# The association between androgen levels and premature coronary artery disease in men

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***Objective*** **The relationship between androgens and the risk of development of coronary artery disease has not been clarified well. This study was planned to determine the relationship between serum androgen levels and premature development of coronary artery disease in men.**

***Methods*** **Sixty-nine men below 45 years of age with documented coronary artery disease (mean age 41.0 ± 4.7) constituted the study group. Control group consisted of 56 men with similar age and normal coronary angiograms (mean age 41.3 ± 3.8). Total and free testosterone, estradiol, and fasting plasma total, low-density lipoprotein, and high-density lipoprotein cholesterol, and triglyceride levels were measured, and compared between the two groups.**

***Results*** **Mean age, body mass index, and the frequency of hypertension were similar between the two groups; however, diabetes mellitus, smoking, hyperlipidemia, and family history of coronary artery disease were more frequent in the coronary artery disease group. Total and free testosterone levels of the patients with coronary artery disease were significantly lower than those of controls, whereas estradiol levels did not differ. Multivariate logistic regression analysis revealed that free testosterone levels ($P = 0.014$; odds ratio = 0.90; 95% confidence interval = 0.87–0.99), hyperlipidemia ($P < 0.001$; odds ratio = 8.2; 95% confidence interval = 3.17–21.0), and smoking ($P = 0.026$; odds ratio = 3.12; 95% confidence interval = 1.15–8.48) were independent predictors of premature coronary artery disease. Moreover, using receiver operating characteristic analysis, patients with free testosterone levels below the cut-off value of 17.3 pg/ml had an adjusted 3.3-fold risk of developing premature coronary artery disease compared to those with free testosterone levels above the cut-off level (odds ratio = 3.3; 95% confidence interval = 1.57–6.87).**

***Conclusion*** **A low level of free testosterone may be related to the development of premature coronary artery disease.** ***Coron Artery Dis*** **18:159–162 © 2007 Lippincott Williams & Wilkins.**

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## Introduction

When compared with women of similar age coronary artery disease (CAD) is more prevalent in men. Mortality and morbidity associated with CAD is lower in pre-menopausal women. Rapid increase of CAD incidence in post-menopausal period, which levels with that of men, has been attributed to the beneficial effects of endogenous estrogen [1]. Although favorable effects of estrogen replacement therapy on women have been demonstrated in observational studies, this finding has not been supported by comprehensive prospective studies [2,3].

Androgens were thought to be responsible for the higher prevalence of CAD in men. The probable negative effects of androgens on lipid profile was supposed to be one of the mechanisms leading to CAD [4–6]. In contrast to observational studies, the results of some recent studies are suggestive of favorable effects of androgens on cardiovascular system [7]. A study on castrated male animals has shown that natural androgen replacement therapy inhibits atheroma formation [8]. Another study involving humans has shown that the androgen level of men with CAD is lower than those with normal coronary angiograms [9]. This study is striking as it suggests inaccuracy of the belief that high androgen levels are proatherogenic. Nevertheless, the relationship between androgens and CAD has not been thoroughly established yet.

Although there has been research about the androgen levels of men with CAD, the relationship between premature atherosclerosis and androgen levels is not clearly established. This study was planned to investigate whether androgen levels are indicators of premature atherosclerosis development.

## Methods

### Patients

One hundred and twenty-five men, under 45 years of age, who were admitted to Ankara University School of

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Medicine Cardiology Clinic for coronary angiography were included in the study. Sixty-nine patients with angiographically documented CAD and/or a history of myocardial infarction younger than 45 years of age constituted the study group. Fifty-six men in the same age group with angiographically normal coronary arteries constituted the control group. The reasons for coronary angiography in control group were for chest pain or rhythm disturbance evaluation in 39 of the cases and before heart valve surgery in 17. Those who had a history of hypogonadism, myocardial infarction in the last 3 months, unstable angina, and heart failure NYHA class III–IV and unwilling to give consent were excluded. Patients who were treated with lipid lowering drugs that can affect serum sex hormone levels were excluded from the study. Hyperlipidemia was defined as serum total cholesterol levels > 200 mg/dl. The body mass index was calculated for each patient and all patients signed an informed consent. The study is approved by the local ethics committee.

### Measurement of sex hormones and lipid parameters

Fasting blood samples were drawn between 7.00 and 8.00 h for total and free testosterone, estradiol, total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) measurements. After centrifugation plasma was stored at $-20^{\circ}$C and collected specimens were tested twice a week. Serum free-testosterone levels were measured by radioimmunoassay method (Diagnostic Products Corporation, Los Angeles, USA), and total testosterone and estradiol levels were measured by chemiluminescence method (Immulite 2000, Diagnostic Products Corporation).

### Statistical analysis

Statistical analysis was performed using the SPSS version 10.0 software package (SPSS Inc., Chicago, Illinois, USA). Categorical variables were analyzed by $\chi^2$ test. Among continuous variables estradiol levels, which showed normal distribution, were analyzed by Student's *t*-test. All other continuous variables were tested for significance by Mann–Whitney *U*-test. Multivariate logistic regression analyses were performed to adjust for the characteristics that were significant correlates (with $P < 0.10$) of CAD in the univariate analysis. Receiver operating characteristic (ROC) curves were used to determine cut-off point of free testosterone levels development of premature CAD. Correlations were determined with the Pearson rank correlation test. *P* values $< 0.05$ were considered statistically significant.

## Results

Clinical and metabolic characteristics of the CAD and control participants are shown in Table 1. Mean ages and body mass index were similar between the CAD and control groups. Although there were no differences in the prevalence of hypertension; diabetes mellitus, smoking, hyperlipidemia, and a family history of premature atherosclerosis were significantly higher in the CAD group. Total and free testosterone levels were significantly lower in the premature CAD group when compared with the controls ($P = 0.001$ and 0.026) without any significant differences in estradiol levels ($P = 0.577$). CAD patients had higher total and LDL cholesterol concentrations, but HDL cholesterol and triglyceride levels were similar between the two groups. Multivariate logistic regression analysis was performed to test the independency of free testosterone levels, diabetes mellitus, family history of CAD, hyperlipidemia, and smoking which were significant correlates of CAD in the univariate analysis shown in Table 1. As shown in Table 2, multivariate logistic regression analysis revealed that low free-testosterone levels, hyperlipidemia, and smoking were independently associated with the development of premature CAD. One unit decrease in free testosterone levels was associated with a 1.1-fold increase in risk of development of premature CAD [$P = 0.014$; odds ratio (OR) = 0.90; 95% confidence interval (CI) = 0.870–0.990]. As total and free testosterone levels may affect each other, they were not analyzed in the same multivariate analysis. When total testosterone levels were analyzed instead of free testosterone, total testosterone levels were also found to be independently associated with the development of premature CAD ($P = 0.004$; OR = 0.996; 95% CI = 0.994–0.999). ROC curves were drawn to determine a cut-off value for free testosterone levels increasing premature CAD (area under curve:

**Table 1 Clinical and metabolic characteristics of the CAD and control participants**

| | CAD ($n=69$) | Control ($n=56$) | *P* |
|---|---|---|---|
| Age[a] | 41.0 ± 4.7 | 41.3 ± 3.8 | 0.698 |
| BMI (kg/m$^2$)[a] | 26 ± 1.9 | 25.7 ± 2.0 | 0.711 |
| Hypertension (%) | 33.3 | 19.6 | 0.091 |
| Diabetes mellitus (%) | 21.7 | 1.8 | 0.001 |
| Smoking (%) | 75.4 | 53.6 | 0.01 |
| Hyperlipidemia (%) | 68.1 | 19.6 | <0.001 |
| Family history of CAD (%) | 56.5 | 30.4 | 0.003 |
| Total testosterone (ng/dl)[a] | 308.6 ± 169.7 | 408.7 ± 205.0 | 0.001 |
| Free testosterone (pg/ml)[a] | 15.7 ± 8.6 | 17.9 ± 7.1 | 0.026 |
| Estradiol (pg/ml)[a] | 26.3 ± 12.1 | 25.3 ± 7.3 | 0.577 |
| Total cholesterol (mg/dl)[a] | 194.7 ± 54.2 | 181.1 ± 40.6 | 0.002 |
| HDL-cholesterol (mg/dl)[a] | 40.4 ± 17.1 | 43.7 ± 17.3 | 0.375 |
| LDL-cholesterol (mg/dl)[a] | 119.8 ± 48.8 | 109.7 ± 34.1 | 0.002 |
| Triglyceride (mg/dl)[a] | 218.9 ± 152.5 | 182.4 ± 131.1 | 0.107 |

BMI, body mass index; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Data are expressed as mean ± SD.

**Table 2 Independent predictors of premature CAD**

| | *P* | OR | 95% CI |
|---|---|---|---|
| Low free testosterone (<17.3 pg/ml) | 0.026 | 3.3 | 1.57–6.87 |
| Diabetes mellitus | 0.050 | 5.85 | 1.0–34.1 |
| Family history of CAD | 0.081 | 2.27 | 0.91–5.68 |
| Hyperlipidemia | <0.001 | 8.2 | 3.17–21.0 |
| Smoking | 0.026 | 3.12 | 1.15–8.48 |

CAD, coronary artery disease; CI, confidence interval; OR, odds ratio.

$0.62 \pm 0.05$; $P = 0.026$; 95% CI = 0.52–0.72) and cut-off value was determined to be 17.3 pg/ml. Those with free testosterone levels lower than 17.3 pg/ml had an adjusted 3.3 times more risk for premature CAD than those with levels above the cut-off value ($P = 0.026$; OR = 3.3; 95% CI = 1.57–6.87).

Total cholesterol levels showed a weak positive correlation with free testosterone levels in the correlation analysis ($r = 0.26$, $P = 0.004$), whereas no significant correlation was found between free testosterone levels and LDL cholesterol, HDL cholesterol, and triglyceride levels.

## Discussion

The higher incidence of CAD in men when compared with postmenopausal women is suggestive of negative effects of androgens on the cardiovascular system [10]. This is supported by the evidence that chronic androgen administration negatively affects the lipid profile, and androgenic type of body fat distribution is associated with an increased risk of atherosclerosis in both sexes [4–6]. On the contrary in some studies, intramuscular administration of near-physiological doses of testosterone resulted in a decrease in total and LDL cholesterol levels without significantly affecting HDL cholesterol levels [11–13]. In a study conducted by Wranicz *et al.* [14] no significant association could be found between serum lipid levels and testosterone levels.

Although the effects of testosterone could partially explain the difference in the CAD prevalences between the two sexes, there is no definite evidence available confirming increased incidence of myocardial infarction and CAD by testosterone. Moreover, there are data suggesting that testosterone in fact may have protective effects against CAD [8,9,15–17]. Some studies report that low-dose testosterone therapy in men with CAD reverses exercise-induced myocardial ischemia and acute intravenous testosterone administration has anti-ischemic effects [10,18,19]. Intracoronary administration of physiologic concentrations of testosterone was shown to increase coronary blood flow by dilating the coronary arteries in patients with CAD and cause vasodilation in both coronary and systemic arteries of animal models *in vitro* [20,21]. This vasodilation could be attributed to increased endothelial nitric oxide release [22]. These findings when considered together with the decreased levels of testosterone by advancing age may suggest that the decrease in plasma testosterone concentrations may be one of the factors contributing to increased incidence of CAD by increasing age [23].

Although the exact mechanism of the beneficial effects that testosterone exerts on atherosclerosis has not yet been understood, it is proposed that it may cause coronary vasodilation directly by metabolic pathways or, after peripheral conversion of testosterone to estrogen by aromatase enzyme in the adipose tissue, estrogen may exhibit vascular effects and may slow down the progression of atherogenesis in men [4,6,20]. Hyperinsulinism is induced by low free-testosterone levels, which in turn leads to insulin resistance [24]. Testosterone levels were shown to be negatively correlated with insulin, fibrinogen, and plasminogen activator inhibitor-1 in men with CAD [15]. The relatively hypercoagulable state induced by low free-testosterone may have a contributory effect to atherosclerosis development. In an animal study, a decrease in plaque burden and an increase in tissue androgen-receptor mRNA was observed if testosterone was added to the medium after endothelial damage [25]. These findings suggest a probable vascular androgen receptor-mediated mechanism for the beneficial effects of testosterone. Another possible explanation for the beneficial effects may be that testosterone, rather than having direct preventive effects on atherosclerosis, is actually an indicator of good health status, so high levels can rarely be associated with CAD [17,26].

In our study, the free and total testosterone levels of the patients with premature CAD were lower than those of the control group. As expected, conventional risk factors of CAD, namely diabetes mellitus, smoking, family history of premature atherosclerosis, and hyperlipidemia were significantly higher in the CAD group. Multivariate logistic regression analysis revealed that low free-testosterone levels were an independent risk factor for premature CAD.

The variability in the results of the studies assessing the relationship between testosterone levels and atherosclerosis may be owing to the absence of an appropriate control group for subclinical CAD in some epidemiological studies and presence of heterogeneity between the study and the control groups. Moreover, inappropriate techniques for testosterone assays, difficulties in the determination of the reference limits because of the variability of the normal population, diurnal variations in the testosterone levels, and different blood sampling timings may cause such variations. As 68% of circulating testosterone is inactive, bound to sex hormone-binding globulin, the results of the studies assessing total testosterone alone may be misleading. The variability in the results of different androgen-administration studies may be related to the variations in the efficacy depending on the route of administration, and the androgen used.

The results of this study should be interpreted carefully owing to several limitations. As always in observational studies, numerous factors, which are not measured or recorded may confound our analysis. Furthermore, the sample size is relatively small. Although free testosterone

measurement by direct immunoassay method is simple and fast, there has been debate on its reliability [27]. As a strong association between both free and total testosterone levels was found, however, the measurements are supposed to be valid. Another limitation could be that sex hormone-binding globulin levels were not analyzed in our study. Patients with subclinical CAD, lesions that could not be detected angiographically, might falsely be included in the control group, and this, similar to some other studies, is a limitation of our study. The use of more invasive procedures like intravascular ultrasound for the determination of the atherosclerotic plaque and for an accurate grouping in patients with normal coronary angiograms, however, is not feasible practically and ethically.

In conclusion, contrary to the belief that high androgen levels in men increase the risk of atherosclerosis, we found that low level of free testosterone may be related to the development of premature CAD. Larger studies are needed to support these findings and in case other studies should be planned to determine the effects of testosterone therapy on the development of CAD for selected populations.

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