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Original article

Association of sex hormones with metabolic syndrome among Egyptian males

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ABSTRACT

Background: Studies have shown that testosterone and estradiol (E2) are associated with metabolic syndrome (MetS). To our knowledge, few studies, if any about the association of endogenous sex hormones with MetS have been done in Egypt.
Aim: To study the relation between endogenous sex hormones and MetS among Egyptian males.
Subjects and method: For the study, 80 Egyptian males were enrolled: 40 males with MetS and 40 healthy age-matched males. Anthropometric measurements and blood pressure were taken for both groups. FBG, TC, HDL-C, TG, testosterone, and E2 levels were determined; LDL-C was calculated.
Results: Males with MetS had significantly lower testosterone levels and significantly higher E2 levels compared to those without MetS (p value 0.0001). The lowest quartile of testosterone was most prevalent among males with MetS (19/40 males, 47.5%) compared to those without MetS (0/40 males, 0%, p value 0.011). Estradiol in the third quartile was most prevalent among males with MetS (19/40 males, 47.5%) compared to those without MetS (1/40 males, 2.5%, p value 0.0001). Serum testosterone and E2 levels were independent predictors of MetS with optimum cut off value ($\leq$2.37 ng/ml) for testosterone and ($>$16.78 pg/ml) for E2.
Conclusion: Endogenous testosterone and estradiol are independently associated with MetS with potential utility as predictors of MetS.

Introduction

The metabolic syndrome (MetS) can predispose to type 2 diabetes and cardiovascular disease, even it can predict the occurrence of sudden death. According to National Cholesterol Education Program's Adult Treatment Panel III report (ATP III), MetS is diagnosed if 3 of the following 5 components are present: abdominal obesity, raised triglycerides, reduced HDL, elevated blood pressure, and raised fasting plasma glucose. The presence of only 1 or 2 of these components increases the overall mortality [1–3]. MetS has a high, worldwide prevalence especially in the Middle East. This leads to a negative public health potential. The direct risk of MetS in men needs to be fully investigated. Epidemiological studies show that a low testosterone level is associated with an increased risk of MetS among men [4–6]. Moreover, studies showed that the severity of the features of MetS is negatively related to plasma testosterone [6,7]. Estradiol (E2) also has been reported to be associated with the pathogenesis of MetS as it can affect insulin sensitivity, glucose homeostasis, body weight, and adiposity [8,9]. Interestingly, Saltiki and his colleagues found that endogenous estrogen levels were independently related to endothelial function among males [10]. However, most of the studies showing the association of testosterone with MetS were conducted on Caucasians [1]. In addition, as previously mentioned, studies about the association between E2 and MetS in males are still limited [11]. To our knowledge, very few, if any, were done in Egypt. The aim of the current study was to study the relation between endogenous sex hormones and MetS among Egyptian males.

Subjects and methods

This study was conducted on 80 males recruited from the outpatient clinic of Ain Shams University Hospitals, which is a tertiary hospital in Cairo, Egypt. They were divided into 2 groups:

Group 1

In this group, 40 males with MetS (defined as satisfying at least 3 of the following criteria: waist circumference (WC) $>$ 102 cm, triglycerides $\geq$ 150 mg/dl, HDL $<$ 40 mg/dl, blood pressure $\geq$ 130/

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85 mmHg or the use of the medication for hypertension, and a fasting glucose ≥ 100 mg/dl) [12].

Group 2

This group had 40 apparently healthy males matched for the same age.

Inclusion criteria: Age 18–40 years; exclusion criteria: current illness such as diabetes mellitus (DM), hepatic or renal disease, current malignancy; cerebrovascular, or heart disease, use of hormones, antiandrogen treatment, antifungal drugs, steroidal agents, or any drug affecting sex hormones, smoker, or alcoholic.

The study was approved by the Institutional Research Ethics Committee of Ain Shams University which follows the Declaration of Helsinki Guidelines, and informed consent was obtained from each participant.

A detailed medical history was obtained from all subjects followed by a clinical examination performed by the experienced staff at Ain Shams University Hospitals. Height, weight, and WC were measured with the subject standing. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured at the midpoint between the lower border of the rib cage and the upper hip bone, during expiration. Blood pressure (BP) was measured with an appropriate-sized cuff on the upper right arm using a standard mercury sphygmomanometer after a 15 min rest in the sitting position. Three consecutive systolic and diastolic BP measurements were done at an interval of 1-min, and we used the average for analysis. After a 12- h overnight fast,blood samples were collected from the antecubital vein of each subject. Serum was separated from the samples on-site. Total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), fasting blood glucose, and triglycerides (TG) were determined from the samples using enzymatic methods. The rest of the serum samples were stored at −70 °C until the analysis of testosterone, estradiol, and insulin.

We calculated the Low density lipoprotein cholesterol (LDL-C) using the Friedewald equation [13]. If TG exceeded 400 mg/dl, direct measurement of LDL-C was to be performed after sequential ultracentrifugation.

Serum levels of testosterone were estimated using a human testosterone Enzyme Linked Immunosorbent Assay (ELISA) kit (abcam., catalogue number: ab108666). According to the manufacturer's protocol, intra-assay precision was ≤5.8% while inter-assay precision was ≤10.5% with a 0.05 ng/ml limit of detection.

Serum levels of estradiol (E2) were estimated using a human estradiol ELISA kit (mybiosource., catalogue number: MBS732799). According to the manufacturer's protocol, intra-assay precision was <9% while inter-assay precision was <10% with a 1 pg/ml limit of detection.

Serum levels of insulin were estimated using a human insulin ELISA kit (abcam., catalogue number: ab200011). According to the manufacturer's protocol, intra-assay precision was <8.6% while inter-assay precision was <4.9%, with a 0.158 mIU/L limit of detection.

Calculation of homeostatic model assessment of insulin resistance (HOMA-IR) using the standard formula: Fasting insulin × FBG (mg/dl)/405. Patients were considered insulin resistant if HOMA-IR >2 [14].

Statistical analysis

Statistical analysis was performed using SPSS version 21. Continuous data were expressed in the form of mean and standard deviations, while categorical data were expressed in numerical form and as percentages. Comparison of continuous data was performed using student's *t*-test while that of categorical data was done using chi-square test. Relations between variables were investigated by Pearson's correlation coefficient. Logistic regression analysis was used to find out independent predictors of MetS. A receiver operating character (ROC) curve was used to illustrate sensitivity and specificity of testosterone and estradiol serum levels for prediction of MetS. The p-value < 0.05 was considered significant, while the p-value < 0.01 was considered highly significant.

Result

The clinical and biochemical characteristics of the studied population are shown in Table 1. It was found that males with MetS had significantly lower testosterone levels and significantly higher E2 levels compared to those without MetS (p 0.0001) (Table 1).

Among males with MetS, 100% of them (i.e. 40 males) had abdominal obesity (waist circumference > 102 cm) and a triglyceride level >150 mg/dl, 82.5% (33/40 males) had BP ≥ 130/85 mmHg or used medication for hypertension, 90% (36/40 males) had fasting glucose ≥100 mg/dl, 52.5% (21/40 males) had HDL-C <40 mg/dl.

Testosterone and E2 levels were categorized into quartiles to facilitate finding and interpreting the relation of these sex hormones with MetS. The lowest quartile of testosterone was most prevalent among males with MetS (19/40 males, 47.5%) compared to those without MetS (0/40 males, 0%, p value 0.011). Regarding E2, the third quartile was most prevalent among males with MetS (19/40 males, 47.5%) compared to those without MetS (1/40 males, 2.5%, p value 0.0001) (Table 2).

In contrast, the highest quartile of testosterone and the lowest quartile of E2 were most prevalent among males without MetS (21/40 males 52.5%, 18/40 males 45%, respectively) (Table 2).

Testosterone levels showed significant correlation with all the components of MetS except the blood pressure and significant correlation with insulin resistance represented through HOMA-IR. However, the only component of MetS to which E2 was correlated was the FBG (Table 3).

Among the studied population, serum testosterone and serum E2 levels were independent predictors of MetS after adjustment for age and BMI (Table 4). The odds ratio of MetS was the highest for the first quartile of testosterone (17.4 [95% CI: 0.1–0.7]) in relation

Table 1
Clinical and biochemical characteristics of the studied population.

	Males with MetS (n = 40)	Males without MetS (n = 40)	p-value
Age (Years)	32.0 ± 5.4	30.7 ± 4.6	0.25
BMI (Kg/m^2) *	32.3 ± 3.8	28.4 ± 4.0	0.0001
WC (cm) *	110.5 ± 7.0	100.7 ± 6.4	0.0001
SBP (mmHg) *	135.5 ± 12.1	117.3 ± 3.6	0.0001
DBP (mmHg) *	94.3 ± 10.6	74.9 ± 3.4	0.0001
TC (mg/dl) *	275.4 ± 32.2	155.7 ± 29.9	0.0001
HDL-C (mg/dl) *	39.6 ± 7.0	50.2 ± 4.8	0.0001
LDL-C (mg/dl) *	175.4 ± 34.9	77.8 ± 31.1	0.0001
TG (mg/dl) *	301.6 ± 29.9	138.3 ± 24.5	0.0001
FBG (mg/dl) *	111.1 ± 6.9	90.8 ± 9.5	0.0001
Fasting insulin (mIU/L) *	6.9 ± 1.6	4.1 ± 1.7	0.0001
HOMA-IR*	1.89 ± 0.48	0.93 ± 0.39	0.0001
Testosterone (ng/ml) * ng/ml	2.1 ± 0.64	3.27 ± 0.58	0.0001
E2 (pg/ml) * ng/ml	20.3 ± 4.3	14.6 ± 5.6	0.0001
T: E ratio*	0.11 ± 0.05	0.25 ± 0.09	0.0001

BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure. TC: total cholesterol, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein-cholesterol, TG: triglycerides, FBG: fasting blood glucose. HOMA-IR: homeostatic model assessment for insulin resistance, T: E testosterone E2 ratio.
* highly significant.

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