

Fluctuations of testosterone in acute coronary syndrome

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Abstract

Objective: Fluctuations of serum testosterone after acute coronary syndrome (ACS) are infrequently reported. This study was done to determine the optimal time point for blood sampling for testosterone levels after ACS and to observe the trend of serial estimates of testosterone up to 12 weeks (84 days) following the acute event.

Methods: Eight patients with ACS; five with ST-segment-elevated-myocardial infarction (STEMI) and three with unstable angina (UA) were included. Five blood samples were taken; on admission (day one), day three, day 24 and day 84 (12 weeks) later. Serum total testosterone (TT) was estimated by radioimmunoassay.

Results: Mean age was 53±5 years. Mean serum TT level on admission (day one) was 3.60±1.74 ng/mL and on day three, it was 3.98±2.04 ng/mL. The values rose to 5.09±2.24 ng/mL on day five and peaked to 6.17±2.98 ng/mL at 24 days after. Thereafter, the TT levels declined to a mean level of 4.14±2.06 ng/mL by 12 weeks, similar to that observed in the first three days after the acute episode. No significant difference was observed between the mean TT levels on admission, day three and at day 84 ($p = 0.407$, $p = 0.628$).

Conclusion: Serum testosterone fluctuates after ACS. The optimal time to obtain blood for total testosterone level that represents baseline appears to be within the first three days from the onset of the event.

Key words: testosterone; acute stress response; acute coronary syndrome

Introduction

Evidence is accumulating that sex hormones play an important role in the pathogenesis of coronary heart disease. It is found that the men with coronary artery disease have relatively low levels of testosterone and testosterone replacement therapy improves the ischemic threshold in men with angina (1-3). There is a suggestion that checking the level of testosterone in such patients and initiating appropriate replacement may improve the cardio-vascular outcome of these patients.

It is evident that there are fluctuations of total testosterone (TT) level with acute stress caused by acute coronary syndrome (ACS). Several studies have demonstrated that TT levels either fall following acute myocardial infarction, (4, 5, 6, 8, 13) or are lower in patients with a new myocardial infarction (MI) than in old MI and normal controls with normal coronary angiograms (8-9). Some studies found a rise in TT levels during the early days after a MI (7, 10).

Therefore, there is conflicting data on the optimal time to obtain blood samples that would reflect the basal level of testosterone in patients presenting with the acute coronary syndrome. Our study was aimed to determine the optimal point for blood sampling, after ACS for serum TT and to observe the trend of TT up to 12 weeks after the acute event.

Materials and methods

This research was conducted as a part of a larger study investigating the association of total testosterone with coronary artery disease and its severity in men. The ethical clearance was obtained from the Ethical Review Committee of Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka. The protocol for this study was approved by the authorities of Teaching Hospital, Karapitya, Galle, Sri Lanka. Informed written consent was obtained from all participants of the study. Study subjects included were male patients admitted to the Emergency Treatment Unit and the Coronary Care Unit with acute coronary syndrome.

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Diagnosis was made on the basis of typical history and electrocardiographic changes and all recruited patients fulfilled the American College of Cardiology/American Heart Association criteria for acute coronary syndrome (11-12).

Consecutive male patients in the age range of 30-73 years were included within a period of three months. During the baseline interview on discharge from the hospital, information was gathered using an interviewer-administered questionnaire. Height and weight were also recorded. The hospital stay of the patient varied from three to five days.

The level of serum total testosterone was estimated in eight male patients with ACS, which included five patients with ST-segment-elevated-myocardial infarction and three patients with unstable angina. Three samples of blood were collected during the hospital stay; first sample on admission (day one), second sample on day three and a third sample on day five after admission. Following discharge from the hospital, two further samples were obtained at 24 days and 84 days (12 weeks) after the acute ischaemic episode.

Patients who were admitted in the morning hours were enrolled (before 1000 hours) to overcome the effect of diurnal variation of serum testosterone. The 'on admission' sample was obtained at a mean of 8.8 hours from the onset of symptoms. Blood samples (5ml) were drawn by venipuncture and serum was separated by centrifugation and stored at -70°C until assayed.

Total testosterone was measured by radioimmunoassay kit (IMMUNOTECH SAS – A Beckman Coulter Company, France). The analytical range of the test kit was 0.025-20 ng/mL, and intra-assay and inter-assay coefficients of variation were less than 15%. Total serum cholesterol and plasma glucose were measured by enzyme-based colorimetric methods using commercially available test kits (PorDia International UAE).

Data was analyzed using Minitab software (version 15 for Windows). Raw data was inspected for normality and presented as mean±SD. Testosterone levels at different time intervals were analyzed by paired t-test and ANOVA as appropriate. Statistical significance was accepted when p≤0.05.

Results

Out of the 12 patients who were recruited, one died of recurrent myocardial infarction before the final sample was obtained and three patients defaulted follow up. The data of eight patients are presented. Basic characteristics of the patients are shown in Table 1.

Table1. Characteristics of subjects admitted with acute coronary syndrome

Subjects	Patients (n = 08)
Age (yrs)	53 ± 5
Body mass index (kgm ⁻²)	21 ± 3
Total cholesterol (mmol/l)	4.9 ± 0.6
Fasting blood sugar (mmol/l)	5.8 ± 1.9
Systolic blood pressure on admission (mmHg)	147 ± 20
Diastolic blood pressure on admission (mmHg)	90.7 ± 17
Ejection fraction on 2DEcho	52.5 ± 0.1%
Pulse rate on admission (beats/min)	73 ± 19
Number of current smokers	5 (62.5%)
Diabetes mellitus	2 (25%)
Hypertension	3 (37.5%)

Mean serum total testosterone concentration on admission and on day three were 3.60±1.74 ng/mL, 3.98±2.04 ng/mL respectively and a significant difference was not observed between them (p=0.476) values. Thereafter, the concentration rose to 5.09±2.24 ng/mL on day five and peaked to a level of 6.17±2.98 ng/mL at 24 days after. The concentration decline thereafter to 4.14±2.06 ng/mL at 84 days, similar to values observed from 'on admission' to the day after the acute episode. Fluctuations of mean serum total testosterone concentration at different time intervals are demonstrated in Figure 1.

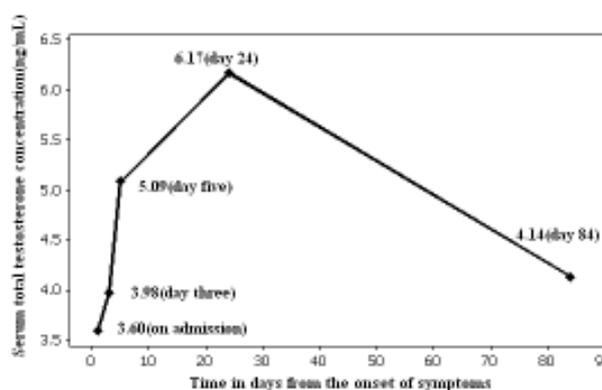


Figure 1. Changes of total testosterone concentration following an event of ACS.

Figure 1: The testosterone concentration on admission (3.60 ± 1.74 ng/mL), day three (3.98 ± 2.04 ng/mL) and on day 84 (4.14 ± 2.06 ng/mL) were not significantly different.

The highest concentration was achieved on day 24 (6.17 ± 2.98 ng/mL) and was significantly different from the concentration (3.60 ± 1.74 ng/mL vs 6.17 ± 2.98 ng/mL, $p = 0.029$), day three concentration (3.98 ± 2.04 ng/mL vs 6.17 ± 2.98 ng/mL, $p = 0.005$) and the day 84 (4.14 ± 2.06 ng/mL vs 6.17 ± 2.98 ng/mL, $p = 0.001$) concentration.

It was noted that no significant difference was observed between the mean TT concentration on admission vs. on day 84 (3.60 ± 1.74 ng/mL vs 4.14 ± 2.06 ng/mL, $p = 0.407$) day vs. day 84 (3.98 ± 2.04 ng/mL vs 4.14 ± 2.06 ng/mL, $p = 0.628$) concentration.

Discussion

Our study demonstrated that serum testosterone fluctuates after an episode of acute coronary syndrome with the concentration rising and peaking on day 24 before decreasing towards the concentrations seen during the first three days after the ACS event.

Fluctuations of serum testosterone after acute myocardial infarction have been reported, with some were rising while others were falling after the acute event. Yet, the direction of fluctuation of serum testosterone after ACS is unclear. Sapin et al. demonstrated a rapid reduction of the total testosterone and free testosterone levels after an acute myocardial infarction (minimum at day one) and then a gradual rise in testosterone levels till day 21(7). Markova et al in a study of 50 patients with acute myocardial infarction also revealed a rise in total testosterone concentration during the acute phase of the illness compared to stable ischaemic heart disease patients (10). The findings of these two studies are in line with our study in which the lowest level was observed on admission (day one) and then rose till day 24. Our study differs from the others, where we studied the TT level until day 84 (12 weeks) from the event; when the effect of acute response would very likely have settled, giving a more accurate picture of the variation of the testosterone.

Tripathi et al reported that following acute myocardial infarctions, the lowest levels of testosterone occur on the day of admission and remains unchanged on fifth and tenth day as compared to controls (8). Mohamad et al. reported significantly lower levels of TT in patients with acute MI than in patients having old MI and healthy controls with normal coronary angiograms (9). These two studies are also in congruence with our study in that they have observed minimum level of TT on day one.

There are several studies that have reported a transient reduction of the serum testosterone concen-

tration following myocardial infarction (4-7). Wang et al reported reduction of testosterone level to the lowest by day four, which was accompanied by a compensatory rise in luteinizing hormone (LH) (4). Geisthovel et al. in their study reported a rapid decrease in total testosterone concentration in the first 11 hours from admission and the free testosterone fraction showed no significant change in the concentration (5). Ruhlmann et al has observed reduction in testosterone concentration in the early phase of acute myocardial infarction (6). Pugh et al showed a fall in both TT and bioavailable testosterone following MI, where the lowest levels were seen on day two (13). The time interval of blood sampling and point at which the lowest testosterone concentrations occurred varied among different studies. Therefore, the point at which the serum testosterone become lowest, highest and stabilized are not consistent according to the findings of these studies.

Mechanism for the fluctuation of serum testosterone in the presence of an episode of acute coronary syndrome is still unclear. A fall in TT and bioavailable testosterone could be related to testicular dysregulation with possible effects at both testicular and pituitary level. Except for one study where a compensatory rise in LH was observed (4), the fall in testosterone was not accompanied by a reduction or compensatory rise of pituitary gonadotrophins (13). It is evident that many stressors decrease LH by inhibiting luteinizing hormone releasing hormone (LHRH) synthesis and release from the hypothalamus and consequent reduction of TT level (14). However it is a well known fact that the suppression of gonads during stress is not always a result of pituitary dysfunction, but could also be caused by a decreased sensitivity of testicles to LH (15). Geisthovel et al suggested that the reduction of serum testosterone was due to generalized impaired perfusion following myocardial infarction (5). There are other studies supporting the hypothesis that during stressful events, the blood level of testosterone is reduced due to the reduced blood flow to the testicles (16). It is also possible that the reduction of testosterone is due to the inhibitory action of glucocorticoids (cortisol) secreted during the acute stress (5,17). The action of stress could lead to the initiation of oxidative stress within the testicles that inhibits steroidogenesis in gonads (18).

Contradictory to the mechanisms that describe the fall in testosterone, the rise in testosterone is thought to be due to catecholamine release during an acute response which activates the secretion of testosterone during stress by stimulating the production of GnRH (gonadotropin releasing hormone) and LH (19-20). In animal studies, the elevation of testosterone levels during stressful events was due to a special vasodilatory effect of catecholamines in dominant rats leading to a rise in the blood supply to the testicles inducing the testosterone secretion (21). In spite of the conflicting pattern of LH and testosterone secretion, the temporary elevation of testosterone

concentration in the blood in the initial phase of stress, with relatively stable LH levels, could be due to the increased sensitivity of testicles to the circulating LH. This increase in sensitivity is a result of the activation of the sympathetic nervous system leading to a norepinephrine type of response, which has a greater affinity for α -adrenoreceptors. Therefore, it has the potential to promote steroidogenesis in gonads leading to a higher testosterone level (22). One limitation of our study is that counter-regulatory hormones (LH, Cortisol, Adrenocorticotropic hormone etc.) were not measured concurrently. Therefore it is difficult to comment on the mechanisms based on the findings of our study.

Conclusion

Total serum testosterone fluctuates after ACS. The optimal time to obtain blood sample that reflect the baseline total testosterone level in a patient presenting with ACS appears to be within first three days from the onset of ACS event. If this time window is missed, blood sampling for testosterone should be delayed until 12 weeks to assess baseline levels.

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