PHARMACIA

Pharmacia 71: 1–5
DOI 10.3897/pharmacia.71.e113755

Research Article

Testosterone, estradiol and their ratio in male patients with acute coronary syndrome

Savi Shishkov[1], Kiril Hristozov[1], Atanas Angelov[2], Svetoslava Slavcheva[2], Yana Bocheva[3], Mila Boyadzhieva[1]

1 *Second Department of Internal Diseases, Faculty of Medicine, Medical University of Varna, Varna, Bulgaria*
2 *First Department of Internal Diseases, Faculty of Medicine, Medical University of Varna, Varna, Bulgaria*
3 *Department Clinical Laboratory, Medical University of Varna, Varna, Bulgaria*

Corresponding author: Savi Shishkov (savirshishkov@gmail.com)

Received 8 October 2023 ♦ **Accepted** 22 February 2024 ♦ **Published** 25 March 2024

Citation: Shishkov S, Hristozov K, Angelov A, Slavcheva S, Bocheva Y, Boyadzhieva M (2024) Testosterone, estradiol and their ratio in male patients with acute coronary syndrome. Pharmacia 71: 1–5. https://doi.org/10.3897/pharmacia.71.e113755

Abstract

The role of androgens and estrogens in cardiovascular disease is a subject of ongoing studies. Therefore, we aim to explore the association of testosterone (T), estradiol and their ratio with cardiovascular risk factors and severity of cardiac ischemia in male patients with acute coronary syndrome. (ACS) n = 72 and controls (n = 35) Lower values of both total and free T were found in the ACS group compared to controls (8.97 vs. 10.98 nmol/l, p = 0.001 for total T and 0.189 vs. 0.223 nmol/l, p = 0.006 for free T). Patients with myocardial infarction with ST-elevation had significantly lower T fractions compared to ACS without ST-elevation. The T to estradiol ratio was significantly lower in the ACS group compared to controls and is lowest in those with STEMI. Also, all testosterone fractions – free, bioavailable, and free T, are lower in patients with ACS compared to controls. Based on these observations a conclusion can be drawn that amore estrogenic environment is associated with ST-elevation and correlates with the severity of ACS in male patients.

Keywords

acute coronary syndrome, testosterone, estradiol, ratio, testosterone to estradiol ratio

Introduction

The well-known association of male sex with increased cardiovascular disease is attributed to the androgens, the principal one being testosterone (T) (Kappert et al. 2012). Even so, there is conflicting data on the effect of testosterone on the development of cardiovascular disease (CVD) (Gencer and Mach 2016). On the one hand, testosterone is associated with beneficial effects, i.e., vasodilation and reduction of infarct zone size. On the other hand, adverse effects, i.e., the induction of inflammation and activation of signaling pathways related to apoptosis were also reported (Oskui et al. 2013; Herring et al. 2022). Furthermore, observational studies have shown an association between low endogenous testosterone levels and mortality in coronary heart disease (Araujo et al. 2011).

On the other hand, there is no conclusive evidence of CVD safety with androgen-replacement therapy. Higher cardiovascular risk has been suspected in some of the past trials (Snyder et al. 2018). Newer data provide evidence about safety in terms of cardio-vascular outcomes but suggests that higher incidence of venous thromboembolism or acute kidney injury may be an issue (Lincoff et al. 2023).

In a study Pesonen et al. propose the hypothesis that the decline in T levels during the acute period of acute coronary syndrome (ACS) is an adaptive mechanism providing

better survival. In contrast, a number of investigators present evidence of increased mortality with low baseline T during ACS (Pesonen et al. 2016; Gencer et al. 2021).

Besides androgens, estrogens are also relevant to the cardiovascular system. Their involvement in the pathogenesis of atherosclerotic cardiovascular disease has been suggested (Wu and Von Eckardstein 2003). Therefore, a method allowing the simultaneous consideration of hormones that are assumed to be functionally dependent is increasingly sought. Such an attempt to objectify hormone interactions and balance is sought through hormone ratios, i.e. an index that is viewed as an indicator of the balance between two endocrine systems (Maninger et al. 2009).

In the current study our aim is to explore the association of testosterone, estradiol and their ratio with cardiovascular risk factors and severity of the cardiac ischemia in male patients with acute coronary syndrome.

Materials and methods

Study population and design

Our research was performed as a cross sectional study of male patients with acute coronary syndrome, with or without known CVD (n = 72). Subjects were recruited in the cardiology clinics in "St. Marina" Varna, Bulgaria. Age and BMI matched controls (n = 35) were recruited from the general population. The group ACS consists of patients with myocardial infarction (MI) with ST-elevation (STEMI), Non–ST-elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP) (Thygesen et al. 2018). Mean patients' age was 56.75 (±9.73) years, mean control age was 54.22 (±7.23) years. Exclusion criteria were the presence of decompensated endocrinopathies, cancer, chemo and radiotherapy in the past three months, and testosterone replacement therapy. Chronic exacerbated kidney, pulmonary insufficiency, acute comorbidities not related to the ACS and psychiatric medications were also part of the exclusion criteria. Information on patients' comorbidities was acquired from the hospital database. For the control subject a history of cardiovascular, endocrine, or other systemic chronic disease qualified as exclusion criteria.

Laboratory analyses

Blood samples were drawn in the morning between 8:00 h – 9:00 h for both patients and control subjects. For patients the samples were taken 36 to 48 hours after the onset of the ACS. Free testosterone concentration was calculated based on total testosterone, SHBG and albumin using Vermeulen formula (Vermeulen et al. 1999). Testosterone, estradiol and SHBG is determined using the Siemens IMMULITE 2000 system. The estradiol essay has analytical sensitivity of 55 pmol/L with male reference ranges up to 146 pmol/l. SHBG assay has an analytical sensitivity of 0.02 nmol/Lwth reference ranges for male 10–57 nmol/l. Troponin was measured with the same assay with reportable range between 0.2 to 180 ng/mL Albumin levels were determined by Siemens Advia 1800 system. In the current study low testosterone was defined based as total testosterone less than 9.2 nmol/l or free testosterone less than 0.220 nmol/l (Bhasin et al. 2018; Yeap et al. 2022).

Statistical analysis

Statistical analysis was done using SPSS 26 statistical package. Methods used to compare mean was analysis of variance and parametric analysis – Student's t independent samples (Independent t-test). For variables not meeting the criteria for normal distribution Mann-Whitney non-parametric analysis was applied. The testosterone to estradiol ratio was calculated as total testosterone divided by estradiol both in units nmol/l. Lower values of the aromatization index are coherent with a more estrogenic environment and higher denominator value in mathematical terms. Spearman nonparametric correlation coefficient was used to determine the strength of association between two variables.

Ethical considerations

The ethical commission in Medical University Varna approved the study. All patients provided written informed consent.

Results

Clinical characteristics

In both the patients and the control group age, BMI and smoking did not differ statistically. The control group did not include patients with a history of cardiovascular comorbidities or the intake of medications. Concerning the ACS group mixed dyslipidemia and diabetes type two were the most common comorbidities in 100% and 22.5% respectively (Table 1).

Testosterone in ACS

Among the patient group low total testosterone (<9.2 nmol/l) was present in 52.78% (n = 38) of cases while in the control group the percentage is 29.41% (n = 10). As absolute value in the ACS group mean total T was 8.97 compared to 10.98 nmol/l for controls, the difference between groups is statistically significant (p = 0.001). The same tendency for lower values in the ACS group is present for both free and bioavailable T with 0.189 vs. 0.223 nmol/l (p = 0.006) and 4.14 vs. 5.63 nmol/l (p = 0.001) respectively. (Table 2.) If a criterion for free T less than 0.220 nmol/l is used the rate of hypotestosteronemia for ACS and controls is 65.28% and 45.71% respectively.

Additional subgroup analysis was conducted to determine the differences in androgen levels between patients with ACS with ST-elevation (STEMI) and ACS

Table 1. Baseline characteristics.

Parameter	ACS (N = 72)	Controls (N = 35)	P-value
Age	56.12 ± 9.73 (53.73–58.51)	54.22 ± 7.23 (51.61–56.83)	ns
BMI	28.54 ± 4.37 (27.4–29.62)	28.98 ± 3.52 (27.7–30.25)	ns
Troponin (ng/ml)	58.9 ± 69.2 (42.71–75.22)	n/a	
Smoking	51 (72.9%)	23 (65.7%)	ns
Comorbidities			
Diabetes	N = 16 (22.5%)	n/a	
dyslipidemia	N = 72 (100%)	n/a	
heart insufficiency	8 (11.27%)	n/a	
other atherosclerotic disease	9 (12.85%)	n/a	
Medications use			
ACEi	23 (32.4%)	n/a	
diuretic	16 (22.5%)	n/a	
beta-blocker	29 (40.3%)	n/a	
statin	19 (26.8%)	n/a	
Ca-channel blocker	17 (23.9%)	n/a	

Data is presented as mean ±SD and 95% CI in brackets. Comorbidities and medications are exclusion criteria for control group, therefore are not available. ACS – acute coronary syndrome; STEMI Non–ST-elevation myocardial infarction; UAP – unstable angina pectoris; ACEi – ACE inhibitors; ns – no statistical significance p > 0.05.

Table 2. Mean values of hormone concentration are patients with ACS and controls.

Parameter	ACS (n = 72)	controls (n = 35)	*p*-value
total T (nmol/l)	8.97 ± 4.11 (8.0065–9.9379)	10.98 ± 2.17 (10.16–11.81)	0.001
Estradiol (pmol/l)	185.34 ± 76.04 (167.473–203.208)	163.49 ± 40.08 (148.24–178.73)	0.07
free T (nmol/l)	0.18993 ± 0.09 (0.16878–0.21108)	0.223 ± 0.038 (0.209–0.238)	0.006
bioavailable T (nmol/l)	4.41 ± 2.15 (3.9016–4.9123)	5.63 ± 0.90 (5.29–5.97)	0.001
SHBG (nmol/l)	30.71 ± 10.89 (28.15–33.27)	31.55 ± 10.46 (27.96–35.14)	0.706
T/E	51.7 ± 29.151 (44.850–58.550)	71.71 ± 25.98 (61.83–81.59)	<0.001

Data is given as mean value ±SD and 95% CI in brackets. *P*-values denote significance between subgroups. T – testosterone, T/E – total testosterone to total estradiol ratio, SHBG – sex hormone binding globulin.

without ST-elevation (NSTEMI and UAP). These results are shown in Table 3. All fractions of testosterone were lower in the STEMI subgroup: for total T 8.17 vs. 10.9 nmol/l (p = 0.02); free T 0.176 vs. 0.226 nmol/l (p = 0.03); bioavailable T 4.05 vs 5.36 nmol/l (p = 0.01).

No difference in SHBG levels was established between ACS and controls or between STEMI and non-ST ACS (p = 0.706 and p = 0.876 respectively).

In the ACS group no correlation between BMI and either total T (r_s = -2.05, p = 0.099), bioavailable T (r_s = -0.220, p = 0.076) and free T (r_s = -0.188, p = 0.130) was observed.

Weak negative correlation was established between bioavailable T (r_s = -0.293, p = 0.012) and troponin and between free T and troponin (r_s = -0.266, p = 0.024). Similar was the correlation coefficient for total T and troponin (r_s = -0.217) but this did not reach statistical significance (p = 0.067).

Table 3. Mean concentrations of hormones and T/E ratio in ACS with or without ST-elevation.

Parameter	ACS with ST-elevation (n = 52)	ACS without ST-elevation (n = 20)	*p*-value
Testosterone (nmol/l)	8.1674 ± 3.8 (7.12–9.22)	10.94 ± 4.13 (8.89–12.99)	**0.024**
Estradiol (pmol/l)	185.87 ± 81.56 (163.39–208.35)	182.94 ± 61.47 152.37–213.51	0.833
free T (nmol/l)	0.176 ± 0.09 (0.151–0.200)	0.226 ± 0.078 (0.187–0.265)	**0.034**
bioavailable T (nmol/l)	4.05 ± 2.2 (3.44–4.65)	5.36 ± 1.72 (4.51–6.22)	**0.013**
SHBG (nmol/l)	30.65 ± 10.8 (27.651–33.63)	30.183 ± 11.3 (24.56–35.81)	**0.876**
T/E	46.91 ± 28.96 (38.93–54.89)	64.18 ± 26.41 (51.052–77.314)	**0.014**

ACS without ST-elevation includes NSTEMI and UAP. Data is given as mean value ±SD and 95% CI. *P*-values denote significance between subgroups. T – testosterone, T/E – total testosterone to total estradiol ratio, SHBG – sex hormone binding globulin.

Estradiol and estradiol to testosterone ratio

Concerning estradiol concentration, no statistically significant difference was found between ACS and control groups or between STEMI and ACS without ST-elevation subgroups.

The testosterone to estradiol ratio, on the other hand, was significantly lower in the ACS group compared to the control subjects. The patient group had a mean value of 51.7 compared to 71.7 in the controls. (p<0.001). (Table 2) The same tendency is valid when comparing ACS with ST-elevation to ACS without ST-elevation with lower value in the STEMI subgroup (49.9 vs. 64.1, p = 0.014).

In the ACS group higher BMI was associated with higher T/E ratio. (r_s = -0.277, p = 0.024).

Discussion

The important findings of this study are that middle-aged male patients with ACS have lower aromatization index compared to age and BMI matched controls. Bioavailable and free, but not total testosterone concentrations correlate negatively with troponin values and all T fractions are lowest in the STEMI subgroup compared to ACS without ST-elevation (NSTEMI and UAP).

We determined that the ACS group is not homogenous in terms of T levels. As evident from Table 2, patients with ST-elevation MI had the lowest levels of T. Similar results concerning T levels and the type of ACS subtype are described by Hu et al. (Hu et al. 2011). An explanation can be found in the severity of the acute coronary syndrome. Here we can assume the ST elevation as a sign of a bigger necrotic section of the myocardium. It is also associated with worse short-term prognosis (Khan et al. 2020).

Despite the sensitivity of troponin assay up to 180 ng/ml the negative correlations presented allows us to think

that free T and bioavailable T better reflect the ACS severity compared to total T. Support for this claim can be found in the work of other researchers (Sapin et al. 1991; Hu et al. 2011; Gencer et al. 2021). The average total T level in the ACS group is 8.97 nmol/l. This value is in the gray zone between hypo- and eugonadism where free testosterone calculation is required. In the present research this is verified by the increase of hypogonadal subjects using the free testosterone measurement. Therefore, the increase in low T incidence using free T, rather than total T support the idea that the biologically active T fraction (free T) better reflects the functional state of the gonadal system in ACS.

The rationale behind this can be found in the fact that most of the T is albumin and SHBG bound, and the free fraction can be most susceptible to rapid changes. The changes in bioavailable and free T cannot be attributed to SHBG alterations by the ACS as there is no significant difference in the protein concentration between patients and controls in our study. No changes in SHBG during acute illness have been described in other studies.

Contradictory is the issue of T concentrations with stable angina pectoris. Some investigators find correlation (Phillips et al. 1994; Rosano et al. 2007) and others not (Semerdzhieva 2015).

There is no correlation between BMI and any of the T fractions in the ACS group and STEMI subgroup. We hypothesize that the lack of this association with BMI, is due to the decline in T that occurred over the course of the ACS (Wang et al. 1978; Wang et al. 2018).

Concerning total testosterone to total estradiol (T/E) ratio a difference was found when comparing STEMI with non-ST-elevation ACS (NSTEMI and UAP) – with a lower aromatization index in STEMI. Because no statistically significant difference in total estradiol or free estradiol levels was found between the ST-elevation ACS (STEMI) and non-ST-elevation ACS (NSTEMI+UAP) groups, we assumed that the differences in T/E between the two groups were primarily on account of a relative change in E versus T and a change in the absolute value of T. On the basis of these observations, we can assume an increase in aromatization in more severe myocardial injury, leading to a decrease in the T/E ratio. Another possibility is that the relatively greater decrease in T in STEMI is responsible for the shift in the ratio in favor of E. It is possible that both causes contribute in varying degrees to the shift in the T/E ratio.

Estrogens have beneficial effects on the neovascularization of ischemic tissues. They have been shown to play a role in the recruitment of endothelial progenitor cells, and improve the process of myocardial recovery after ischemia/reperfusion (Hamada et al. 2006; Yuan et al. 2018). In view of these effects, increasing aromatization makes physiological sense. In a 2006 study, Spratt et al. provided evidence of an increase in peripheral aromatization of androgens in the setting of acute systemic disease (Spratt et al. 2006). In this case, the study was done in patients undergoing aorto-coronary bypass grafting. In that study a decline in T levels, similar to our cohort, was described.

Our observations, supported by the literature review, suggest that the decreased T/E ratio may be a specific response to acute physiological stress (the ACS) rather than a casual observation. However, the cause of the increased aromatization could not be determined with our available data. No difference in SHBG was established, therefore we can conclude that differences in free and bioavailable T are solely due to changes in total T concentrations.

Conclusion

In conclusion, our study demonstrates a significant correlation between the levels of testosterone and estradiol to testosterone ratio, and the severity of ACS in male patients. These results underscore the pivotal role of sex hormones in the pathophysiology of acute coronary syndrome. Potentially sex measurement of androgens may be utilized in the risk stratification and management of male patients with this condition. Further research is imperative to elucidate the mechanisms driving these associations and to assess the clinical relevance of sex hormone measurements in acute coronary syndrome management.

Funding disclosures

The research is supported by “Science fund” project No. 19017.

Author contributions

All authors listed have made substantial, direct, and intellectual contribution to the work, and approved it for publication.

Ethics considerations

All subjects have given their written informed consent before taking part in the study. No minors or incapacitated subjects were included. The design of the study is approved by the institution’s ethics committee.

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