Original Article

Association between Androgenic Hormone Levels and Left Ventricular Ejection Fraction

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Abstract

Background: *Androgens have been shown to have diverse effects on the cardiovascular system. The aim of this study was to compare androgenic hormone levels in patients with different left ventricular ejection fractions (EF).*

Methods: *The study population consisted of 515 consecutive men who were referred for angiographic studies and whose results of echocardiography and coronary angiography were available. The patients were classified into four groups: EF < 35%, EF = 35-45%, EF = 45-54%, and EF ≥ 55% to evaluate the trends of baseline characteristics and serum androgens, including free testosterone (fT), total testosterone (tT), and dehydroepiandrosterone sulfate (DHEAS). To better elucidate the difference in the patients with severe heart failure, the patients were divided into two groups according to their EF level, and comparisons were repeated between those with EF < 35% and the ones with EF ≥ 35%.*

Results: *There were statistically significant trends in some characteristics in the patients with different levels of EF. The subjects with higher EF levels were less likely to have diabetes (p value < 0.001), coronary artery lesion (p value < 0.001), or high levels of C-reactive protein (CRP) (p value < 0.001). As regards the patients with severe heart failure, our regression analysis revealed that the fT level was significantly lower in those with EF < 35% than in the ones with EF ≥ 35% (5.82 ± 2.73 pg/mL vs. 6.88 ± 3.34 pg/mL, p value < 0.05).*

Conclusion: *A significant association was found between the level of fT and EF < 35%. There is a need for further controlled prospective studies to delineate any possible causal relationship accurately.*

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Introduction

In spite of the recent advances in the understanding of the pathophysiological processes in chronic heart failure (CHF), this condition remains a heterogeneous syndrome with an overall poor prognosis. CHF is characterized by left ventricular dysfunction, impaired vascular tone, and skeletal muscle changes, contributing to fatigue, breathlessness, and edema. Moreover, the maladaptive neurohormonal and pro-inflammatory cytokine responses contribute to further cardiac dysfunction and cause a metabolic shift favoring catabolism.[1, 2] CHF most frequently arises from coronary artery disease (CAD) or hypertension, and patients generally experience a continuing decline in their health, resulting in an increased frequency of hospitalization and premature death.[3]

Androgens have been shown to have such diverse effects on the cardiovascular system as vasodilatation,[4-8] which contributes to an increased cardiac output and cardiovascular

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function. Although the effects of androgens on neurohormonal activation in CHF have not been studied thoroughly, it seems logical that the general anabolic effects of androgens would oppose excess catabolism.[9, 10] Moreover, experimental models have revealed that androgens significantly reduce the production of certain cytokines that have catabolic effects[9, 11, 12] and also mediate many of the pathophysiological processes of CHF.[13] To our knowledge, there are limited data available in the existing literature focusing specifically on the gonadal function in men with heart failure using New York Heart Association (NYHA) functional class for patient categorization.[14-19] The current study aimed to compare androgenic hormone levels in CHF patients with different ejection fractions (EF) and evaluate the possible underlying role of CAD in this pattern.

Methods

Between May and August 2005, a total of 515 consecutive inpatient or outpatient men who were referred for diagnostic cardiac catheterization and echocardiography by clinicians were enrolled into this study. Patients with acute myocardial infarction within the preceding 14 days, malignant disease, and chronic renal failure requiring dialysis or those who were taking any medications known to affect sex hormone levels (anti-thyroid or anti-seizure drugs) were excluded. Informed, written consent was obtained from all the participants, and the investigation was approved by the institutional Review Board, overseeing the participation of human subjects in research at Tehran University of Medical Sciences. This study conforms to the principles outlined in the Declaration of Helsinki.

Blood samples were taken at 8.30-9.30 A.M. of the day when angiography was planned to be performed. The patients were assessed for serum free testosterone (fT), total testosterone (tT), and dehydroepiandrosterone sulfate (DHEAS). fT was measured with enzyme-linked immunosorbent assay (ELISA), and tT plus DHEAS was measured with radioimmunoassay (RIA). The ELISA kits were IBL for fT, and the RIA tests were conducted with the Immunotech kit (France).

The results of coronary angiography and left ventriculography were available in all the patients. Also, all the patients underwent transthoracic echocardiography, and left ventricular ejection fraction (LVEF) was measured. The patients were then classified according to their EF into four groups: group 1: EF < 35%, group 2: 35% ≤ EF < 45%, group 3: 45% ≤ EF < 55%, and group 4: EF ≥ 55%. CAD was defined according to the "clinical vessel score", with clinically significant atherosclerosis being defined as ≥ 1 stenosis of at least 50% in ≥ 1 coronary artery.

The numerical variables are presented as mean ± SD, while the categorized variables are shown as numbers (percentages). The continuous variables were compared using the Kendall Tau rank correlation test for trends, and the categorized variables were compared utilizing the Mantel-Haenszel chi-squared tests across the four groups as defined by EF. To compare the measurements in the patients with EF < 35% and EF ≥ 35%, a univariate analysis of the baseline characteristics and hormonal assessment was performed within individual groups applying Student's t-test, chi-square, or Fisher's exact test, as appropriate. Variables with p values less than 0.15 were entered into a multivariable logistic regression model to identify the association between fT and EF level (< 35% vs. ≥ 35%) in the presence of confounding factors, including diabetes mellitus, smoking, number of stenotic coronary arteries, and C-reactive protein (CRP). For the statistical analysis, the statistical software SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL) and the statistical package SAS version 9.1 for Windows (SAS Institute Inc., Cary, N.C., U.S.A.) were used. All the p values were 2-tailed, with statistical significance defined by p value ≤ 0.05.

Results

All the baseline characteristics and adrenergic hormone levels were initially compared across the four groups according to the patients' cardiac output. There were statistically significant trends in some characteristics across the groups (Table 1). The Kendall Tau rank test for trend showed that the patients with higher EF values were less likely to have diabetes (p value < 0.001) or coronary artery lesion (p value < 0.001). Likewise, the CRP level was the lowest in the patients with EF ≥ 55% (p value < 0.001). The patients with the highest EF values tended to be younger with a higher body mass index than the lower EF groups (p value = 0.08).

For further elucidation of the differences, all the comparisons were repeated with respect to dual categorization: the patients with severe heart failure (EF < 35%) and those with EF ≥ 35% (Table 2). The univariate analysis revealed that the proportion of diabetes mellitus was significantly higher in the patients with severe heart failure (p value < 0.01), who also had much more atherosclerotic coronary arteries than the patients with EF ≥ 35% (p value < 0.05). According to the androgenic hormonal assessment, the patients with severe heart failure (EF < 35%) showed a significant lower level of fT by comparison with those with EF ≥ 35% (p value < 0.05). To determine the significant difference in the fT levels between those with EF < 35% and the ones with ≥ 35%, the fT level along with all the possible confounding variables (diabetes mellitus, smoking, number of stenotic coronary arteries, and CRP) was included into the model. After adjustments for the confounders, the multivariable analysis identified a significant association between the fT level and EF < 35% (p value < 0.05).

Table 1. Baseline characteristics and androgenic hormone levels in different stages of heart failure*

	EF<35% (n=50)	35%≤EF<45% (n=76)	45%≤EF<55% (n=88)	EF≥55% (n=301)	p value
Age (y)	57.4±10.0	57.4±12.0	55.9±10.2	55.5±10.7	0.08
Diabetes mellitus	18 (36.7)	19 (25.7)	21 (25.3)	45 (15.5)	<0.01
Hypertension	13 (26.0)	21 (28.4)	30 (36.1)	82 (28.1)	0.99
Hyperlipidemia	18 (36.7)	29 (39.2)	31 (37.3)	92 (31.6)	0.21
Smoking	11 (22.0)	21 (28.4)	32 (38.6)	90 (30.8)	0.35
Number of atherosclerotic coronary arteries					<0.01
0	8 (16.0)	5 (6.8)	10 (11.8)	90 (30.3)	
1	7 (14.0)	16 (21.6)	8 (9.4)	51 (17.2)	
2	6 (12.0)	14 (18.9)	25 (29.4)	67 (22.6)	
3	29 (58.0)	39 (52.7)	42 (49.4)	89 (30.0)	
Total T, nm/L	16.3±7.9	16.4±7.1	17.1±6.2	16.5±7.1	0.97
Free T, pg/mL	5.8±2.7	6.8±3.7	7.2±3.4	6.8±3.2	0.29
DHEAS, µg/cL	10.8±6.9	10.5±5.9	11.3±6.9	11.6±7.7	0.43
CRP, mg/dL	14.2±2.2	13.7±2.0	12.7±1.5	9.6±0.5	<0.01
BMI, kg/m^2	26.3±4.5	27.2±4.0	27.4±4.2	27.7±4.6	0.08

*Data are represented as mean±SD or n (%)
EF, Ejection fraction; T, Testosterone; DHEAS, Dehydroepiandrosterone sulfate; CRP, C-reactive protein; BMI, Body mass index

Table 2. Baseline characteristics and androgenic hormone levels in patients with EF ≤ 35% vs. EF > 35%*

	EF<35% (n=50)	EF≥35% (n=465)	p value
Age (y)	57.5±10.0	55.9±10.8	0.32
Diabetes mellitus	18 (36.7)	85 (19.0)	<0.01
Hypertension	13 (26.5)	133 (29.6)	0.65
Hyperlipidemia	18 (36.7)	152 (33.9)	0.69
Smoking	11 (22.4)	143 (31.8)	0.17
Number of atherosclerotic coronary arteries			<0.05
0	8 (16.0)	105 (23.0)	
1	7 (14.0)	75 (16.4)	
2	6 (12.0)	106 (23.2)	
3	29 (58.0)	170 (37.3)	
Total T, nm/L	16.3±7.9	16.6±7.0	0.77
Free T, pg/mL	5.8±2.7	6.9±3.3	<0.05
(DHEAS), µg/cL	10.8±6.9	11.4±7.3	0.63
CRP, mg/dL	14.2±15.9	10.9±11.4	0.06

*Data are represented as mean±SD or n (%)
EF, Ejection fraction; T, Testosterone; DHEAS, Dehydroepiandrosterone sulfate; CRP, C-reactive protein; BMI, Body mass index

Discussion

The results of our study showed that the patients with higher EF values not only were more likely to be younger and less diabetic but also had a lower number of atherosclerotic arteries and CRP levels. Additionally, the patients with severe heart failure (EF < 35%) had lower fT levels than did those who had an EF ≥ 35%; nevertheless, the tT and DHEAS levels were not significantly different between these two groups. Likewise, the number of atherosclerotic coronary

arteries could not be regarded as an independent variable influencing the EF level in the heart failure patients.

Some studies have previously shown that the level of androgens is lower in patients with heart failure. In a study on 23 men with CHF due to idiopathic dilated cardiomyopathy, the fT level was lower than that in the age-matched control group.[18] In a more recent study,[19] despite consistently reduced circulating levels of DHEAS across all the age categories of CHF, the fT and tT levels were reduced only in men with CHF aged ≤ 45 years and ≥ 66 years. Furthermore, these hormones correlated inversely with CHF severity as expressed by NYHA functional class. Fallah et al. proposed a non-linear association of the tT levels with CAD, while lower levels had a preventive effect on CAD and higher values increased the risk of CAD.[20] In contrast to our study, the authors of another study showed the DHEAS and fT levels to be within normal range both in rest and exertion in patients with heart failure.[21] Therefore, although most of the studies conducted thus far have demonstrated lower androgen levels in patients with CHF and/or CAD,[22] controversy still persists over the level of these hormones in cardiac diseases; the differences could be somewhat attributed to different categorization recruited by investigators. Previous studies employed clinical definitions for the categorization of the patients, whereas we used EF levels for classification. To the best of our knowledge, the relationship between different severities of heart failure in terms of EF has not been specifically assessed in previous studies. In a study on a population of patients with CHF of different etiologies and EF ≤ 35% in NYHA classes II to IV, hormone levels were not significantly different in different EF categories of severe heart failure (EF = 30%-35%, EF = 25%-29%, and EF < 25%).[23]

According to our findings, despite a higher number of atherosclerotic arteries in the patients with EF < 35% in comparison to those with EF ≤ 35%, this variable did not remain significant in the secondary analysis using a logistic regressive model. Accordingly, it can be inferred that any significant difference in the number of atherosclerotic coronary arteries in the patients with EF ≥ 35% and EF < 35% might be due to the underlying difference in the fT level and that CAD might not have independently affected the EF level in these patients. It is noteworthy that English et al.[24] previously showed an association between CAD and androgenic hormone levels.

The acute effects of testosterone, including reduced peripheral vascular resistance and improved cardiac index, and its chronic effects such as enhancement in functional capacity have been investigated in different studies.[25-28] Further prospective and clinical studies are required to shed more light on the possible positive effects of androgen therapy in CHF patients.

In the current study, we did not select patients with CHF based on NHYA class or symptoms. Instead, we categorized them only according to EF values reported in echocardiography. Although this may be regarded as a limitation, our aim was to evaluate the association between androgenic hormones and cardiac EF and its level of impairment rather than CHF NYHA class, which shows the severity of symptoms, and is not necessarily related only to EF. Another limitation is that we did not measure the concentration of serum hormone binding globulin and calculate the bioavailable testosterone, which is a more accurate marker for androgenic activity.

Conclusion

The patients with severe heart failure (EF < 35%) had lower fT levels compared with those with an EF > 35%, and CAD could not independently influence the cardiac output in the CHF patients.

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