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Original Article

The Association between Androgenic Hormone Levels and the Risk of Developing Coronary Artery Disease (CAD)

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Abstract

Background: The aim of the study was to evaluate the relationship between the serum levels of androgens and Coronary Artery Disease (CAD) in an Iranian population.

Methods: Male individuals admitted to Tehran Heart Center and Sina Hospital, Tehran, Iran from 2011-2012 were categorized into CAD and control groups based on selective coronary angiography. Baseline demographic data, including age, BMI, diabetes, and a history of hypertension were recorded. Patients were also assessed for their serum levels of total testosterone, free testosterone, estradiol, dehydroepi and rosterone sulfate (DHEA-S), and Sex Hormone Binding Globulin (SHBG). Data analysis was carried out chi-square and ANOVA tests as well as logistic regression analysis.

Results: Two hundred patients were in the CAD group and 135 individuals in control group. In the CAD group, 69 had single-vessel disease, 49 had two-vessel diseases, and 82 had three-vessel diseases. Statistically significant differences were observed between the individuals in the two groups with respect to age ($P<0.0001$), diabetes ($P<0.0001$), and a history of hypertension ($P=0.018$). The serum levels of free testosterone ($P=0.048$) and DHEA-S ($P<0.0001$) were significantly higher in the control group than in the CAD group; however, the serum level of SHBG was higher in the CAD group than in the control group ($P=0.007$). Results of the logistic regression analysis indicated that only age ($P=0.042$) and diabetes ($P=0.003$) had significant relationships with CAD.

Conclusion: Although the serum levels of some of the androgens were significantly different between the two groups, no association was found between androgenic hormone levels and the risk of CAD, due mainly to the effect of age and diabetes.

Keywords: Coronary Artery Disease (CAD), Androgenic hormones, Testosterone, DHEA-S, Estradiol, SHBG

Introduction

Coronary artery disease (CAD) is one of the leading causes of death in all countries. It also significantly affects rates of disability (1). In the past few decades, advances in diagnostic as well as therapeutic methods have dramatically decreased the rate of CAD in many countries. Nevertheless, half of the deaths in industrial countries and 25% of the deaths in developing countries are attributed to CAD. It is also estimated that CAD will surpass infectious diseases and turn into the single leading cause of mortality and disability in the world by 2020 (2). Globally, the chance of developing CAD is 2.2 times greater in men than in women (3), which has been attributed to the role of endogenous estrogens in cardiovascular fitness(4-6). There are also hypotheses linking androgen defi-

ciency to an increased risk of CAD, an intriguing theory given the prevalence of late onset hypogonadism: 30% in men (7).

Therefore, a large number of studies have evaluated the role of androgens in cardiovascular diseases, with conflicting findings. For example, some studies have indicated that the serum levels of androgens can be used as predictors of all-cause and cardiovascular mortality (8-11), while others have failed to observe any significant relationships between the serum levels of androgens and cardiovascular disease (12,13). The effects of androgen therapy in males with andropause have also been evaluated in a number of studies. Similar contradictory findings were observed. Some of the studies have indicated a therapeutic role of oral testosterone for cardiovascular disease status(14-16), but this has not been supported by other studies (17,18).

Considering the existing controversy in the literature, and lack of comprehensive hormonal tests in the previous works, the present study sought to evaluate the relationship between serum levels of androgens and CAD in a sample of Iranian male population.

Methods

Male individuals admitted to Tehran Heart Center and Sina Hospital, Tehran, Iran from June 2011 to August 2012 were categorized into CAD and control groups based on the following criteria. Individuals with positive coronary angiograms were assigned to the CAD group, while those who had normal angiograms and admitted to the above-mentioned centers for reasons other than CAD were assigned to the control group. Patients who were taking hormonal medications, such as flutamide, or those who required dialysis due to renal failure were excluded from the study. In addition, patients in the control group who had a history of heart attack or CCU admission were also excluded. Participants in both groups were included after they signed an informed consent. The study was approved by the Ethical Committee of Tehran University of Medical Sciences, Tehran, Iran. Baseline demographic data, including age, marital status, job, weight, height, a history of smoking, diabetes, and a history of hypertension were recorded in the data collection sheet. Afterwards, patients were assessed for their serum levels of total testosterone, free testosterone, estradiol, dehydroepiandrosterone sulfate (DHEA-S), and sex hormones binding globulin (SHBG) in samples taken between 7:00 and 11:00 A.M. Albeit almost all samplings were done between 8:00 and 8:30 A.M due to both hospital protocols. Equilibrium dialysis was used to measure free testosterone, while total testosterone and DHEA-S were measured by radioimmunoassay (RIA). SHBG and estradiol were measured by the electrochemical immunosensor method and uric acid and cholesterol were measured by colorimetry method. It is noteworthy that all of the samples were tested in a single central laboratory.

Finally, the clinical vessel score was determined for each patient based on a 0-3 scale, and was defined as the number of vessels whose luminal diameter was obstructed by more than 50%, with a Gensini Score also used(19).

Analysis of the collected date was carried out using SPSS software version 18 (Chicago, IL, USA). We used the chi-square test to compare the frequency of patients with diabetes and hypertension between the two groups. ANOVA test was used to compare the mean values of the measured parameters between CAD and control groups. We also used logistic regression analysis to explore the possible relationships between the parameters and CAD. The significance level was set at $P<0.05$.

Results

Two hundred patients were in the CAD group and 135 individuals were in the control group. In the CAD group, 69 had single-vessel disease, 49 had two-vessel disease, and 82 had three-vessel disease. Table 1 presents the comparison between the individuals in the two groups in terms of age, BMI, cholesterol level, uric acid level, presence of diabetes and hypertension. According to the results of chi-square and ANOVA tests, statistically significant differences were observed between the

individuals in the two groups with respect to age (P<0.0001), diabetes (P<0.0001), and a history of hypertension (P=0.018). Table 2 presents the serum levels of total testosterone, free testosterone, DHEA-S, estradiol, and SHBG in both CAD and control groups.

Table 1: Baseline characteristics of the individuals in CAD and control groups

Parameter	CAD group	Control Group	*P.* value
Age (yr), Mean(SD)	60.0 (10.9)	55.0 (11.7)	0.000
BMI*, Mean(SD)	27.8 (3.9)	27.6 (4.3)	0.579
Cholesterol, Mean mg/dl (SD)	159.6 (40.0)	157.4 (36.6)	0.618
Uric acid, Mean mg/dl (SD)	6.7 (2.8)	6.4 (1.3)	0.281
DM**	30.5%	12.6%	0.000
HTN***	66.2%	53.3%	0.018

*: Body Mass Index, **: Diabetes Mellitus, ***: positive history of hypertension

As shown in the table, the serum levels of free testosterone (ANOVA P=0.048) and DHEA-S (ANOVA P<0.0001) were significantly higher in the control group than in the CAD group; however, the serum level of SHBG was higher in the CAD group than in the control group (ANOVA P=0.007). No statistically significant difference was observed between the two groups for other parameters. Results of the logistic regression analysis performed to assess the relationship between the parameters are presented in Table 3. Only age (P=0.042) and diabetes (P=0.003) indicated significant relationships with CAD.

Table 2: The serum levels of androgens in both CAD and control groups

Parameter	Group	Mean	SD*	*P.* value
Total testosterone ng/dl	Control	4.33	1.89	0.853
	CAD	4.36	1.73	
Free testosterone pg/ml	Control	7.28	7.51	0.048
	CAD	5.93	4.74	
DHEA-S**	Control	139.13	84.45	0.000
U/dl	CAD	107.79	66.70	
Estradiol	Control	40.14	15.45	0.077
pg/ml	CAD	36.98	15.67	
SHBG***	Control	50.56	33.18	0.007
nmol/l	CAD	60.50	31.46	

*: standard deviation, **: dehydroepiandrosterone sulfate, ***: sex hormones binding globulin

Table 3: Results of the logistic regression analysis indicating the relationship between the parameters

Standard Error		DF*	*P* Value	Odds Ratio
Age (yr)	.013	1	0.042	1.027
DM**	.308	1	0.003	2.514
HTN***	.254	1	0.222	1.364
Cholesterol	.003	1	0.184	1.004
Testosterone	.082	1	0.776	1.024
Free Testosterone	.024	1	0.529	0.985
DHEAS****	.002	1	0.161	0.997
Stradiol	.008	1	0.188	0.989
SHBG*****	.004	1	0.943	1.000
Constant	1.045	1	0.129	0.204

*: degree of freedom**: Diabetes Mellitus, ***: positive history of hypertension,/ ****: dehydroepiandrosterone sulfate, *****: sex hormones binding globulin

Discussion

The present study was conducted aiming to assess the relationship between serum levels of androgens and CAD in patients admitted to Tehran Heart Center and Sina Hospital. Patients with positive coronary angiograms were included in the case group and participants with normal angiograms were included as the control group; however, we had to exclude patients with a history of heart attack or CCU admission. This was done primarily to eliminate the dilution effect in the control group and to increase the power of study.

Results from the present study indicate significant differences in the serum levels of androgens between CAD and control groups. For example, the levels of free testosterone and DHEA-S were significantly lower in the CAD group than in the control group, whereas that of SHBG was higher in the CAD group than in the control group. Significant differences were also observed between the two groups with respect to age, diabetes, and a history of hypertension. Previous studies have shown that some of the abovementioned baseline characteristics, i.e. age, diabetes, and a history of hypertension, have been known to influence the serum levels of androgens (20-22), suggesting that the serum levels of androgens might have been affected by these parameters; and the reverse has also been considered (23). Therefore, we performed logistic regression analysis taking into consideration all of these parameters to explore the potential relationships among them. Results indicated that CAD was only associated with age and diabetes. In the case of androgenic hormone levels, no significant independent relationship with CAD was observed.

Results from previous studies have shown great inconsistencies. In experimental studies, androgenic hormone levels were shown to have influences on the evolution of atherosclerosis through different mechanisms (24,25). A vast majority of cross-sectional studies have found no association between CAD and serum levels of androgens. For example, in a recent study, the androgenic hormone levels, i.e. free testosterone, total testosterone, and DHEA, were found to be similar in both CAD and control groups (12). However, other studies have shown conflicting findings (26,27). In a cross-sectional study, the authors found that levels of DHEA-S, total testosterone, free testosterone and SHBG were significantly lower and the levels of estradiol and Follicle-Stimulating Hormone (FSH) were significantly higher in the CAD group than in the control group; therefore, they concluded that the androgenic hormone levels could be used as predictors of CAD development in men (26). Results from prospective studies on the association between the level of androgenic hormones and CAD are also somewhat controversial; some have found significant relationships between the serum levels of androgens and CAD (28,29), while others have failed to distinguish any significant association between the two (30).

The major limitation of the present study was posed by its design, i.e. a cross-sectional study design. Another possible source of error derives from our use of a single blood sample in each patient to measure hormone levels, which are known to fluctuate.

The major strength of the present study is our analysis of a broad range of androgenic hormones, i.e. total testosterone, free testosterone, DHEA-S, estradiol, and SHBG. Some of these hormone levels, though potentially important, have not been measured in previous studies.

Conclusion

We can conclude that although the serum levels of some of the androgens were significantly different between the two groups, no independent association was found between androgenic hormone levels and the risk of CAD. Rather, these significant differences were possibly due to the effects of age and diabetes on the serum levels of androgens.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or fal-

sification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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