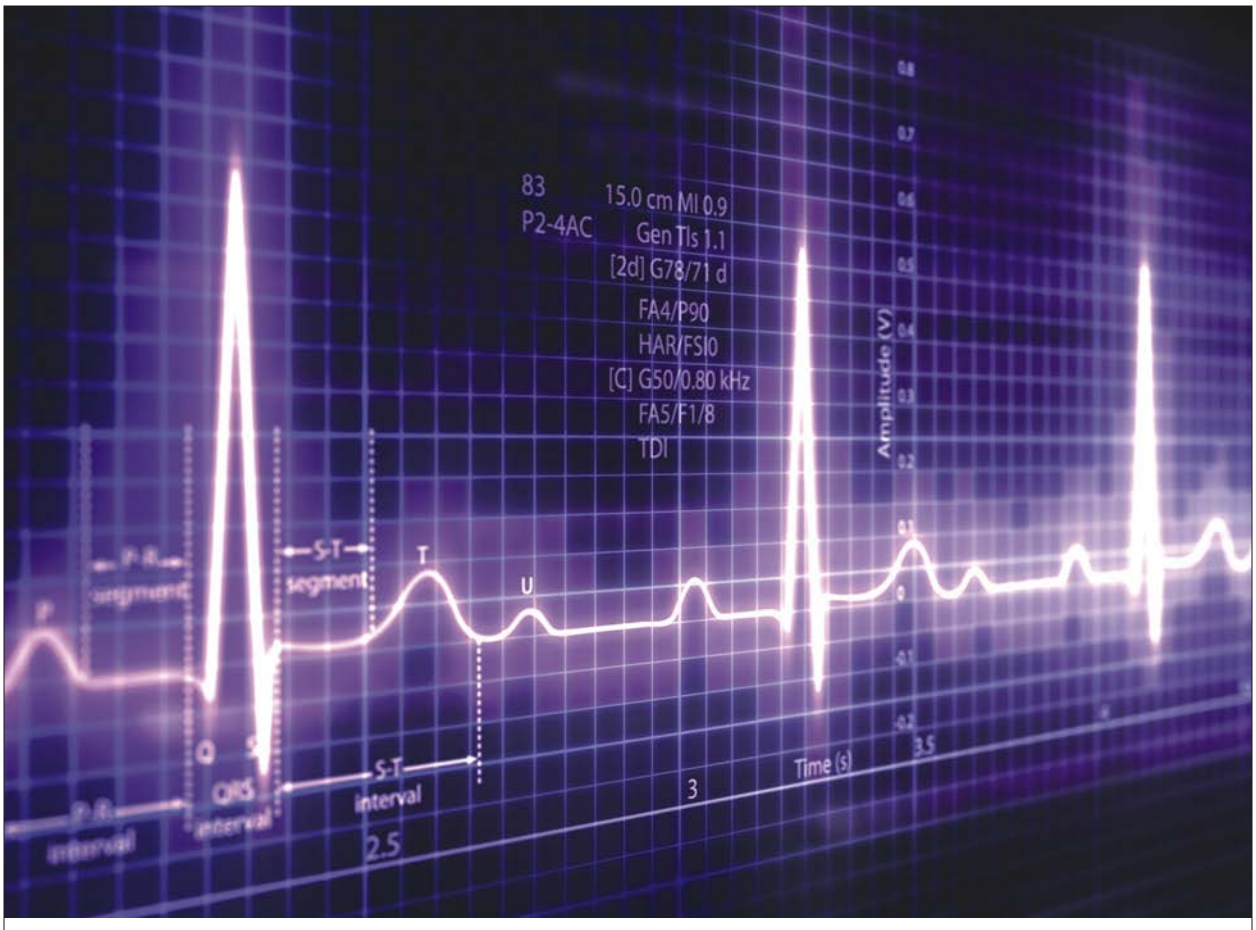

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Research Article
Correlation between Serum Testosterone Levels and Functional Capacity in Males with Congestive Heart Failure

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Abstract

Background and Objectives: Congestive heart failure (CHF) is an important and growing public health concern, leading to high mortality. Despite the advances in the treatment modalities of CHF, reducing the rate of hospitalization due to CHF is still an unresolved challenge. Regarding the significant role of anabolic hormones in the reduction of muscle mass, strength and endurance. This study aimed to determine the effects of serum testosterone levels on the functional capacity in males with CHF. **Materials and Methods:** This cross-sectional study was conducted on 49 males with CHF, referring to private cardiac clinics in Mashhad, Iran, during 2015-16. Data were collected, using clinical examinations and Echocardiography results. The transthoracic Echocardiographic assessment (M-mode, Doppler and two dimensional) was performed for all of the patients, using a GE Vivid 3 ultrasound system. Blood samples were collected from all patients to assess the testosterone levels and N-terminal pro-brain natriuretic peptide (NT-proBNP). Furthermore, to test the patients' exercise tolerance, the six-minute walk test (6 MWT) was employed. The correlation between subjects' serum testosterone level and other variables were evaluated. One-way ANOVA, Spearman correlation coefficient and SPSS was used to analyze the data. **Results:** The mean age of the study subjects were 60.71±7.41 years. The comparison between the studied variables and testosterone showed that there was no significant correlation between age ($r = -0.279$, $p = 0.052$), BMI ($r = 0.057$, $p = 0.697$), left ventricle (LV) diastolic size ($r = -0.12$, $p = 0.41$), right ventricular (RV) systolic function ($r = 0.206$, $p = 0.156$), NT-proBNP ($r = -0.197$, $p = 0.174$) and testosterone. Furthermore, there was a significant correlation between 6 MWT ($r = 0.854$, $p<0.001$), RV size ($r = -0.313$, $p = 0.028$), LV ejection fraction ($r = -0.415$, $p = 0.03$) and testosterone. **Conclusion:** According to the findings of this study, 6 MWT score was higher in patients with high testosterone level. In addition, RV size and LV ejection fraction were affected by testosterone levels. Consequently, this study demonstrated that the testosterone affected the physical activity in the males with CHF.

Key words: Motor activity, CHF, testosterone, cardiac, systolic

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Congestive heart failure (CHF) is an important and growing public health concern, which annually leads to hospitalization of nearly 1.2 million people[1] and high mortality rate[2]. The CHF involving multiple organ systems, begins with left ventricular dysfunction and is characterized by systemic hormonal, neurohormonal and cytokines changes[3].

Today, lowering the rate of hospital admission due to CHF remains an unresolved problem[4]. The majority of the patients with CHF suffer from decreased muscle mass, strength and endurance, which are caused by relative shortage of anabolic hormones[5]. According to the literature, testosterone deficiency affects a high rate of males with CHF and can lead to exhaustion and decreased skeletal muscle mass[6]. Low testosterone status is associated with decreased cardiac output and reduced exercise tolerance in the males with CHF, therefore, the testosterone replacement therapy can be helpful in this regard. In addition, this treatment can be effective in decreasing the circulating levels of inflammatory mediators in the patients with established coronary artery diseases[7].

The exercise training can enhance the exercise potentials in the stable CHF patients[8]. However, few studies have investigated the correlation between serum testosterone levels and physical activity in males with CHF. Regarding the low functional capacity in the males with CHF, interventions reinforcing exercise rehabilitation are evidently necessary for these patients[8]. With this background in mind, this study aimed to investigate the correlation between serum testosterone levels and functional capacity in males with CHF.

MATERIALS AND METHODS

This cross-sectional study was conducted on 49 males with CHF, referring to private cardiac clinics in Mashhad (located in Northeast of Iran), using convenience sampling method during 2015-16. All the patients had a history of classes II or III CHF for at least 6 months and their LVEF was less than 45%. The diagnosis of CHF was confirmed by transthoracic Echocardiography performed by single cardiologist of the study. The exclusion criteria included the history of cirrhosis, chronic alcohol consumption, the use of testosterone and consumption of anabolic steroids within the last month. On the other hand, the patients with the diseases limiting exercise testing (e.g., advanced hepatic and renal diseases) and malignancies as well as those unwilling to continue participating in this project were excluded from the study.

The data collection was carried out, using clinical examinations (e.g., 5 cc blood sample) and Echocardiography results. The transthoracic Echocardiographic assessment (M-mode, Dopler and two dimensional) was performed for all of the patients, using a GE Vivid 3 ultrasound system (model: 238645-3, made in the United States of America, 2012) with a frequency of 50 MHz. Blood samples (5cc) were collected from all patients to assess the testosterone levels and N-terminal pro-brain natriuretic peptide (NT-proBNP). In addition, the six-minute walk test (6 MWT) was administered for all patients during which they walked in the rehabilitation unit corridor for 6 min and their oxygen saturation (SO_2) and traveled distance were measured. The 6 MWT was stopped in the case of weakness, dizziness, shortness of breath and dyspnea.

Ethical consideration: The study was approved by regional ethics committee of Islamic Azad University of Mashhad. The subjects participation was voluntary and upon obtaining the informed consent. The study had no extra-expense for the patients and the study protocol did not disrupt the patients' treatment.

Statistical analysis: All data were recorded in a checklist and then entered in Social Sciences (SPSS) software (version 13.0 for Windows; SPSS Inc., Chicago, IL) to be analyzed. For analyzing the quantitative data, this study employed descriptive statistics (mean and standard deviation), One-way ANOVA and Spearman correlation coefficient. The $p-<0.05$ was statistically significant.

RESULTS

As the results demonstrated, the patients had the mean age of 60.71±7.41 years (age range: 44-75 years). The mean of body mass index (BMI) was found to be 21.38±1.32 kg m^{-2}, which ranged between 18.9 and 25 kg m^{-2}. The mean of the variables examined in this study illustrated in Table 1. According to the Kolmogorov-Smirnov test, all variables were demonstrated to be normally distributed. The patients were well matched at baseline for left ventricle (LV) variables.

The rates of LV ejection fraction were <30% (severe), 30-39% (moderate) and >40% (mild) in 59.18, 32.65 and 0.08% of the patients, respectively. The descriptive statistics regarding the patients with various rates of LV ejection fraction is presented in Table 2.

According to the results of the present study, the LV diastolic function had no significant correlation with

Table 1: Mean, minimum and maximum of the Echocardiographic and laboratory findings of CHF subjects

Variables	Mean	SD	Minimum	Maximum
Six minute walk test (m)	318.2	125.4	108	580
Left ventricle diastolic size	6.69	0.50	5.8	8
Right ventricle size	3.54	0.471	2.4	5
Left ventricle ejection fraction (mm)	25.87	8.303	10	44
TAPSE (mm)	16.73	4.66	6	27
NT-ProBNP (pg mL^{-1})	1709	1409.4	120	4631
Testosterone level (nmol L^{-1})	5.309	1.94	2.13	10

NT-ProBNP: N-terminal pro-brain natriuretic peptide, TAPSE: Tricuspid annular plane systolic excursion

Table 2: Patient demographic variables with different left ventricle ejection fraction

	Less than 30% (N = 29)		Between 30-39% (N = 16)		Between 40-49% (N = 4)	
Variables	Mean	±SD	Mean	±SD	Mean	±SD
Age (years)	61.620	6.571	59.8800	9.025	57.500	6.658
BMI (kg m^{-2})	21.079	1.218	21.8375	1.439	21.750	1.347
Six minute walk test (m)	285.862	133.823	371.6250	104.728	339.000	62.960
Left ventricle diastolic size (mm)	6.875	0.558	6.51688	0.459	6.350	0.387
Right ventricle size (mm)	3.675	0.409	3.3438	0.5501	3.375	0.250
TAPSE (mm)	17.344	12.444	17.5000	3.521	24.250	3.095
NT-ProBNP (pg mL^{-1})	1886.948	1477.769	1479.7063	1238.468	1338.250	1720.966
Testosterone level (nmol L^{-1})	4.807	1.9949	5.8938	1.755	6.615	1.238

NT-ProBNP: N-terminal pro-brain natriuretic peptide, TAPSE: Tricuspid annular plane systolic excursion

NT-proBNP and the levels of testosterone ($F = 0.571$, $p = 0.425$ and $F = 2.776$, $p = 0.073$, respectively).

The comparison between the studied variables and testosterone showed that there was no significant relationship between age ($r = -0.279$, $p = 0.052$), BMI ($r = 0.057$, $p = 0.697$), left ventricle (LV) diastolic size ($r = -0.12$, $p = 0.41$), right ventricular (RV) systolic function ($r = 0.206$, $p = 0.156$), NT-proBNP ($r = -0.197$, $p = 0.174$) and testosterone level. Furthermore, there was a significant correlation between 6 MWT ($r = 0.854$, $p<0.001$), RV size ($r = -0.313$, $p = 0.028$), LV ejection fraction ($r = -0.415$, $p = 0.03$) and testosterone level.

DISCUSSION

According to the findings of this study, 6 MWT score was higher in patients with high testosterone levels. Furthermore, the RV size and LV ejection fraction was correlated with testosterone. Decreased serum concentrations of testosterone were highly prevalent among the participants of the current study.

The findings of the present study are consistent with those of the previous studies. In a study conducted by Jankowska *et al.*[3], demonstrated that low testosterone levels lead to decreased exercise capacity. Testosterone level is widely considered to represent the threshold for androgen deficiency, which may result from decreased levels of total testosterone. In a study by Stout *et al.*[8], the elderly male patients with CHF who had low testosterone levels were exercised during a 12 week rehabilitation program. The mean total testosterone level of the patients was reported to be 10.9 nmol L^{-1} and the testosterone therapy during exercise rehabilitation was concluded to be effective for these patients[8]. In another study by Vermeulen[9], the mean total testosterone level of the patients was 11.0 nmol L^{-1}. As can be seen, this value was much lower in the present study (5.3 nmol L^{-1}), compared to the aforementioned ones[9]. This may be due to the fact that the participants of the current study were older than those of the mentioned studies.

Wu *et al.*[10] reported high prevalence of decreased serum concentrations of androgens in the elderly patients with CHF. Furthermore, they demonstrated that the total testosterone and free testosterone levels in these patients were below the tenth percentile of their healthy peers in nearly 25% of the subjects. In addition, about one third of the patients were reported to suffer from late-onset hypogonadism. The serum total and free testosterone levels were correlated with NT-pro-BNP level, indicating the correlation between androgen level and CHF severity. Moreover, the patients with testosterone deficiency had higher rate of mortality in the course of the follow-ups, compared to those without such deficiency[11].

Androgen deficiency can play an important role in the pathogenesis of cardiovascular disease[9]. Several studies reported low testosterone levels in the patients with CHF[3,10,11], while other studies did not yield such results[12]. These contradictions may be due to different definitions of the testosterone deficiency in various studies. In some studies

investigating the diagnosis and treatment of late-onset hypogonadism, the lower normal ranges for total and free testosterone were suggested to be less than 230 ng dL^{-1} and 225 pmol L^{-1}, respectively[13,14].

In the present study, a negatively correlation was found between the decline in serum total testosterone and physical activity, which is consistent with the findings of Jankowska *et al.*[3]. Jankowska *et al.*[3] showed that serum total and free testosterone levels negatively correlated with New York Heart Association Functional Classification in the males with CHF. Similar to this study, there was a correlation between the total testosterone levels and Echocardiography results of the LV systolic function.

Few studies have investigated the prognostic significance of serum levels of androgens on CHF. Jankowska *et al.* showed that total and free testosterone levels were predictive of mortality, independent of age and pro-BNP levels[3]. Recently, Guder *et al.*[15] conducted a study on 191 patients with CHF, which revealed no association between the patient outcome and total and free testosterone levels[15].

The role of the testosterone in the pathophysiology of CHF is not specified, nevertheless, the effect of the testosterone therapy on CHF is investigated in numerous studies. Pugh *et al.*[16] and Malkin *et al.*[6] demonstrated that testosterone injections improved the functional capacity in CHF patients.

According to the literature, testosterone therapy can be considered a new therapeutic method for the patients with CHF, which improves functional potency, while leaving little or no effects on the cardiac function[17,18]. Likewise, Caminiti *et al.*[19] indicated that long-acting testosterone therapy improved exercise capacity and muscle strength in the males with CHF. This therapy was also demonstrated to be effective for the female subjects[4]. Caminiti *et al.*[19] showed that testosterone supplementation improved large-muscle performance in the patients with CHF. They reported that the plasma levels of testosterone led to functional capacity improvement, which was not related to the changes in the left ventricular function[19].

Deficiencies in circulating gonadal and adrenal androgens, associated with decreased testosterone levels, are mostly prevalent among elderly males[20]. The levels of these androgens are reported to significantly decrease in the males with CHF[21]. Besides, these patients suffer from impaired exercise capacity due to the reduction of circulating testosterone[22].

The limitations of the present study were as follows: Small sample size (limited to 49 males), lack of a control group, not examining other sex hormones and not measuring the free testosterone levels.

CONCLUSION

According to the findings of this study, 6 MWT score was higher in patients with high testosterone level. The comparison between the studied variables and testosterone showed that with the increase of the age, the rate of testosterone was decreased. In addition, RV size and LV ejection fraction was correlated with testosterone levels. Consequently, this study demonstrated that the testosterone is correlated with the physical activity in the males with CHF.

SIGNIFICANCE STATEMENTS

This study discovers the effectiveness of testosterone level on the physical activity in the males with CHF that can be beneficial for CHF patients. This study will help the researcher to uncover the critical areas of functional capacity in CHF patients that many researchers were not able to explore. Thus a new theory on effectiveness factor on the physical activity in the patients with CHF may be arrived at.

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