TOTAL TESTOSTERONE LEVELS IN MEN WITH ACUTE CORONARY SYNDROME

Savi Shishkov[1], Kiril Hristozov[1], Mila Boyadzhieva[1], Svetoslava Slavcheva[2]

[1]Second Department of Internal Diseases, Faculty of Medicine, Medical University of Varna
[2]First Department of Internal Medicine, Faculty of Medicine, Medical University of Varna

ABSTRACT

INTRODUCTION: When acute systemic illness occurs due to stress, dysfunction of some of the endocrine axes often occurs. However, the specific mechanisms have not been elucidated. Acute coronary syndrome (ACS) is one model of acute physiological stress in which the hypothalamic-pituitary-gonadal axis is also affected.

AIM: The aim of this study was to investigate the difference in total testosterone (T) levels in men with ACS compared to controls.

RESULTS: In 72 patients with ACS, the level of total testosterone was studied until the 48th hour after its onset. Thirty-five controls were also included in the study. After statistical processing of the data, we found that total T in the ACS group was statistically significantly lower compared to the controls group (t=-3.20, p=0.001) There was also a statistically significant difference in the incidence of hypotestosteronemia between the two groups with 52.8% (n=38) in the ACS group and 28.6% (n=10) in the control group. ($\chi^2(1)=4.705$, p=.030).

CONCLUSION: Low levels of total T are common in patients with ACS. However, T values in the acute period after the onset of ACS should be interpreted with caution because of the changes occurring in the regulation of gonadal function.

Keywords: *acute coronary syndrome, testosterone, men, cardiovascular*

INTRODUCTION

The relationship between coronary artery disease and gonadal function is highly relevant due to the high incidence and social significance of cardiovascular pathology. The transient disturbances induced by acute systemic illnesses in the hypothalamic-pituitary-gonadal (HPG) axis are known, yet the long-term clinical significance of these facts remains unclear. Gonadal dysfunction associated with tissue resistance to luteinizing hormone or altered affinity for sex hormone-binding globulin has also been described in men after acute coronary syndrome (ACS) (1). The incidence of erectile dysfunction is also increased (2). It remains unclear whether this transient hypogonadism has an adaptive or maladaptive role.

Address for correspondence:
Savi Shishkov
Faculty of Medicine
Medical University of Varna
55 Marin Drinov St
9002 Varna
e-mail: savirshishkov@gmail.com

Received: November 7, 2022
Accepted: December 10, 2022

This issue is complicated by the unclear incidence of hypogonadism preceding acute illness.

Observational studies have shown that low levels of testosterone are common in men with ACS, especially in those with glucose abnormalities, further demonstrating the many confounders influencing the testosterone levels (3).

There are a number of publications in the literature that provide evidence of lower total, free, and bioavailable testosterone in the early days after ACS (4). Wang et al. (5) first found a decline in testosterone (T) levels in the acute period of myocardial infarction, with the lowest levels on the fourth day. Other authors have attributed the decline in total, bioavailable, and free T levels to dysfunction in the HPG axis under conditions of acute physiological stress (6). The cited studies also demonstrate a recovery of T levels in the recovery period in the following weeks and months. However, studies evaluating T levels after ACS cannot answer the question of whether hypotestosteronemia results from the incident or precedes it.

The question of the clinical and prognostic value of the mentioned observations (of lower T in ACS) is also relevant. The issue is controversial, different conclusion are reached by different investigators. Lower free T levels are associated with worse response to revascularization and lower incidence of ST-elevation recovery (7). Lower T levels (<10 nmol/L) were also an independent predictor of short-term mortality (8). Another prospective study by Gencer et al. (9) found a higher risk of death one year after the onset of ACS in men with the lowest baseline T (0–9.3 nmol/L) compared with those with the highest T (14.4–40 nmol/L) in the study population. Despite this observation, the addition of T to the GRACE scoring did not improve its predictive value. Lower T values were also associated with a riskier patient profile. Testosterone levels in other studies in middle-aged men have also been assessed as a marker of the severity of coronary artery disease (10). Contrary to that Pesonen et al. predict better survival with lower T levels after ACS (11).

AIM

The aim of the present study was to investigate the difference in total T levels in men with ACS compared to controls.

PATIENTS AND METHODS

The patients were selected from among the hospitalized men in the cardiology clinics mainly at the St. Marina University Hospital in Varna. A total of 72 patients with ACS at a mean age of 56.12 (age range 36–77 years) and 35 controls at a mean age of 54.22 years (age range 44–68 years) were included. The group of controls was recruited mainly among outpatients. In the control group, blood was drawn between 8 and 10 AM, 36–48 h after the onset of myocardial ischemia. Inclusion criteria for the patient group were the presence of ACS—acute myocardial infarction with or without ST elevation, or hospitalization for unstable angina pectoris (12).

Exclusion criteria were the presence of uncompensated endocrinopathies, including a history of hypogonadism, intake of psychotropic medications, anabolic steroids, hormone therapy in or intake of glucocorticoids in the last 6 months, the presence of decompensated organ insufficiency, concomitant acute illness and recent surgery. For the control group, history of cardiovascular disease (arterial hypertension, ischemic heart disease) was an additional exclusion criterion.

In defining the lower limit of T in the present study, we used a criterion based on recommendations for good clinical practice of the Bulgarian Society of Endocrinology and the Endocrine Society (13,14). A value of 9.2 nmol/L was considered the lower limit of normal

Data analysis was performed using SPSS version 19. Parametric analysis and Student's t-criterion were used to compare the means of two independent samples (Independent t-Test) with normal distribution. For indicators that lacked a normal distribution, a non-parametric Mann-Whitney analysis was used to compare medians.

RESULTS

In the ACS group, the mean T value was 8.97 nmol/L with a standard deviation of 4.11 nmol/L. In the control group, the mean was 11.1 nmol/L with a standard deviation of 2.38 nmol/L. When comparing the hormonal values between the two groups, a statistically significant difference was found in terms of T levels at the expense of a higher value in the control group (t=-3.20, p=0.001) (Fig. 1.) In the group of patients with ACS, 52.8% (n = 38) had a total T val-

ue below the lower limit of 9.2 nmol/L. In the control group, 28.6% (n = 10) had a total T value below the lower limit of normal. In view of these values, the difference in hypotestosteronemia between the two groups was statistically significant ($\chi 2(1)=4.705$, p=.030) (Fig. 2.) Given the lack of normal distribution for the body mass index and age parameters, a nonparametric method was used to compare Mann-Whitney medians. The differences described between the two study groups were against a background of similar mean age (U=1056.5 p=0.176) and body mass index (U=960.5 p=0.469).

DISCUSSION

After a detailed study of T, some differences were found between the cases and controls. Our study showed that total T was lower in the ACS group compared to controls, a higher incidence of hypogonadism was also found with similar age and body mass index.

Obesity and older age are associated with lower levels of total T. In our study, there was no difference in these indicators between the two groups. This allows us to rule out the influence of these well-established confounders on T levels and to assess the effect of acute cardiac ischemia. Against this background, we found a statistically significant difference between the number of patients with low T levels in the two groups. For this purpose, we used a threshold value of 9.2 nmol/L for T. These values were adopted for the general population, but in this case we studied patients with a mean age of 56.3 yrs. This is

Table 1. The table shows the means of age, body mass index, and T levels with standard deviation and 95% confidence interval.

		ACS (n = 72)	Controls (n = 35)	Statistical Significance
Age	mean ± SD (95% CI)	56.12 ± 9.73 53.73–58.51	54.22 ± 7.23 51.61–56.83	U = 1056.5 p = 0.176
Body mass index	mean ± SD (95% CI)	28.54 ± 4.37 (27.47–29.62)	28.98 ± 3.52 (27.7–30.25)	U = 960.5 p = 0.469
Testosterone	mean ± SD (95% CI)	8.97 ± 4.11 8.01–9.94	11.1 ± 2.38 10.26–11.93	**t = -3.20** **p = 0.001**

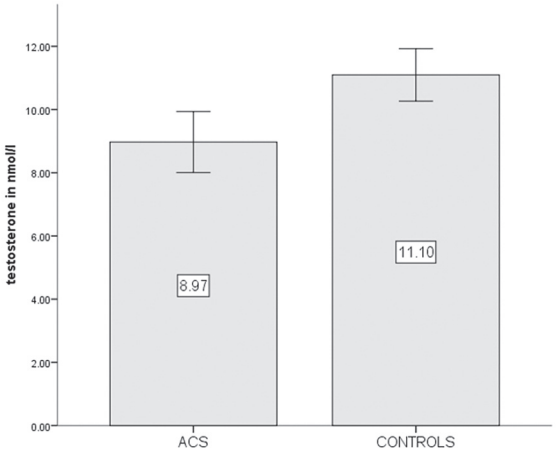

Fig. 1. The graph shows the mean T values in the ACS group (left) and the control group (right). The labels in the columns indicate the mean value for each study group.

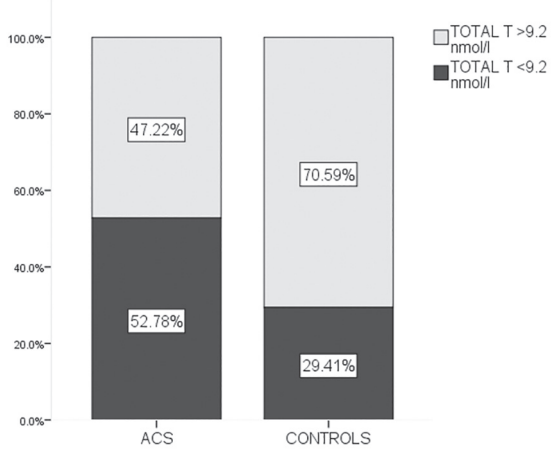

Fig. 2. Distribution of patients with hypotestosteronemia. The dark part of the columns is the percentage of patients with low T (< 9.2 nmol/L), whereas the light grey part is the percentage of patients with T within the reference range (> 9.2 nmol/L).

the age at which late onset hypogonadism is expected leading to physiological decline in T levels, further complicated by diseases, environmental factors, and other hormonal systems.

Other studies have examined differences between patients with stable ACS and controls, demonstrating a correlation between the severity of coronary ischemic pathology on T levels (15,16). In the cited studies, severity was estimated as the number of affected branches and by a summation of angiographic indices. In a Bulgarian study by Semerdzhieva, on the other hand, no association was found between the value of T with troponin levels or with SYNTAX score (17).

Alterations in hypothalamic regulation in severe systemic disease are likely to underlie the dynamic changes in T levels observed in the present study (18). In a prospective study by Pugh et al. both total and bioavailable T were found to be transiently suppressed during the first 24 h after acute myocardial infarction (6). The authors proposed the hypothesis that this sharp decline in T levels after the onset of the incident was due to a disruption of the HPG axis. Suppression of the HPG axis leads to lower T levels via a decrease in luteinizing hormone (LH). In addition to replicating the transient results of other investigators demonstrated an increase in serum T at one-year follow-up (11). The presence of insulin resistance, obesity, and diabetes mellitus type 2 suggests a more vulnerable LH axis resulting in more difficult adaptation to acute stress. Leydig cell function is affected by inflammatory cytokines and local growth factors, there is also the presence of insulin receptors. These facts and other experimental studies demonstrating the relationship between insulin resistance and Leydig cell response to HPG axis are consistent with the observation that insulin resistance increases in the course of ACS (19).

In view of these studies, it can be assumed that the decrease in T is due to a decrease in LH secretion, a decrease in Leydig cell sensitivity to LH, or a combination of these mechanisms. Our results of T decrease in the acute period of ACS support these hypotheses.

CONCLUSION

We found lower T levels in the acute period after ACS, a fact also reported in other cross-sectional studies. We attribute the decline in T to the physiological stress induced by the acute cardiovascular event, by pathophysiological mechanisms that are not fully understood. The trend of increasing T over time demonstrated by other investigators supports this hypothesis. These changes mean that T values in the acute period after the onset of ACS should be interpreted carefully and are subject to follow-up.

REFERENCES

1. Corona G, Goulis DG, Huhtaniemi I, Zitzmann M, Toppari J, Forti G, et al. European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males: Endorsing organization: European Society of Endocrinology. Andrology. 2020;8(5):970-987. doi: 10.1111/andr.12770.
2. Karabay E, Karsiyakali N, Cinier G, Zeren G, Duvar S, Simsek B, et al. Change in frequency and predictors of erectile dysfunction with changes in the international index of erectile function-erectile function domain score in patients with ST-elevation myocardial infarction: a prospective, longitudinal study. J Sex Med. 2020;17(6):1101-8. doi: 10.1016/j.jsxm.2020.03.002.
3. Wang A, Arver S, Flanagan J, Gyberg V, Näsman P, Ritsinger V, et al. Dynamics of testosterone levels in patients with newly detected glucose abnormalities and acute myocardial infarction. Diab Vasc Dis Res. 2018;15(6):511-8. doi: 10.1177/1479164118802543.
4. Niccoli G, Milardi D, D'Amario D, Fracassi F, Grande G, Panico RA, et al. Hypotestosteronemia is frequent in ST-elevation myocardial infarction patients and is associated with coronary microvascular obstruction. Eur J Prev Cardiol. 2015;22(7):855-63. doi: 10.1177/2047487314533084.
5. Wang C, Chan V, Tse TF, Yeung RT. Effect of acute myocardial infarction on pituitary-testicular function. Clin Endocrinol (Oxf). 1978;9(3):249-53. doi: 10.1111/j.1365-2265.1978.tb02207.x.
6. Pugh PJ, Channer KS, Parry H, Downes T, Jone TH. Bio-available testosterone levels fall acutely following myocardial infarction in men: association with fibrinolytic factors. Endocr Res. 2002;28(3):161-73. doi: 10.1081/erc-120015055.
7. Separham A, Ghaffari S, Sohrabi B, Aslanabadi N, Hadavi Bavil M, Lotfollahi H. Association of admission testosterone level with ST-segment resolution in male patients with ST-segment elevation

myocardial infarction undergoing primary percutaneous coronary intervention. Basic Clin Androl. 2017;27:14. doi: 10.1186/s12610-017-0058-7.

8. Militaru C, Donoiu I, Dracea O, Ionescu DD. Serum testosterone and short-term mortality in men with acute myocardial infarction. Cardiol J. 2010;17(3):249-53.

9. Gencer B, Vuilleumier N, Nanchen D, Collet TH, Klingenberg R, Räber L, et al. Prognostic value of total testosterone levels in patients with acute coronary syndromes. Eur J Prev Cardiol. 2021;28(2):235–42. doi: 10.1177/2047487319853343.

10. Gururani K, Jose J, George PV. Testosterone as a marker of coronary artery disease severity in middle aged males. Indian Heart J. 2016;68 Suppl 3(Suppl 3):S16-S20. doi: 10.1016/j.ihj.2016.07.002.

11. Pesonen E, Pussinen P, Huhtaniemi I. Adaptation to acute coronary syndrome-induced stress with lowering of testosterone: a possible survival factor. Eur J Endocrinol. 2016;174(4):481-9. doi: 10.1530/EJE-15-0757.

12. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018;72(18):2231-64. doi: 10.1016/j.jacc.2018.08.1038.

13. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, Snyder PJ, Swerdloff RS, Wu FC, Yialamas MA. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103(5):1715-44. doi: 10.1210/jc.2018-00229.

14. Bulgarian society of endocrinology. Recommendations for good clinical practice in gonadal diseases. Sofia; 2019. (in Bulgarian).

15. Rosano GM, Sheiban I, Massaro R, Pagnotta P, Marazzi G, Vitale C, et al. Low testosterone levels are associated with coronary artery disease in male patients with angina. Int J Impot Res. 2007;19(2):176-82. doi: 10.1038/sj.ijir.3901504.

16. Phillips GB, Pinkernell BH, Jing TY. The association of hypotestosteronemia with coronary artery disease in men. Arterioscler Thromb. 1994;14(5):701-6. doi: 10.1161/01.atv.14.5.701.

17. Semerdzhieva, N. Gender determined characteristics of acute coronary syndromes: role of steroid hormones, oxidative stress and inflammation. Medical University Sofia; 2015. (in Bulgarian).

18. Langouche L, van den Berghe G. Chapter 8: Hypothalamic–pituitary hormones during critical illness: a dynamic neuroendocrine response. In: Fliers E, Korbonits M, Romijn JA, editors. Handbook of clinical neurology. Vol. 124. Elsevier; 2014. pp. 115–26.

19. Pitteloud N, Hardin M, Dwyer AA, Valassi E, Yialamas M, Elahi D, et al. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. J Clin Endocrinol Metab. 2005;90(5):2636-41. doi: 10.1210/jc.2004-2190.