



Evaluation of Androgen Levels in Patients with Acute Coronary Syndrome

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Abstract

The aim of the study was to determine plasma levels of free Testosterone (fT) and dehydroepiandrosterone sulphate (DHEA-S) in male patients with acute coronary syndrome. We measured the serum fT and DHEA-S levels of 30 healthy male subjects and 64 male patients with acute coronary syndrome whose coronary artery diseases were confirmed by coronary angiography. We observed no difference between two groups on the level of fT while DHEA-S level was significantly lower ($p = 0.01$). No correlation had existed between lipid parameters and levels of fT and DHEA-S. More comprehensive studies are needed to clarify whether lower levels of DHEAS are contributed to acute coronary syndrome or not.

Key words: Free testosterone, dehydroepiandrosterone sulphate, acute coronary syndrome, coronary artery disease

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Introduction

Acute coronary syndrome (ACS) is one of the leading causes of mortality and morbidity in adults [1]. Risk of coronary artery disease (CAD) is higher in men than in premenopausal women, but this risk increases in favor of women in postmenopausal period [2]. One of the explanations for early occurrence of ACS in men is the abundance of proatherogenic testosterone and/or absence of cardioprotective estrogens [3]. In comparison to men, the lower incidence of cardiovascular disease in women in the premenopausal period is attributed to the protective effects of estrogen. On the other hand, it is well known that testosterone, free testosterone (fT), and dehydroepiandrosterone sulfate (DHEA-S) converted to estrogen in the peripheral tissues, particularly in adipose, thereby, exhibiting a cardioprotective effect [4].

DHEA, and its sulfated form, DHEA-S, are all secreted by the adrenal gland, and are weak androgens in terms of receptor binding and biological activity. However, they serve as precursors to produce testosterone and estrogen. There is a discrepancy in study outcomes that discuss the relationship between androgens and cardiovascular diseases.

In the present study, the aim was to examine a possible relationship between circulating levels of androgens and ACS by measuring fT and DHEA-S in male patients.

Materials and Methods

Written informed consent was taken by the participants or relevant. This study was approved by local ethics committee, and complied with the declaration of Helsinki.

64 male patients who were admitted to the coronary care unit with ACS diagnosis enrolled this study. ACS includes unstable angina, non ST elevation myocardial infarction and ST elevation myocardial infarction. Mean age was 52.67 ± 7.34 SD. The control group was consist of age matched 30 outpatient males without known chronic disease or chronic use of medication. Patients with chronic diseases (diabetes mellitus, acute or chronic renal failure, cerebrovascular disease, chronic inflammatory disease, hypogonadism or sexual dysfunction history), surgery or trauma, severe active infection, malignancy, and individuals taking chronic disease medications (testosterone, spironolactone, statins, 5- α reductase inhibitors) were excluded from study. Control group does not have ischemic changes in

electrocardiogram. Body mass index (BMI) was calculated according to the formula body weight divided by the square of the height (kg/m^2).

For fT and DHEA-S, fasting venous blood samples were taken at 08:00 A.M after rested for 15 minutes in the supine position for both groups. Plasma was stored at -70°C until analyses. fT was measured by enzyme-linked immuno-sorbent assay (Roche, Monza, Italy) and DHEA-S by auto-analyzer using commercially available kits (Olympus A2700, Diamond Diagnostics; USA). The sensitivity of the fT assay was 7 pg/mL , and the intra- and interassay coefficients of variation were 4.2% and 5.8%, respectively. Values were $2\text{ }\mu\text{g/dL}$, 4.5%, and 5.5% for the DHEAS assay. Fasting venous blood samples were also taken at 08:00 A.M (within the first 24 hours period started after the hospitalization for patients and any days for control group) to assess lipid parameters (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL]) (Elecsys E170 Moduler, Roche). An electrocardiogram was performed in all subjects (Cardiofax, Nihon Kohden, Japan).

Statistical analyses were performed by using GraphPad Prisma V.3 software. Besides definitive statistical methods (mean, standard deviation), independent t test was used in comparison of dual groups. Pearson correlation test was used to determine inter-variable relations. $p < 0.05$ was considered significant.

Results

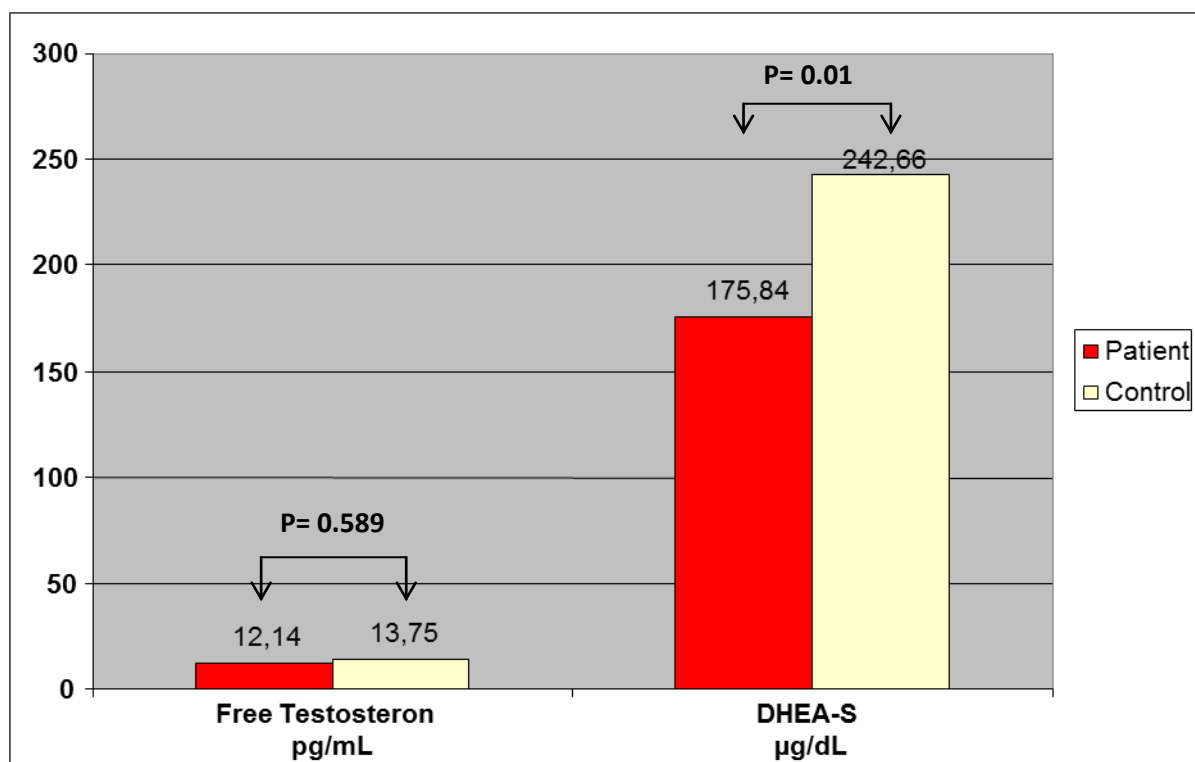
Demographic and biochemical data of both groups are shown in Table 1. The patient group and control group was similar in terms of body mass index [BMI (kg/m^2); $26.79 \pm 3.87\text{ SD}$ and $27.67 \pm 4.28\text{ SD}$, respectively; $p = 0.324$].

No significant difference was found between the patient and control groups in terms of total cholesterol, triglyceride, LDL, and HDL ($p = 0.315$, $p = 0.670$, $p = 0.406$, and $p = 0.903$; respectively).

Table 1: Demographic and biochemical datas

	Patient group	Control group	t	p
Age (years)	52.67 ± 7.34	53.13 ± 6.42	1.140	0.254
Weight (kg)	78 ± 11.62	81.70 ± 11.30	-1.452	0.150
Body mass index (kg / m2)	26.79 ± 3.87	27.67 ± 4.28	-0.992	0.324
Waist circumference (cm)	93.48 ± 1.30	98.23 ± 7.42	-0.724	0.471
Triglyceride (mg / dL)	194.69 ± 138.33	183 ± 82.71	0.428	0.670
Total cholesterol (mg / dL)	210.22 ± 53.26	198.57 ± 49.43	1.011	0.315
LDL (mg / dL)	132.19 ± 39.47	125.3 ± 30.77	0.835	0.406
HDL (mg / dL)	42.41 ± 8.06	42.63 ± 8.22	-0.123	0.903
Free testosterone (pg / mL)	12.14 ± 10.75	13.75 ± 17.67	-0.543	0.589
DHEA-S (µg / dL)	175.84 ± 120.65	242.66 ± 94.42	-2.636	0.01

Figure 1: Mean levels of free testosterone and DHEA-S in patient and control groups



The mean DHEA-S level was significantly lower in the patient group. It was 175.84 ± 120.65 $\mu\text{g/dL}$ in patient group, whereas it was 242.66 ± 94.42 $\mu\text{g/dL}$ in healthy controls ($p = 0.01$). Although no statistically significant difference was detected, fT level was lower than control group in patient group (13.75 ± 17.67 pg/mL ; 12.14 ± 10.75 pg/mL ; $p = 0.589$) (Figure-1).

No statistically significant relation was found between DHEA-S and total cholesterol ($r = 0.009$, $p = 0.932$), triglyceride ($r = -0.055$, $p = 0.598$), LDL ($r = 0.011$, $p = 0.922$), and HDL ($r = 0.095$, $p = 0.370$). Also, no statistically significant relation was found between fT and total cholesterol ($r = -0.015$, $p = 0.883$), triglyceride ($r = 0.107$, $p = 0.306$), LDL ($r = -0.111$, $p = 0.304$), and HDL ($r = -0.076$, $p = 0.472$).

Discussion

The effects of androgens on the cardiovascular system are still being argued, and conflicting results have been obtained through various studies. It becomes more complex due to conversion of testosterone to dehydrotestosterone and/or estradiol. It still has not been clarified cause and effect relationship between cardiovascular diseases and androgen levels.

DHEA-S and testosterone might play a protective role on the endothelial function of males [5, 6]. Testosterone decreased within first 24 hours after myocardial infarction [7]. Helaly et al found that patients with ACS had lower values of fT in comparison to control group [8]. In contradiction with these studies, as evidenced in our study, there are many studies showing no correlation between CAD and testosterone level [9-14]. These different results may be due to differences of assay methods and testosterone types.

Although the studies evaluating a correlation between DHEA-S level and CAD has shown conflicting results with each other, the opinion that there might be a negative correlation between DHEA-S level and CAD has become more pronounced. Elevated DHEA-S levels were associated with retarded progression of atherosclerosis measured by coronary artery angiography, ultrasound carotid wall thickness and pulse wave velocity aorta calcification [15]. Low level of DHEA-S causes the insulin resistance, central obesity, cardiovascular disease, immune system dysfunction and psychological problems, and it also accelerates

the atherogenic mechanisms [16 - 17]. It decreases the inhibition of fibroblast formation and differentiation and adversely affects the lipid profile, as well as decreasing the inhibition of platelet aggregation [18]. No other endogenous androgen has been shown to have such a strong correlation with incidence of cardiovascular disease as DHEA-S [16]. For instance, VITA study shows that the low DHEA-S level is associated with CAD, diabetes mellitus and hypercholesterinemia (total cholesterol > 250 mg/dL) but the low testosterone level is not associated with these factors [10]. Also Slowinska-Srzednicka et al found out a correlation between the low level of DHEA-S and occurrence of CAD. However, the same correlation was not found out between testosterone level and occurrence of CAD [12]. In our study we found that DHEA-S level was quite lower when compared with the level of control group. Thus, we reached a conviction that the low level DHEA-S might play a role for coronary endothelial disease or CAD may result in reduction of DHEA-S level in male.

Testosterone, in addition to the above defined mechanism, has also a significant role for the development of atherosclerosis through the lipid-dependant pathways. Testosterone is inversely related to the levels of total cholesterol, LDL, triglyceride and lipoprotein (a) while it is directly related to HDL. These correlations have created a risk for the occurrence of ischaemic CAD [19]. The relationship between DHEA-S and lipid levels is considered to be conflicting. DHEA-S levels have a negative correlation with triglyceride and total cholesterol levels, and a positive correlation with HDL level [20]. On the other hand, the existence of a significant correlation has not been determined in many studies [19-21]. High androgen levels seem to be correlated with desired lipid profile for males [22].

In our study, the lipid levels of patients with ACS have not found different from the lipid levels of control group. Moreover, no statistically significant correlation were found among the levels of fT, DHEA-S, total cholesterol, triglyceride, HDL and LDL. Pitt et al shown that patients with ACS had low serum lipid levels within 24 hours of admission to hospital, then these levels increased over the subsequent two days [23]. They concluded that this decrease might reflect causes related to hospitalization, such as altered oral intake or intravenous hydration. Additionally, heparin and cardiac catheterization are known to affect serum lipid components [24,25]. These factors may have influenced the results of our study.

We acknowledge the following limitations of our study. Firstly, the smoking habit (which lowers the androgen levels) of patient and control groups, and the cardiovascular risk factors

such as family history of heart disease could be questioned. Secondly, along with the fT it could be possible to work with bio-available testosterone and/or fT index.

In conclusion, we detected that the DHEA-S level of patients with ACS was significantly lower when compared with the control group. More comprehensive studies are needed about whether the lower DHEA-S levels in patients with ACS are the result or the cause of the disease. We are in the belief that the equalization of male's cardiovascular risk with the risk of female in advanced aged could not be only explained by the low level of androgen. Therefore the other probable factors which may lead to the occurrence of cardiovascular disease should be thoroughly studied. More comprehensive and prospective studies should be conducted in order to better understand the correlation between androgen and cardiovascular disease.

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