The Association Between Serum Testosterone Levels and Coronary Artery Disease in Men

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Abstract

Background: Death due to coronary artery disease (CAD) is twice higher in men than women, and older men are more susceptible to the disease. Serum testosterone levels decrease with increasing age.

Objectives: In this study, we aim to study the association between serum testosterone levels and Gensini scores in men.

Methods: This cross-sectional study was conducted on 60 men above 40 years who had undergone coronary angiography. Thirty of them had normal coronary vessels, and 30 had coronary artery disease. For each group, the Gensini score was calculated.

Results: Serum testosterone levels in the CAD group and the control group were 4.04 ± 2.56 and 5.59 ± 2.20 ng/mL, respectively ($P < 0.05$), and free testosterone levels in the CAD patients and the control groups were 7.32 ± 5.24 and 12.91 ± 3.27 pg/mL respectively ($P < 0.001$). Sex hormone binding globulin (SHBG) levels in the CAD and the control groups were 28.88 ± 15.30 and 38.2 ± 19.9 nmol/mL, respectively ($P = 0.04$). Univariate analysis showed a significant association between Gensini score and total and free testosterone levels. The receiver operating characteristic curve (ROC) showed that the cut-off point of 7.97 had a sensitivity of 73.3% and specificity of 90% in predicting a high Gensini score (AUC = 0.799, $P < 0.001$).

Conclusions: Findings of our study demonstrated that serum free testosterone levels have a significant correlation with Gensini score and CAD severity.

Keywords: Testosterone, Coronary Artery Disease, Gensini Score

1. Background

In recent decades, cardiovascular diseases have been known as the most common cause of mortality worldwide. One study in Iran, which included 3723 persons, demonstrated that 11.3 % of the population had symptoms of cardiovascular diseases, and 1.4% had a history of previous myocardial infarction. The prevalence of cardiovascular diseases is estimated to be as high as 21.8% in those above 30 years in Tehran, the capital of Iran (1).

Coronary artery disease (CAD) is a chronic inflammatory disease recognized by remodeling and obstruction of coronary vessels, and is caused by a constellation of genetic and environmental factors such as smoking, diet, and lack of physical activity (2).

Death due to coronary artery disease is twice higher in men than women. In this regard, endogenous estrogen before menopause and postmenopausal exogenous estrogen are demonstrated to be protective against CAD in women (3, 4).

Testosterone and dihydrotestosterone (DHT), the most biologically active androgen, function through binding to androgen receptors. Some other biological effects of testosterone are due to its aromatization to estradiol which binds to estrogen receptors (5).

Serum testosterone levels decrease with increasing age, especially after the age of 40 years (by 3.1 - 3.5 ng/dL per year). This can be potentially compensated by means of exogenous testosterone therapy (6). Moreover, conditions such as type 2 diabetes mellitus (DM), obesity, human immunodeficiency virus (HIV) infection, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and chronic opioid abuse can decrease testosterone levels (7). Decreased serum testosterone levels may be associated with different chronic diseases such as metabolic syndrome, diabetes melitus (DM), dyslipidemia, hyperten-

sion (HTN), renal failure, malignancies, atherosclerosis, and cardiovascular events (8).

In men, decreased testosterone levels have negative effects on the masculine characteristics and general health, and quality of life. In addition, symptoms such as decreased libido, erectile dysfunction, irritability, and depression may appear. Nonetheless, there are concerns about negative effects of hormone replacement therapy on the cardiovascular system in men (9).

Low serum levels of endogen testosterone can increase the risk of CAD through a wide range of inflammatory mechanisms and mediators such as IL6, TNF, CRP (8, 10, 11).

The protective effects of testosterone on cardiomyocytes are exerted though inhibition of apoptosis and cardiac fibrosis (12). Moreover, it is demonstrated that testosterone has an anti-ischemic effect on the myocardial tissue in rats and in humans (13), and has therapeutic effects on the heart following ischemia and reperfusion episodes (14).

There are controversial reports regarding the effect of testosterone replacement therapy on cardiovascular events in hypogonadal men, particularly in the elderly and those with known CAD (15). Testosterone replacement therapy has been demonstrated to improve patients' exercise capacity in those with congestive heart failure (16).

A contradicting associations between testosterone replacement therapy (TRT) and cardiovascular events has been reported by Onasanya et al. cited in Goodale et al. (5).

According to some previous studies, there is an inverse association between CAD and total serum testosterone levels. Ohlsson et al. followed 2416 men who were 69 to 81 years old (10). They noted that low testosterone levels could predict cardiovascular events (10).

In another study, serum testosterone levels were low in patients with CAD, and an inverse relation was observed between serum testosterone levels and the severity of the disease (17).

Arnlov et al. showed that high serum levels of estradiol were associated with decreased risk of CAD, but the relationship between serum testosterone levels and CAD was not significant (18).

In another study designed to investigate the predictive value of low serum testosterone levels in patients with CAD, no association was detected in this regard (19).

2. Objectives

Since the effects of testosterone on the cardiovascular system are hitherto unknown and the prevalence of CAD in men is significantly high, in this study, we aimed to evaluate the correlation between serum testosterone levels and CAD in men above the age of 40 years who had undergone the angiography procedure.

3. Methods

This cross-sectional study was conducted in the Urmia University of Medical Sciences between January 2018 and January 2020. We evaluated the association between serum testosterone levels and CAD in men above 40 years. The study was carried out on 60 men above 40 years who had undergone coronary angiography, amongst whom 30 patients had normal coronary vessels, and 30 had coronary artery disease.

The power of the study was intended to be 99%, and the formula:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \times \left(S_1^2 + S_2\right)}{(\mu 1 - \mu 2)^2} \tag{1}$$

$Z_{1-\alpha/2} = 3.29$, $Z_{1-\beta} = 2.33$

was used for calculation of the sample size; comparison of the means and standard deviations of serum testosterone levels in the case and control groups was conducted (according to Gururani et al. study) on 27 patients in each group (17).

Our inclusion criteria were: Male gender, having had exertional chest pain or stable angina confirmed by positive moderate- to high-risk noninvasive tests (including treadmill exercise test, stress echocardiography test, and nuclear heart scan) or having had significant stenosis in coronary CT angiography and an ejection fraction of less than 40% with a possible diagnosis of CAD. Only new-onset heart failure cases who were not on aldosterone antagonist treatment were included.

A CAD case was defined as having had an occlusion of at least one coronary artery by more than 50% demonstrated by angiography or more than 30% obstruction in the left main coronary artery.

Patients with any history of previous revascularization, hypogonadism, prostate cancer, the use of anti-androgenic drugs such as spironolactone, renal failure, liver failure, recent MI, and active or recent infection were excluded.

Following 12 hours of fasting, a 3 mL blood sample was obtained from the patients between 8, and 10 am. Total cholesterol, triglyceride, fasting blood sugar, LDL, creatinine, total, and free testosterone, and sex hormone binding globulin (SHBG) were measured. Total and free testosterone levels were measured with the use of Eliza method and Demeditec kits. Sex hormone binding globulin was measured by DiaMetra kits.

Coronary artery involvement was assessed by Gensini score. This score is based on the number of involved vessels, location of the involved segments, and the severity of occlusion.

For calculation of the Gensini score, the severity of each coronary stenosis was estimated by the following method: One point was considered for $\leq 25\%$ narrowing, and 2, 4, 8,

16, and 32 points were recorded for 26 to 50%, 51 to 75%, 76 to 90%, 91 to 99% narrowing (and total occlusion) respectively. Then, each lesion score was multiplied by a score according to the importance of the lesion's position in the coronary circulation. For example, 5 was considered for the left main and 1 for the right coronary artery. Ultimately, the Gensini score was calculated through summation of the coronary segment scores (20, 21).

Angiographic scoring was performed by a cardiologist who was unaware of the serum testosterone levels of patients. All patients were matched according to the conventional cardiovascular risk factors, including diabetes mellitus (DM), hypertension (HTN), hypercholesterolemia, and smoking. Matching was done using a 1: 1 matching method in which we paired one patient in the normal coronary artery angiography (CAG) group with similar conventional risk factors in the CAD group. For example, when a patient with diabetes mellitus entered the CAD group, we allocated the patient to another group to match a patient with diabetes mellitus. For the receiver operating characteristic curve (ROC), we used MedCalc software to estimate the best lesion point (www.medcalc.org). The ROC curve was plotted though charting the true-positive rate against the false-positive rate. We used the ROC curve to define the most suitable free testosterone cut-off point for differentiation of CAD patients from the control group with the best balance of sensitivity and specificity. This study was approved by the Ethics Committee of the University.

3.1. Statistical Analysis

Data analysis was conducted using SPSS software version 20. Pearson correlation coefficient (Spearman's rank correlation coefficient) was used for the evaluation of the correlation between Gensini score and total and free testosterone and SHBG.

4. Results

The mean age of the patients was 57.35 ± 12.36 years. Serum testosterone levels in the CAD group and control group were 4.04 ± 2.56 and 5.59 ± 2.20 ng/mL, respectively ($P < 0.05$), and free testosterone levels in the CAD and the control groups were 7.32 ± 5.24 and 12.91 ± 3.27 pg/mL respectively ($P < 0.001$). Sex hormone binding globulin levels in the CAD and the control group were 28.88 ± 15.30 and 38.2 ± 19.9 nmol/mL respectively ($P = 0.04$). Demographic characteristics of the patients and their laboratory data are presented in Table 1. There were no significant correlations between the case and control groups in terms of conventional atherosclerosis risk factors such as smoking, dyslipidemia, hypertension, and diabetes mellitus.

Univariate analysis showed a significant correlation between the Gensini score and total and free testosterone

Table 1. Demographic and Laboratory Data of Patients [a]

	Coronary Artery Disease	Normal Coronary Artery Angiography	P-Value
Age	59.63 ± 11.62	54.86 ± 13.57	0.149
Smoking	16 (53.3)	10 (33.3)	0.118
Hyperlipidemia	14 (46.7)	10 (33.3)	0.292
Body mass index	25.85 ± 3.82	25.73 ± 3.55	0.899
Hypertension	9 (30.0)	8 (26.7)	0.774
Diabetes mellitus	6 (20.0)	5 (16.7)	0.739
Hemoglobin	12.68 ± 2.26	13.0 ± 2.25	0.399
Creatinine	1.29 ± 0.58	1.28 ± 1.16	0.949

[a] Values are expressed as mean $\pm$ SD or No (%).

levels, but no such relationship was found regarding SHBG levels (Table 2).

The receiver operating characteristic curve (ROC) revealed that a cut-off point of 7.97 had a sensitivity of 73.3% and specificity of 90% in predicting a high Gensini score (AUC = 0.799, P < 0.001) (Figure 1).

5. Discussion

Our study demonstrated that although free testosterone, total testosterone, and SHBG all had a significant correlations with severe single coronary artery stenosis, only low levels of free testosterone had a significant independent association with a high Gensini score (which reflects the severity and progression of coronary artery disease). Coronary artery disease is a chronic inflammatory condition which is characterized by remodeling and stenosis of coronary arteries, and can present as stable angina, acute coronary syndrome, and sudden cardiac death. This adverse health condition is a multifactorial disease caused by different genetic and environmental factors (such as smoking, diet, and sedentary lifestyle) (2).

Several studies have demonstrated that cardiovascular events and metabolic disorders are more common in men with low testosterone levels (22). Testosterone is a known regulator of metabolic functions in the liver, adipose tissue, muscles, coronary vessels, and the heart. Therefore, testosterone therapy can potentially decrease the risk of CVD. Nonetheless, there are concerns that testosterone replacement therapy may be associated with a higher risk for adverse cardiovascular events (6).

Possible mechanisms of the protective effects of testosterone on cardiomyocytes include: Increasing the level of peroxisome proliferator-activated receptor a (PPARa) (which is an important nuclear regulator of fatty acid

Table 2. The Association Between Gensini Score and Risk Factors

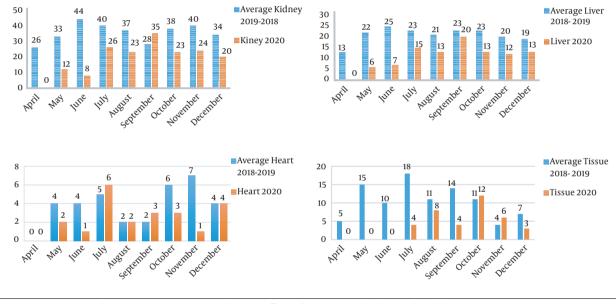|	OR	95% CI for OR		P-Value
		Lower	Upper	
Age	0.970	0.930	1.011	0.151
Body mass index	0.991	0.862	1.139	0.896
Diabetes mellitus	1.250	0.336	4.644	0.739
Hypertension	1.179	0.383	3.629	0.775
Smoking	2.286	0.804	6.495	0.121
Dyslipidemia	1.750	0.616	4.973	0.294
Testosterone	1.334	1.043	1.707	0.022
Free Testosterone	1.307	1.137	1.502	< 0.001
Sex hormone binding globulin	1.032	0.999	1.065	0.055

Figure 1. Receiver operating characteristic curve shows that with a 7.97 cutoff point, free testosterone levels can predict a high Gensini score.

metabolism) (23), decreasing oxidative injury through enhancement of NFKB expression (24), and Akt activation (25). Moreover, nuclear factor-kappa B (NF-κB) has a prominent role in regulation of anti-apoptotic genes, and testosterone can reduce cellular injury and necrosis through its regulation (26). Furthermore, testosterone administration decreases cardiomyocyte apoptosis and oxidative stress via upregulation of Akt phosphorylation in cardiac myoblasts (27). In addition, impaired mitochondrial function can decrease ATP production and increase reactive oxygen species (ROS) formation (28) (as seen in aging), and testosterone has a protective effect on the mitochondria.

At the physiologic levels, testosterone inhibits ROS formation. However, a supra-physiologic level of testosterone can have opposite effects through reducing nitric oxide formation and increasing oxidative stress at a cellular level (29), and can lead to mitochondrial dysfunction (30).

The relation between low testosterone levels and obesity, inflammation, atherosclerosis and its progress, and cardiovascular mortality has been confirmed in several epidemiological studies. It is demonstrated that testosterone replacement therapy can be effective in reducing fat mass, vasodilation, reducing blood pressure, improving insulin sensitivity and lipid profiles, enhancement of anti-inflammatory and anticoagulation properties, and reduction of carotid intima-media thickness. It has been shown that testosterone therapy can decrease CVD risk in men with androgen deficiency (31).

Our findings demonstrated that there is a significant inverse relationship between total and free testosterone levels and the Gensini score. In accordance with our results, findings of a cohort study by Ohlsson et al. demonstrated a significant inverse relationship, and a major correlation between total testosterone and SHBG levels and CAD (P < 0.05) (10). Nonetheless, contrary to our result, they did not find any correlation between free testosterone levels and CAD (10).

Moreover, in Gururani et al. study carried out on 92 patients between the ages of 40 and 60 years, a strong inverse association was found between total testosterone levels and Gensini score (17). In another study by Li et al., a significant inverse relationship was observed between total testosterone levels and Gensini score in 803 men who had undergone angiography (32).

In another study by Hu et al., a significant inverse relationship between low serum testosterone levels and Gensini score was observed (33). In this regard, in our study, although univariate analysis demonstrated a significant relationship between total testosterone levels and Gensini score, only free testosterone levels had an independent association with Gensini score (33).

Malkin et al. evaluated the relationship between serum testosterone levels and cardiovascular events (34). They investigated the relationship between serum testosterone levels and mortality by means of COX proportional hazard. Results showed that testosterone deficiency was more common in men with CAD. Moreover, a significant correlation between testosterone levels lower than 2.6 nmol/L and patient life expectancy was noted (34).

Contrary to our study, Araujo et al. found that although lower levels of free testosterone were associated with decreased fatality due to IHD, there was no significant correlation between total testosterone levels and cardiovascular mortality (35). In addition, SHBG and dihydrotestosterone levels showed an inverse correlation with IHD-related mortality (35). Nonetheless, we did not investigate cardiovascular mortality. Our results also demonstrated that with increased testosterone concentrations, the prevalence of DM and HTN were decreased and the levels of physical activity increased, and smoking was more common in patients with very high serum testosterone levels (10).

In a study on 1114 American men without any history of cardiovascular disease, the relationship between serum testosterone levels, estradiol, SHBG, and cardiovascular mortality was investigated. At the end of the 9-year follow-up period, no statistically significant difference was seen between these variables and cardiovascular mortality. They also reported that men with low total and free estradiol, low free testosterone, low bioavailable testosterone, low testosterone to SHBG ratio, and high estradiol to SHBG ratio were more susceptible to death due to cardiovascular

disease (36). Our study also showed that there was a correlation between SHBG and Gensini score although this relationship was not statistically significant.

After the age of 40 years, serum testosterone levels decrease about 3.1 - 3.5 ng/dL per year. Although exogenous testosterone therapy can be beneficial in terms of reducing related adverse consequences, there are some concerns about its potential cardiovascular adverse effects. Nonetheless, no significant relationship between testosterone therapy and increased CV mortality has been found hitherto, and this relationship remains controversial (6). We propose that future studies should focus on the potential beneficial effects of testosterone on the cardiovascular system.

5.1. Conclusions

Our study demonstrated that low serum free testosterone levels had a correlation with Gensini score and CAD severity.

Footnotes

Authors' Contribution: All listed authors have equally contributed to this work.

Conflict of Interests: Authors declare none.

Ethical Approval: This study is approved by the university medical ethics committee and registered as follows: ethics.research.ac.ir/IR.UMSU.REC.1398.068.

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Informed Consent: Informed consent is obtained.

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