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Research Article

Association Between Testosterone Levels and Clinical Markers of Atherosclerosis

Rezanezhad B[1*], Borgquist R[2], Elzanaty S[3]

[1]Department of Internal Medicine, Skåne University Hospital, Lund University, Lund, Sweden

[2]Associate Professor, Department of Clinical Sciences, Cardiology, Lund University Hospital, Lund, Sweden

[3]Associate Professor, Department of Translational Medicine, Skåne University Hospital, Lund University, Malmö, Sweden

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2. Key words

Eugonadal; Exercise test; Hypogonadal; Testosterone

1.Abstract

1.1. Objectives: To investigate the association between testosterone levels and parameters obtained from the clinical exercise stress test from 119 middle-aged Swedish men.

1.2. Material and Methods: All subjects underwent a clinical exercise stress test and data on maximal heart rate, systolic pressure, diastolic pressure; and ST-segment levels in lead augmented vector foot (lead aVF) and lead left precordial voltage 5 (lead v5) were collected. Serum testosterone levels were measured. Data on age, body mass index (BMI), smoking, alcohol consumption, and family history of cardiovascular diseases (CVD) were gathered. Men were classified into two groups: hypogonadal (testosterone ≤ 12 nmol/L), and eugonadal (testosterone > 12 nmol/L).

1.3. Results: We found a significant negative correlation between testosterone and maximal systolic pressure (r= -0.30, P=0.01). Hypogonadal men had significantly higher systolic pressure and more depressed ST-segment in lead V5 compared to eugonadal men (225mmHg vs. 210mmHg; p=0.01), (-0.13mm vs. 0.27mm; p=0.04), respectively. In a multivariate regression analysis test adjusted for the age of subjects, BMI, smoking, alcohol consumption, and family history of CVD, a significant negative association was found only between testosterone and maximal systolic pressure (β= -0.829, p=0.04, 95% CI= -1.636, -0.022).

1.4. Conclusions: Our findings of an inverse relationship between testosterone levels and parameters of clinical stress test suggest that low testosterone may be a cardiovascular risk factor.

3. Introduction

Testosterone, the main androgen in men is not only essential for male reproduction and virilisation [1], but also for general health and well-being [2]. Hypogonadism is a medical term for men with either lower testosterone levels and no clinical symptoms (chemical hypogonadism) [3], and/or men with lower testosterone levels who express symptoms of hypogonadism such as lower sexual desire, decreased level of concertation, sleeping difficulties, increased body weight (chemical/clinical hypogonadism) [4].

Cardiovascular diseases (CVD) are a major cause of death in men and women worldwide, and atherosclerosis is the most common underlying pathology [5]. A number of diagnostic and prognostic tests for atherosclerosis are available, one of these is the clinical exercise stress test [6-7]. The clinical exercise stress test is commonly used as a screening test to identify myocardial ischaemia. Thus, limitation of coronary blood flow during the test due to obstructive coronary artery disease (CAD) may lead to myocardial ischaemia and its subsequent ECG changes. The sensitivity of the ECG exercise stress test in diagnosing obstructive CAD is approximately 50%, with a specificity of approximately 90% [8]. The American Heart Association recommending clinical stress test for adult patients with intermediate pre-test probability of CAD [9].

ST-segment depression during clinical exercise stress test is known to correlate with coronary artery atherosclerosis. Testosterone concentration is known to gradually decrease with aging [10]. In the same line, Ezaki et al observed a gradual reduction in the levels of ST-segment in lead V5 in men as their age increased [11], suggesting a role of low testosterone levels in the age-related differences in the levels of ST-segment.

In our previous studies we found an inverse relation between serum levels of testosterone and biomarkers of atherosclerosis, thus hypogonadism was associated with higher levels of high sensitive C-reactive protein, apolipoprotein B, apolipoprotein B-to-apolipoprotein A-1 ratio [12]. We also demonstrated a link between

Corresponding Author (s): *Babak Rezanezhad, Department of Internal Medicine, Skåne University Hospital, Lund University, Entregatan 7, 22185 Lund, Sweden, Tel: +460733207200, E-mail: babak.rezanezhad_zanjani@med.lu.se*

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testosterone and risk factors for atherosclerosis, thus men with hypogonadism were associated with higher levels of BMI, systolic blood pressure, fasting glucose, and levels of lipoproteins [13]. Herein we aimed to investigate the association between serum levels of testosterone and clinical markers of atherosclerosis, namely parameters of the clinical exercise stress test, based on data from 119 middle-aged men from the general population.

4. Material and Methods

The present study was based on data from 119 men from the general population collected at the Department of Cardiology, Malmo University hospital between 2005 and 2011. Detailed information about the recruitment process was published elsewhere [12].

To be part of the study, the men should not have any physical or psychological diseases, not taking any medications during the last 6 months before the inclusion, and should not be younger than 45 and not older than 60 years at the start of the study.

Each man was asked to deliver a blood sample for analysis of testosterone. Blood samples were collected between 07:00 and 10:00 PM on day one. The day after they delivered the blood samples, each man underwent a clinical stress test at the department of Cardiology.

4.1. Clinical Exercise Stress Test

The exercise stress test was performed starting at 10 W with continuous load increases of 10 W. min-1 with the participant sitting on an electrically braked bicycle ergometer. The test was terminated when limiting symptoms occurred, usually chest pain of a degree 5/10, dyspnoea of 5/10 or at exertional degree of 17/20 using the Borg scales [14]. The test was also terminated if any of the following prespecified conditions occurred: ST-segment depression ≥ 4 mV, fall in blood pressure > 20 mmHg measured once or 10 mmHg measured twice with 1 min intervals or serious arrhythmia. A 12-lead ECG was obtained before and continuously monitored during and for 10 min after finishing the test. Heart rate was measured every minute and systolic blood pressure every third minute. ST-segment depression during the stress test was measured 0·06 s after the J-point. For the present study, the following parameters were recorded: maximal heart rate, maximal systolic blood pressure, maximal diastolic blood pressure, and levels of ST-segment in lead aVF and in lead V5.

4.2. Testosterone Measurements

Plasma samples were stored in the biological bank at -80 °C. Serum testosterone concentrations were measured using Two-step competitive method with Electro Chemi Luminiscence Immunoassay (ECLI) detection technique based on Ruthenium (Ru) derivatives, which has an intra-and interassay coefficient of variation (CV) of 5%, and a reference ragne 5.0–30 nmol/L (Department of Clinical Chemistry, Malmö University Hospital, Malmö, Sweden).

The Institutional Review Board Committee at Lund University of Medical sciences reviewed and approved the design of the study. A written informed consent was obtained from each participant.

5. Statistical Analyses

Statistical analyses were performed using the SPSS software, version 16 (SPSS, Inc; Chicago, IL). The correlations between testosterone and parameters of the clinical exercise stress test were examined with the non-parametric Spearman's rho.

Men were classified into two groups based on serum levels of testosterone: hypogonadal (testosterone ≤12 mmol/L), and eugonadal (testosterone >12 mmol/L), and maximal heart rate, maximal systolic blood pressure, maximal diastolic blood pressure, levels of ST-segment in lead aVF, and levels of ST-segment in lead V5 were compared between groups using non-parametric Mann-Whitney test.

The association between testosterone levels and parameters that showed significant difference between hypogonadal and eugonadal men (maximal systolic blood pressure, and levels of ST-segment in lead V5) were tested in a multivariate regression analysis model adjusted for the age of subjects (46-50, 51-55, 56-60 50 years), BMI (< 25 kg/cm2, ≥ 25 kg/cm2), smoking (past/present, never), alcohol consumption (< 10, 10-20, > 20 cL/week), and family history of CVD. P-values below 0.05 were considered statistically significant.

6. Results

Descriptive statistics of the study population is summarized in (Table 1). A significant negative correlation between testosterone and maximal systolic blood pressure was found ($r = -0.30$, $p = 0.01$). On the other hand, no significant correlations between testosterone and maximal diastolic blood pressure, levels of ST-segment in lead aVF, and levels of ST-segment in lead V5 were found ($p > 0.05$) (Table 2).

Men who were classified as being hypogonadal had significantly higher maximal systolic blood pressure, and more depressed ST-segment levels in lead V5 compared to men who were classified as being eugonadal men (225 mmHg vs. 210 mmHg; $p = 0.01$), (-0.13 mm vs. 0.27 mm; $p = 0.04$), respectively. In contrast, maximal heart rate, maximal diastolic blood pressure, and levels of ST-segment in lead aVF did not differ significantly between groups ($P > 0.05$) (Table 3).

In a multivariate regression analysis test adjusted for the age of subjects, BMI, smoking, alcohol consumption, and family history of CVD; a significant negative association was only found between testosterone and maximal systolic blood pressure ($\beta = -0.829$, $p = 0.04$, 95% CI = -1.636, -0.022) (Table 4).

Table 1: Descriptive statistics of the study population.

Variables	n	Mean (±SD) or n (%)	Median (range)
Age (years):	119		
≤ 46-50		17 (14 %)	-
51-55		33 (28 %)	-
56-60		69 (58 %)	-
BMI (kg/m²):	119		
< 25		42 (35 %)	-
≥ 25		77 (65 %)	-
Smoking:	118		
Never		61 (51 %)	-
Past/current		57 (49 %)	-
Alcohol consumption (Cl/week):	119		
< 10		56 (47 %)	-
Oct-20		41 (34 %)	-
> 20		22 (19 %)	-
Family history of CVD	117		
Yes		30 (25 %)	-
No		87 (75 %)	-
Clinical exercise test	119		
Maximal heart rate (bpm)		155 (±16)	157 (113–181)
Maximal systolic blood pressure (mmHg)		216 (±24)	220 (145–270)
Maximal diastolic blood pressure (mmHg)		91 (±12)	90 (60–130)
ST-segment levels in lead aVF (mm)		-0.24 (±1.65)	-0.50(-2.10–10)
ST-segment levels in lead V5 (mm)		-0.39 (±0.67)	-0.40 (-2.0–1.1)
Testosterone (nmol/L)	113	15.4 (±6.0)	15 (0.6–32)

BMI= body mass index.

Table 2: Correlations coefficients (r) between testosterone levels and maximal heart rate, maximal systolic blood pressure, maximal diastolic blood pressure, levels of ST-segment in lead aVF, and levels of ST-segment in lead V5 during clinical stress test obtained from 119 middle-aged men from the general population.

Variables	Testosterone (nmol/L)	
	r	p
Maximal heart rate (bpm)	0.11	0.3
Maximal systolic blood pressure (mmHg)	-0.3	0.01
Maximal diastolic blood pressure (mmHg)	-0.18	0.09
ST-segment levels in lead aVF (mm)	0.16	0.09
ST-segment levels in lead V5 (mm)	0.09	0.4

Statistical analysis was performed using Spearman's rho test. P-vales < 0.05 are considered statistically significant.

Table 3: Comparison of maximal heart rate, maximal systolic blood pressure, maximal diastolic blood pressure, levels of ST-segment in lead aVF lead, and levels of ST-segment in lead V5 during clinical stress test between hypogonadal (testosterone ≤ 12 nmol/L) and eugonadal (testosterone >12 nmol/L) men.

Variables	Testosterone (nmol/L)		p
	≤ 12 nmol/L (n = 35)	> 12 nmol/L (n = 68)	
Maximal heart rate (bpm)	153 (±11)	156 (±17)	0.2
Maximal systolic blood pressure (mmHg)	225 (25)	210 (23)	0.01
Maximal diastolic blood pressure (mmHg)	95 (11)	90 (12)	0.06
ST-segment levels in lead aVF (mm)	-0.02 (0.81)	0.41 (1.15)	0.09
ST-segment levels in lead V5 (mm)	-0.13 (73)	0.27 (1.02)	0.04

Data are mean (±SD). Statistical analysis was done using Non parametric Mann-Whitney test. P-values less than 0.05 were considered statistically significant.

Table 4: Association between maximal systolic blood pressure & levels of ST-segment in lead V5 during clinical stress test and serum levels of testosterone from 119 middle-aged men.

Variables	Testosterone (nmol/L)			
	β	P	95% CI of β	
			Lower	Upper
Maximal systolic blood pressure (mmHg)	-0.829	0.04	-1.636	-0.022
ST-segment levels in lead V5 (mm)	0.002	0.9	-0.029	0.033

Statistical analysis was performed using a multivariate regression analysis model adjusted for the age of subjects (46-50, 51-55, 56-60 years), BMI (<25, ≥ 25kg/cm2), smoking (past/present, never), alcohol consumption (< 10, 10-20, >20 cL/week), and family history of CVD (yes, no). P-values below 0.05 were considered statistically significant.

7. Discussion

Testosterone levels showed a significant negative correlation with maximal systolic blood pressure. Hypogonadal men had significantly higher maximal systolic pressure, and more depressed levels of ST-segment in lead V5 compared to the eugonadal men. In a multivariate regression analysis test adjusted for the age of subjects, BMI, smoking, alcohol consumption, and family history of CVD, testosterone showed significant negative association only with maximal systolic blood pressure. Our results indicate an inverse relationship between testosterone levels and parameters of clinical exercise stress test suggesting a role of low testosterone levels in the pathogenesis of atherosclerosis.

Normally, the heart rate rises during exercise due to a decrease in parasympathetic and an increase in sympathetic tones, resulting in increased oxygen supply to the vital organs in the body. The maximal heart rate during exercise is influenced mostly by the age of individuals [15]. The hypogonadal and eugonadal men in our study were closely related in age, which can explain our findings of non-significant difference in maximal heart rate between the men in the two groups. In this study, men with low testosterone levels were associated with significantly higher maximal systolic blood pressure compared to those with normal testosterone levels. And it was the only variable showing significant negative association with testosterone levels in our adjusted multivariate regression analysis test. Interestingly, Haider et al observed a significant and steady decrease of systolic blood pressure in 77 hypogonadal men with a history of CVD, who were under long-term testosterone replacement therapy [16]. The suggestive mechanisms behind the negative effect of testosterone on blood pressure are not well understood. However, other researchers believe it to be due to a vasodilatory effect of testosterone on vascular and non-vascular smooth muscle by inhibiting the calcium-dependent elements of vascular contraction [17,18].

In the study by Jaffe, 50 men with known post exercise ST-segment depression of at least 1 mm underwent 3 clinical stress tests; baseline, 4 weeks, and at 8 weeks after receiving either placebo (n = 25) or 200 mg/ml of testosterone cypionate (n = 25). In men who treated with testosterone, the sum of ST-segment depression significantly decreased by 32% at 4 weeks, and by 51% at 8 weeks compared to the placebo group [19]. Moreover, testosterone treatment in hypogonadal men was associated with a significant increase in testosterone levels and in time to 1-mm ST-segment depression compared to placebo [18,20,21]. Furthermore, androgen deprivation therapy in men with prostate cancer significantly lowered ST-segments that closely resembled the ST-segment levels in age-matched female control [11]. The possible mechanisms behind the positive effect of testosterone treatment on ST-segment depression including: increased oxygen carrying capacity of the blood due to an increase in the blood haemoglobin levels [20], direct coronary-relaxing effect [22,23], anti-inflammatory effect associated with immune modulating effect [21]. It has been suggested that an ST-segment depression of 1 mm or greater is a strong predictor of

significant coronary artery diseases, irrespective of other findings at the stress test [24]. It is important to mention that the levels of ST-segment depression in our hypogonadal men was not sufficient lower to have a clinical significance regarding significant coronary artery diseases. However, it suggests that hypogonadism contribute to ECG-changes during the clinical exercise stress test.

Our study has some limitations. The participation rate in this study was only 16%, and one could question whether this group of men represent the general population of middle-aged Swedish men. Since no information was available about the men who chose not to reply to the questionnaires, the characteristics of this group could not be compared to that of the included group of men. We are aware that our study is based on a relatively small sample size compared to other studies, but the statistical and interim analysis revealed striking results in such a small population. We believe, therefore, that the results are still valid and support the hypothesis that there is a relationship between serum levels of testosterone and clinical markers of atherosclerosis in this group of men. Our results have some clinical application. Thus, analysis of testosterone level should be part of the work up of men with abnormal results of clinical stress test in particularly those with increased risk for atherosclerosis.

In conclusions, we documented an inverse association between testosterone levels and clinical stress test parameters, mainly maximal systolic pressure and ST segment levels in V5 lead. These results indicate that low testosterone levels in middle-aged men may be associated with increased cardiovascular risk.

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