship between testosterone components and MetS is known clearly. Although the free testosterone level has an inconsistent relationship with some MetS components, SHBG has demonstrated a constant inverse relationship [13]. Therefore, in this study, we measured serum total testosterone (TT) and evaluated several metabolic factors, such as waist circumference, diabetes, dyslipidemia, hypertension, and hyperglycemia, among healthy older men to clarify this association. This large-scale cross-sectional study aims to determine and compare the prevalence of MetS among men with and without hypogonadism in Amirkola, Mazandaran province, North of Iran.

Material and Methods

Study design and patients

This cross-sectional study was a part of the Amirkola Health and Aging Project (AHAP) [14] and was approved by the Medical Research Ethics Committee of Babol University of Medical Sciences. This study was conducted on 800 healthy males aged 60 years old and older. Subjects were excluded if they had malignancies or acute illnesses such as liver cirrhosis, diabetes mellitus type I and II, infection, and inflammation. Also, men who were under testosterone replacement therapy or taking anti-androgen and steroidal agents were excluded. All participants signed an informed consent form.

Laboratory, anthropometric and clinical data collection

Weight (to the nearest 0.1 kg) and height (to the nearest 0.1 cm) were measured following standard procedures; waist and hip circumference was also measured to the nearest 0.5 cm in all participants with a non-elastic tape. Body mass index (BMI) was calculated by dividing the weight (kilograms) by the square of height

(meters). Blood pressure was measured using standardized sphygmomanometers by a trained nurse after a 10-15 min rest in a sitting position. Venous blood was collected in the morning in a fasting state to detect total testosterone, fasting blood sugar (FBS), total cholesterol (T-Chol), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG). Total testosterone levels were measured using a DiaMetra kit made in Germany by the ELISA method (ng/ml). The subjects with a history of androgenic drug intake during the last month were excluded from the study.

BMI 18-25 kg/m² were defined as normal, 25-30 kg/m² and ≥ 30 kg/m² were defined as overweight and obese, respectively. To define MetS, we used the Iranian National Committee of Obesity (INCO) criteria [15]. According to INCO, metabolic syndrome involves having at least three of the following symptoms: waist circumference >95 cm, triglyceride level >150 mg/dl (1.7 mmol/L), HDL-C <40 mg/dl (1.03 mmol/L), blood pressure $>130/85$ mmHg and fasting plasma glucose >100 mg/dl (5.6mmol/L); or patients were under medical treatment [15]. According to the Clinical Practice Guidelines of the Endocrine Society for androgen deficiency syndromes in adult men, hypogonadism was defined as total testosterone < 3.0 ng/mL [16, 17]. Therefore, according to total testosterone, subjects were divided into two groups. Group (1): TT ≥ 3 as a reference group and group (2): TT < 3 as the hypogonadal group.

Statistical analysis

The values were expressed as mean \pm standard deviation as a percentage for descriptive statistics. Mean differences of total testosterone between the MetS group and reference group were assessed using the independent sample t-test. Different MetS prevalence, according to each group, was calculated using the chi-square test. The relationship between total testosterone and MetS were assessed with logistic regression analysis after adjusting for age and BMI. Statistical significance was set at $p < 0.05$. Statistical analyses were performed with SPSS version 18.0.

Results

The mean age of the subjects was 69.7 ± 7.5 years, and the prevalence of MetS, according to the INCO criteria, was 64.9%. The average serum total testosterone was 4.78 ± 4.1 ng/ml. According to the BMI, 44.3% of subjects were overweight and 15.2% were obese. About 34.3% were current smokers, and 4.4% were alcoholics.

Table 1 shows the general characteristics of the study subjects. The mean total testosterone of the MetS group was significantly lower than that of the non-MetS group (4.5 ± 4.1 ng/ml vs. 5.1 ± 4.08 ng/ml; $p=0.042$). The mean values of MetS components in hypogonadal men and

reference groups are presented in Table 1. The average waist circumference ($p=0.03$), hip circumference ($p=0.016$), and BMI ($p=0.005$) were significantly different among the two groups. However, there was no significant difference in age, LDL-C, HDL-C, TG, total cholesterol, FBS, and systolic/diastolic blood pressure (BP).

The risk of metabolic syndrome was statistically significant in the crude model but also after adjustment for age, smoking status, and alcohol intake (model 1). However, TT showed no significant association with MetS after adjustment for BMI (model 2) (Table 2). Also, the odds ratio of the hypogonadal group for MetS components were assessed (Table 3). Total testosterone

Table 1: General characteristics of the subjects and mean values of MetS components in hypogonadal and reference groups.

Characteristics	Mean(SD)			p-value
	Total	TT<3ng/ml (n:263)	TT≥3 ng/ml (n:527)	
Age (year)	69.74 (7.59)	70.23 (8.26)	69.49 (7.23)	0.198
BMI (kg/m ²)	26.06 (4.00)	26.63 (4.13)	25.78 (3.91)	0.005*
Waist circumference (cm)	95.06 (10.38)	96.19 (10.91)	94.50 (10.07)	0.031*
Hip circumference (cm)	99.86 (7.71)	100.8 (8.17)	99.39 (7.44)	0.016*
Systolic blood pressure (mmHg)	142.73(21.95)	142.21 (20.95)	142.99 (22.44)	0.636
Diastolic blood pressure (mmHg)	81.14 (12.05)	81.29 (11.91)	81.07 (12.14)	0.812
Fasting blood sugar (mg/dl)	112.97 (40.09)	112.61 (38.12)	113.14 (41.07)	0.861
Total-cholesterol (mg/dl)	188.07 (38.46)	188.76 (44.44)	187.72 (35.17)	0.723
TG (mg/dl)	148.83 (79.14)	153.38 (82.93)	146.56 (77.16)	0.254
HDL-C (mg/dl)	38.41 (4.06)	38.35 (4.34)	38.43 (3.92)	0.792
LDL-C (mg/dl)	122.63 (39.90)	123.02 (44.39)	122.43 (37.51)	0.846
Total testosterone (ng/ml)	4.77 (4.11)			

Note: BMI: Body Mass Index; FBS: Fasting Blood Sugar; BP, Blood Pressure; * p-value less than 0.05 was considered significant.

Table 2: Odds ratio of metabolic syndrome according to the TT level.

Group	Crude OR (CI)	Model1 OR (CI)	Model2 OR (CI)
TT≥3 (ng/ml)	1	1	1
TT <3 (ng/ml)	1.43(1.047-1.977)*	1.51(1.089-2.092)*	1.245 (0.860-1.802)

Note: Model 1: adjusted for age, smoking status, alcohol intake;
Model 2: adjusted for all covariates in model 2 and BMI.

Table 3: Odds ratios of metabolic syndrome components according to the TT level.

Group	BP >130/85 (mmHg) OR (CI)	FBS >100 (mg/dl) OR (CI)	WC ≥94 (cm) OR (CI)	TG >150 (mg/dl) OR (CI)	HDL <40 (mg/dl) OR(CI)
TT ≥3 (ng/ml)	1	1	1	1	1
TT <3 (ng/ml)	0.975 (0.677–1.404)	1.067 (0.793–1.437)	1.481 (1.091–2.009)*	1.354 (1.006–1.824)*	1.078 (0.77–1.509)

Note: Model 1: adjusted for age, smoking status, alcohol intake;
Model 2: adjusted for all covariates in model 2 and BMI.

showed significant strong associations with TG (OR: 1.354, $p=0.04$) and WC >94 (OR: 1.481, $p=0.01$). Therefore, subjects with low TT levels had a risk of higher TG and WC values compared with the normal group.

Discussion

Different cutoff values for total testosterone were used to define hypogonadism. In our study, the cutoff level of 3.0 ng/ml for total testosterone was used to define hypogonadism as recommended by the Clinical Practice Guidelines of the Endocrine Society [18, 19]. This level of testosterone was considered enough to improve certain parameters of sexual function in men that suffer from hypogonadism [20]. In this regard, since hypogonadism is not a specific MetS symptom, it is challenging to diagnose and treat. Therefore, it is important to combine the MetS symptoms of androgen deficiency with low testosterone levels to establish the diagnosis of clinical hypogonadism [20]. In the present cross-sectional study, we showed a clear significant association of total testosterone levels with MetS independent of age and BMI in generally healthy Iranian men. Meanwhile, total testosterone was associated with only two components of MetS, e.g., TG and waist circumference. Similarly, a study in Taiwan concluded that waist circumference and total testosterone levels are strongly associated [21] while other studies depicted that a low level of sex hormones have been associated with many risk factors for MetS such as central obesity, insulin resistance, diabetes, and unfavorable lipid profile, which are prominent in men with a normal BMI and the negative relationship of lower

levels of sex hormone and MetS is consistent with other studies [11, 22–25]. Additionally, in the present study, the mean value of BMI in the hypogonadal group was significantly greater than the reference group. TT level was lower in men with MetS compared with men without MetS and both type 2 diabetes and MetS independently predicted low testosterone level for age and BMI. The testosterone level decreased significantly along with an increase in the number of MetS components, showing a significant correlation even after adjustment for age, BMI, and waist circumference [26, 27]. This association between BMI and low testosterone was reported in several studies [23, 28, 29], and low serum testosterone levels could also be considered as one of the many adverse consequences of obesity [30, 31].

On the other hand, through the conversion of testosterone to estradiol by the aromatase enzyme in obese subjects, obesity is considered as a factor that is associated with subnormal testosterone levels. However, we did not measure estradiol and were unable to assess the possible role of aromatization on these outcomes. However, a study that included Japanese men showed that a decrease in androgen production and low or inappropriately normal levels of luteinizing hormone in obese middle-aged men moderately led to a decrease in testosterone production [32]. Low sex hormones and MetS produce a vicious circle with synergistic characteristics through bidirectional effects in which low sex hormone levels lead to the development of MetS, which, in turn, is associated with a further decline in sex hormone levels [33, 34]. Therefore, it seems that total testosterone and SHBG have a protective role against MetS as high testosterone and SHBG were associated with a decrease in

the MetS risk, independent of body composition [34]. Another study on middle-aged Japanese men also reported that serum testosterone level was significantly related to the MetS associated conditions, included obesity and hypertension. Compared to the highest tertile, subjects in the lowest tertile of testosterone were approximately four times more likely to have diabetes [28]. A linear increase in serum TG levels was found in men with low TT and SHBG, which was inversely and independently associated with TG, and positively and independently associated with HDL [35]. Moreover, men with HDL < 0.90 and TG > 1.8 had significantly lower levels of TT and SHBG [35]. In our study, hypogonadism was associated significantly with hypertriglyceridemia, but the mean values of TG showed no significant difference between the two groups. We suggest that an association between low serum TT level and hyperglycemia can cause metabolic changes, rather than the direct effect. To the best of our knowledge, many studies on testosterone and MetS have been performed in Western countries, whereas relatively few studies for Asians have been reported despite the different definitions of MetS. Our study analyzed a large sample from the Iranian population, which can support data on the effects of sex hormones on MetS in Iranian men. However, the present study contains some limitations. First, it was a cross-sectional study, which explains associations but not causality. Second, as our data were from the general Iranian population, it is not enough to expand to other ethnic/racial groups. Third, we used radioimmunoassay instead of mass spectrometry for total testosterone determination. Data derived using immunoassay is technically simple, rapid, and relatively inexpensive at the cost of poor accuracy and sensitivity. However, immunoassay of total testosterone is a widely accepted method used in large studies since the measurement of total testosterone by mass spectrometry is impractical. Fourth, free testosterone and sex hormone-binding globulin analyses and levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were not determined; thus, we were not able to classify the type of hypogonadism, whether it is primary or secondary.

Conclusions

In conclusion, testosterone is negatively associated with MetS independently and after adjustment for age, smoking status, and alcohol intake among Iranian men. Among MetS components, TG and WC were strongly associated with testosterone levels among elderly males regardless of obesity. Further studies, including clinical trials, are needed to confirm our findings.

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Conflict of Interest

The authors declare no conflict of interest.

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