Original Article

The Association between Premature Coronary Artery Disease and Level of Testosterone in Young Adult Males

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Abstract

Objective: Low testosterone levels in men have been associated with an increased risk of cardiovascular disease. We aimed to identify the association between serum testosterone level and premature coronary artery disease (CAD) and its predictors in young adult males.

Methods: In this cross sectional study, consecutive male candidates for coronary angiography with unstable angina, no previous CAD and age ≤45 years were included. Serum levels of free (FT) and total testosterone (TT) as well as demographic and cardiovascular characteristics were compared between the CAD-positive and normal coronary subjects. The cutoff point for low TT was 2.5 ng/L. Additionally, the relationships between all the variables and the number of affected vessels and FT and TT and predictors of CAD were assessed.

Results: In this study, 191 patients with premature CAD were compared with 94 normal coronary subjects. Patients in the CAD group were significantly older (41.59 ± 3.79 versus 39.27 ± 4.97 years; *P*-value < 0.01), and had higher rates of diabetes mellitus (*P*-value = 0.04) and dyslipidemia (*P*-value = 0.01). Serum levels of FT and TT were significantly lower in the CAD group than the normal coronary subjects (*P*-value < 0.01 for both). The rate of subjects with low TT increased by the number of the affected vessels (p-value for trend <0.01) and there was a significant correlation between the Gensini score and FT and TT (r = -0.37, *P*-value < 0.01 and r = -0.34, *P*-value < 0.01, respectively). After adjustment for confounders, the association between low TT and CAD remained significant (Odds ratio = 4.30, 95% confidence interval: 1.99–9.32; *P*-value ≤ 0.001)

Conclusion: Low levels of testosterone were associated with premature CAD and its severity in young adults.

Keywords: Hypoandrogenism, hypotestosteronism, premature coronary artery disease; testosterone; young adults

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Introduction

The relationship between serum testosterone level and coronary artery disease (CAD) has always been a hot topic in cardiovascular medicine. A significant relationship was observed between cardiovascular risk factors and testosterone in the Framingham study.[1] It has also been shown that testosterone modifies cardiovascular risk factors, particularly the lipid profile,[2] blood pressure,[3] body mass index (BMI), and obesity.[4] Furthermore, levels of plasma androgens are conversely associated with the risk of atherosclerosis in elderly men.[5]

Current data show that testosterone level declines with advancing age in both men and women and is in association with age-related diseases.[6-7] During male aging, serum testosterone level declines gradually,[8] while the risk of cardiovascular and thrombotic events begins to increase.[9] Since the aging process commences after puberty, it can be presumed that the decline in testosterone level starts at a younger age than is generally expected. Thus, younger patients with acquired cardiovascular conditions, particularly CAD, may have a lower level of testosterone. A low level of free testosterone (FT) has been shown to be related to the development of premature CAD, defined as the development of CAD before the age of 45 years.[10-11] However, current evidence is still inconclusive and the role of testosterone in premature CAD has yet to be understood, highlighting the serious need for research on aging process.[12] As testosterone supplementation in the elderly and middle-aged males with hypogonadism has conferred a better cardiovascular state and even deceleration of the atherosclerosis process, it is beneficial to clarify this relationship in this age group.[13]

Premature CAD, defined as the presence of coronary heart disease in men ≤45 years and women ≤55 years[14] is a growing phenomenon in our developing world. The prevalence and magnitude of classical cardiovascular risk factors seem to be more prominent in patients with premature CAD and their first-degree relatives.[15-16] Therefore, it is necessary to identify other risk factors for this condition that may enhance the classical cardiovascular risk factors.

Considering the above-mentioned points, this study aimed to investigate whether serum testosterone level in males with premature CAD is lower than that in peers with normal coronary vasculature. Also, we investigated the determinants of CAD in the study population, considering the effects of testosterone and other classical risk factors for CAD.

Materials and Methods

Study population

In this cross-sectional study, male subjects aged ≤45 years scheduled for elective coronary angiography for the first time at Tehran Heart Center from January to April 2011 were prospec-

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tively enrolled. The exclusion criteria included history of known CAD or myocardial infarction, metabolic syndrome, malignancy, chronic renal insufficiency treated with dialysis, hepatic failure, presence of acute illness, and use of medications that affect sexual hormones, such as anticonvulsants and antithyroid drugs.

Written informed consent was obtained from the participants. The study proposal was approved by the Committee of Medical Ethics and the Research Board of Tehran University of Medical Sciences. This study conforms to the principles outlined in the Declaration of Helsinki.

Demographic and clinical data

Demographic data, past medical history, and physiological measurements were recorded at baseline for all participants. Based on our institutional definitions which were adopted from international guidelines,[17] patients already taking antihypertensive agents and those with two blood pressure readings ≥140/90 mmHg (at least five minutes apart in the sitting posture) were labeled as hypertensive. Also, patients with a history of taking lipid lowering agents, total cholesterol ≥200 mg/dL, or low density lipoprotein ≥130 mg/dL were classified as dyslipidemic. Diabetes mellitus was diagnosed if the patient had a definite history of diabetes and being treated with glucose lowering agents or fasting plasma glucose ≥126 mg/dL or two-hour post-load glucose ≥200 mg/dL. We considered patients who regularly smoked cigarettes or who had stopped smoking within the past one month as smokers.

A trained nurse was responsible for taking each patient's blood pressure (with a mercury sphygmomanometer), height, and weight. Based on the BMI, the participants were categorized as follows: normal = 18–24.9 Kg/m^2; overweight = 25–29.9 Kg/m^2; and obese >30 Kg/m^2.

Laboratory measurements

After an overnight fasting, venous blood samples were obtained on the day of the coronary angiography in order to measure serum biochemistry. Serum biochemistry measurements included fasting blood sugar, lipid profile (i.e., triglyceride, total cholesterol, LDL, and HDL), and serum testosterone. Serum levels of FT and total testosterone (TT) were measured via the ELISA method using commercially available immunoassays and in accordance with the manufacturer's instructions (IBL International, Hamburg, Germany). A cut-point of 2.5 ng/L for TT was considered as the level of low TT and patients were dichotomized around this point to facilitate the analysis.

Angiography

The presence of premature CAD was confirmed by conventional angiography. The angiography was performed in the cath-lab under local anesthesia by an expert cardiologist, and the results were reported by two cardiologists who were blinded to each other's report to increase the intra- and inter-observer reliability. In case of discrepancy between the reports, a consensus session was planned for both cardiologists to review the angiography film. Significant coronary stenosis and thereby CAD was defined according to the guideline of the American College of Cardiology/American Heart Association as a 50% or more narrowing of the lumen diameter in at least one major coronary artery.[18] The patients in whom the presence of premature CAD was confirmed by conventional angiography were classified based on the clinical vessel score [19] and the Gensini score. [20]

In the clinical vessel score, CAD was defined as the presence of ≥50% stenosis in the coronary arteries; single vessel disease (SVD): stenosis of one of left anterior descending artery or left circumflex artery or right coronary artery or main branches of each; two-vessel disease (2VD): stenosis in two coronary arteries other than left main artery; three-vessel disease (3VD): stenosis in three coronary arteries other than left main artery; and left main stenosis (LMS): stenosis in left main artery regardless of existence of stenosis in other arteries. The extent of atherosclerosis was assessed with a "clinical vessel score" on a scale of 0–3.[19]

The Gensini score was calculated by assigning a severity score to each coronary stenosis based on the degree of luminal narrowing and its geographic importance. Reduction in lumen diameter and the roentgenographic appearance of concentric lesions and eccentric plaques were evaluated (reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion were given Gensini scores of 1, 2, 4, 8, 16, and 32, respectively). Each principal vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment: the left main coronary artery, ×5; the proximal segment of the left anterior descending coronary artery (LAD) and the proximal segment of the circumflex artery, ×2.5; the mid segment of the LAD, ×1.5; the right coronary artery, the distal segment of the LAD, the distal segment of the circumflex artery, the right coronary artery, the posterolateral artery, the posterior descending artery, and the obtuse marginal artery, ×1; and diagonal artery and others, ×0.5.[20] Patients with a normal angiography were classified as the control group, and the Gensini score was considered zero for them.

Statistical Analysis

The continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) and were compared using student's *t* or Mann-Whitney U test between CAD and non-CAD groups; while analysis of variance (ANOVA) or Kruskal-Wallis test were used to compare the groups based on the vessel score. Categorical variables were described through frequency and percentage and were compared among the above-mentioned groups using chi-square or Fisher's exact test, where appropriate. The Spearman correlation coefficient was used to assess the relationship between the Gensini score and serum testosterone concentrations because of the skewness of both variables. Variables with *p*-values less than 0.2 in the univariate analysis of CAD and non CAD groups were candidate to enter the multivariable prediction model. A backward logistic regression model with probabilities of 0.05 and 0.1 as entrance and removal probabilities was used to find multiple predictors of CAD. Effects of covariates on CAD were reported as odds ratio (OR) with 95% confidence interval (CI). The discrimination power of the final model was measured using the *c* statistic, which is equal to the area under the receiver operating characteristics (ROC) curve; and model calibration was estimated with Hosmer-Lemeshow goodness of fit test. Covariates which simultaneously had *P*-values less than 0.2 with CAD and low TT were considered as potential confounders. The association between low TT and CAD was adjusted on detected possible confounders, using logistic regression model. *P*-values less than 0.05 were considered statistically significant. The data were analyzed using PASW (Ver. 18.0, SPSS Inc., Chicago, IL).

Results

Out of a total of 285 subjects, 191 (67.02%) with CAD (mean age

= 41.59 ± 3.79 years) were compared with 94 (32.98%) normal coronary subjects (mean age =39.27 ± 4.97 years). In the CAD group, 67 (35.08%) subjects had single-, 57 (29.84%) had two-, and 67 (35.08%) had three-vessel disease. The CAD positive patients were significantly older, with a higher rate of diabetes mellitus and dyslipidemia as well as higher levels of serum triglyceride compared with the CAD negative subjects. More importantly, the number of subjects with low TT was significantly higher in the CAD group (*P*-value < 0.01). The general characteristics of the subjects by the presence or absence of the coronary artery disease are summarized in Table 1.

The levels of FT and TT were significantly lower in subjects with CAD than in the normal coronary group (*P*-value < 0.01 for both) (Table 1). After adjustment for age, diabetes mellitus, and dyslipidemia, this difference was still significant (*P*-value < 0.01 for both). Moreover, there was a significant association between the level of FT and TT and the number of affected vessels within the CAD group. Patients with three-vessel disease had lower levels of FT and TT compared to those with single-vessel and double-vessel disease (*P*-value < 0.01 for both). The results of the comparison between the study variables within the CAD group based on the number of affected vessels are summarized in Table 2. There was a significant increasing trend in the number of subjects with low TT levels based on the vessel score and the degree of involvement, as depicted in Figure 1.

Serum levels of FT and TT were conversely correlated with the Gensini score (r = -0.37, *P*-value < 0.01 and r = -0.34, *P*-value < 0.01, respectively). The unadjusted effect of low TT on CAD showed that low TT is a significant predictor for CAD (OR = 3.94, 95% CI: 1.91–8.12; *P*-value < 0.001). In order to remove the effect of potential confounders, i.e. diabetes mellitus and smoking, and also determine the predictors of CAD, a multivariable regression test was performed including age, diabetes mellitus, dyslipidemia, smoking and low TT, and showed a strong significant association between CAD and low TT (OR = 4.30, 95% CI: 1.99–9.32; *P*-value < 0.01). The predictors of CAD in this study are shown in Table 3.

Discussion

In this study, we found that lower serum levels of FT and TT were significantly associated with premature CAD, the number

Table 1. General characteristics of the study population.

Parameter	Normal coronary (*n* = 94)	CAD (*n* = 191)	*P*-value*
Age (year)	39.27 ± 4.97	41.59 ± 3.79	<0.001
Family history of CAD, *n* (%)	22 (23.4)	56 (29.3)	0.29
Diabetes Mellitus, *n* (%)	9 (9.6)	46 (24.1)	0.04
Hypertension, *n* (%)	22 (23.4)	51 (26.7)	0.54
Hyperlipidemia, *n* (%)	54 (57.4)	137 (71.7)	0.01
Smoking, *n* (%)	32 (34.0)	84 (44.0)	0.1
BMI (Kg/m^2)	25.82 ± 3.86	26.30 ± 3.60	0.3
FBS (mg/dL)	102.38 ± 31.34	114.33 ± 39.97	0.06
Triglyceride (mg/dL)	173.23 ± 83.79	198.23 ± 123.20	0.04
Cholesterol (mg/dL)	179.27± 41.41	188.71 ± 44.98	0.08
HDL (mg/dL)	39.45 ± 8.55	38.88 ± 8.81	0.6
LDL (mg/dL)	112.76 ± 36.27	120.59 ± 34.93	0.08
Free Testosterone (pg/mL)†	5.10 [4.00, 6.12]	4.20 [2.30, 5.40]	<0.001
Total Testosterone (ng/L)†	4.15 [3.27, 4.90]	3.40 [2.10, 4.60]	0.003
Low total testosterone, n (%) ‡	10 (10.6)	61 (31.9)	<0.001

P-value < 0.05 was considered significant; †Data shown as Median [Interquartile range]; ‡Defined as serum total testosterone < 2.5 ng/mL. BMI = body mass index; CAD = coronary artery disease; FBS = fasting blood sugar; HDL = high density lipoprotein; LDL: Low density lipoprotein.

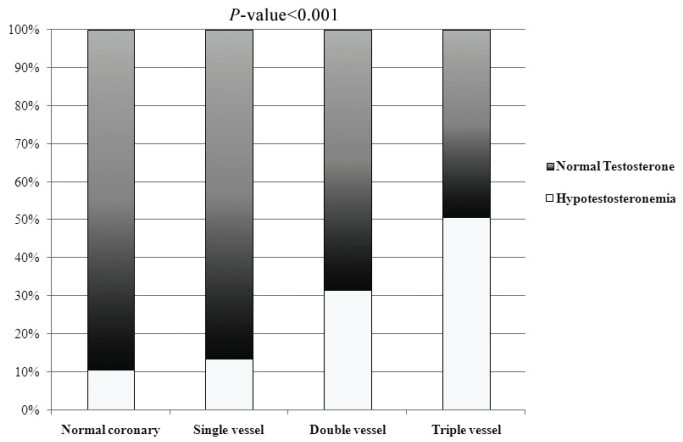

Figure 1. Comparing the percentage of low total testosterone within the study groups, based on the number of involved coronary vessels. *P*-value for trend is indicated.

Table 2. Characteristics of subjects by the magnitude of CAD.

Parameter	1-vessel (*n* = 67)	2-vessel (*n* = 57)	3-vessel (*n* = 67)	*P*-value
Age (year)	41.55 ± 4.03	41.26 ± 4.22	41.90 ± 3.12	0.65
Family history of CAD, *n* (%)	23(34.32)	16(28.07)	17(31.00)	0.5
Diabetes Mellitus, *n* (%)	9(13.43)	15(26.31)	22(32.83)	0.02
Hypertension, *n* (%)	19(28.35)	11(19.29)	21(31.34)	0.29
Hyperlipidemia, *n* (%)	46(68.65)	45(78.94)	46(68.65)	0.35
Smoking, *n* (%)	27(40.29)	29(50.87)	28(41.79)	0.44
BMI (Kg/m^2)	26.35 ± 3.67	26.68 ± 3.53	25.93 ± 3.60	0.51
FBS (mg/dL)	106.82 ± 33.74	115.98 ± 37.86	120.43 ± 46.34	0.13
Triglyceride (mg/dL)	174.10 ± 82.78	217.68 ± 121.17	205.81 ± 153.01	0.12
Cholesterol (mg/dL)	184.82 ± 44.37	195.51 ± 46.83	186.81 ± 43.99	0.38
HDL (mg/dL)	39.13 ± 9.23	38.72 ± 8.91	38.76 ± 8.42	0.95
LDL (mg/dL)	120.21 ± 32.83	129.21 ± 36.46	113.63 ± 34.55	0.38
Free Testosterone (pg/mL)	4.60 [3.90, 5.80]	4.20 [2.30, 5.40]	2.50 [1.20, 4.90]	<0.001
Total Testosterone (ng/L)	4.00 [2.90, 4.60]	3.40 [2.40, 4.30]	2.20 [1.30, 4.10]	<0.001
Low total testosterone, *n* (%)‡	9 (13.4)	18 (31.6)	34 (50.7)	<0.001
Gensini score†	23[14,37]	44[31,68]	70[57,91]	<0.001

**P*-value < 0.05 was considered significant; †Data shown as Median [Interquartile range]; ‡Defined as total serum testosterone < 2.5 ng/mL. BMI = body mass index; CAD = coronary artery disease; FBS = fasting blood sugar; HDL = high density lipoprotein; LDL = low density lipoprotein.

Table 3. Multivariable logistic regression model for predicting premature coronary artery disease.

Parameter	Odds ratio	95% Confidence interval	*P*-value
Age	1.13	1.06 – 1.20	<0.001
Diabetes mellitus	2.60	1.16 – 5.81	0.02
Smoking	1.87	1.07 – 3.27	0.02
Low total testosterone *	4.30	1.99 – 9.32	<0.001

*Defined as total serum testosterone < 2.5 ng/mL; area under the ROC curve: 0.73 (95% CI: 0.68–0.79; $P < 0.001$); Hosmer-Lemeshow test: (Chi-square statistic: 8.70, $P = 0.37$).

of affected coronary vessels, and the Gensini score. This effect remained significant even after adjustment for other well-known cardiovascular risk factors, including age, diabetes mellitus, and dyslipidemia, which were also significant predictors of the presence of CAD in this study.

It seems that the Framingham risk score may underestimate the true cardiovascular risk of an individual[21]; therefore, there is a growing need to introduce new cardiovascular risk factors to improve diagnostic accuracy. In this regard, many factors have been proved useful predictors for premature CAD while some other factors, such as serum uric acid failed to have any predictive value.[22] Not only is the role of sex hormones in the development of cardiovascular disease between the two genders controversial, but also the impact of their changes on the cardiovascular system within each gender is not well-identified.[23] For example, it has been demonstrated that intracoronary infusion of estradiol improved the coronary blood flow in women but not in men with CAD.[24] Even the effects of different male sex hormones, i.e. testosterone versus dehydroepiandrosterone sulfate (DHEAS), were not similar,[25] whereas one study suggested the imbalance of the sex hormones in the male CAD patients rather than the disturbance in the level of individual sex hormones to be associated with CAD.[26] There is an independent, inverse association between the levels of endogenous testosterone and severe aortic atherosclerosis and progression of aortic atherosclerosis in men, while in women, higher levels of testosterone tend to be positively associated with severe aortic atherosclerosis and progression of aortic atherosclerosis.[5]

Despite the debate on the correlation between androgens and CAD, the association between low serum testosterone level and the risk of atherosclerosis, CAD, and mortality in elderly men has been demonstrated.[5,27–30] However, our results clearly demonstrated that the serum levels of FT and TT and were associated with the presence of premature CAD and the number of affected vessels in young adult males. Also, we showed that low TT is a significant predictor of premature CAD in young adult males. Some studies have failed to provide sufficient evidence to confirm the association between serum testosterone concentrations and the severity of CAD,[25] whereas the present study revealed a significant relationship between testosterone level and the number of affected vessels as well as the Gensini score.

The decline in FT and TT with advancing age has been reported previously, although the decrease in FT is often more pronounced.[31–32] The cross-sectional design of the present study precluded us from tracking FT and TT changes in our study population. Nonetheless, based on our findings, both FT and TT exerted a similar effect on the presence of CAD and its severity even after adjustment for possible confounders, i.e., significant predictors of CAD in this study. Among the conventional risk factors of CAD, only diabetes mellitus and dyslipidemia were significantly higher in the CAD group. Our multi-variable regression model revealed FT and TT as well as age above 40 years, diabetes mellitus, and dyslipidemia as independent risk factors for CAD.

In light of our findings, it seems that further studies are required

not only to identify patients who may benefit from testosterone supplementation and the proper age for treatment initiation, but also to determine the dose and duration as well as possible cardiovascular or non-cardiovascular adverse effects during testosterone supplementation therapy.

Study Limitations

This study has some limitations, the first and foremost among which is that its cross-sectional design prohibited the assessment of fluctuations in serum testosterone through time. The effect of unexpected confounding factors on serum testosterone level cannot be entirely excluded. Serum testosterone level is influenced by different factors such as climate, season, age, and drug abuse, none of which was evaluated in our study population. In addition, only FT and TT were measured and the other sex-specific hormones were not evaluated in our study.

In this study in conclusion, a significantly lower serum testosterone level was observed in the young adult males with premature CAD than in normal coronary subjects. Lower levels of testosterone were significantly correlated with a higher number of affected vessels and a higher Gensini score. Also, the number of patients with low TT was greater in premature CAD patients. Based on these results, serum testosterone can be used as a predictive tool for the risk of premature CAD in young adult males. Future studies can test the effect of exogenous testosterone in young males and the effectiveness of this risk scoring system.

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Declaration of Interest

None declared.

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