International Journal of Bioassays
ISSN: 2278-778X
CODEN: IJBNHY
OPEN ACCESS

Original Research Article

RELATIONSHIP BETWEEN SERUM TESTOSTERONE LEVELS AND SHORT TERM MORTALITY IN MEN WITH ACUTE MYOCARDIAL INFARCTION

Sumit Kumar[1*], BS Bal[2], Ravinder Garg[1], Manjit Rai[2], Suraj Kumar[3] and Kirti[4]

[1]Department of Medicine, GGS Medical College & Hospital, Faridkot, Punjab, India.
[2]Department of Medicine, Government Medical College, Amritsar, Punjab, India.
[3]Department of Cardiology, Hero DMC Heart Institute, Ludhiana, Punjab, India.
[4]Department Biochemistry, GGS Medical College, Faridkot, Punjab, India.

Received for publication: September 29, 2014; **Accepted:** October 18, 2014

Abstract: Large prospective studies have not been able to confirm the significant and independent association between endogenous testosterone levels and coronary events in men or women. Still a few small studies have shown inverse correlation between endogenous testosterone level with general and cardiovascular mortality.100 men with first attack of acute myocardial infarction (AMI) were assessed for relationship between serum testosterone levels within first 24 hours and short term (30 days) mortality. The mean age was 59.13±9.6. Out of 100 cases, STEMI was present in 70%, diabetes in 44%, hypertension in 48% and 33% were smokers. At the time of admission, serum free testosterone, hs-CRP, lipid profile and left ventricular ejection fraction were assessed. All cases were analyzed for 30 days mortality. The mean level of serum testosterone was 4.185±1.46ng/ml. There were 77% survivors and 33% non survivors at the end of 30 days follow up. All the non survivors had testosterone levels <3.5ng/dl with mean of 2.801±0.498 versus 4.598±1.392 in survivors (p<0.001). The fall in testosterone level was associated with rise in hs-CRP; total cholesterol; LDL and triglycerides but with fall in HDL (p<0.004) and LV ejection fraction (p<0.026). It signifies direct correlation of rising hs-CRP and falling EF with increase in mortality. A low level of free testosterone in AMI was directly correlated to total short term (<30 days) mortality. It can serve as a marker for assessing the prognosis in fresh myocardial infarction.

Key Words: Testosterone, acute myocardial infarction, cardiovascular mortality, prognosis.

INTRODUCTION

Coronary heart disease (CHD) is becoming a worldwide health epidemic attributing to more than 30% of all cardiovascular diseases[1,2,3]. Cardiovascular disease (CVD) has emerged as the leading cause of death in India with CHD affecting Indian at least 5 to 6 year earlier than their Western counterparts. Current estimates from disparate cross-sectional studies indicate the prevalence of CHD to be between 7-13% in urban and 2-7% in rural India[4].

Increased age is one of the strongest predictors for coronary artery disease. The Telecom Study done of 1400 males aged between 20 and 60 years demonstrated a significant stepwise decrease in testosterone concentration with each decade. This relationship was maintained after the exclusion of patients with chronic disease and statistical correction for body mass index, and alcohol consumption. A significant negative correlation between testosterone level and the presence of CAD has been found in two studies using coronary angiography to detect evidence of atheroma[5,6]. Furthermore, Philips *et al.,* in 1994, found a significant negative correlation between total or free testosterone and the degree of CAD (as defined by the mean % arterial occlusion) in 55 men undergoing coronary angiography[7].

Testosterone has been positively correlated with tissue plasminogen activator (the major stimulator of fibrinolysis) and negatively with the procoaguable factors. Furthermore, exogenous testosterone administration causes a fall in plasma fibrinogen and plasminogen activator inhibitor[8]. Hypotestosteronaemia is therefore implicated in a pro-thrombotic tendency, and theoretically would be associated with an increased risk of acute myocardial infarction and thrombotic stroke, whereas a physiological level of testosterone should decrease thrombotic risk by reducing fibrinogen and increasing fibrinolytic activity.

Work to date provides circumstantial evidence of a link between low testosterone levels, atherogenesis and acute arterial thrombosis. However, studies examining the association between low testosterone and CAD mortality have been inconclusive. Barret-Connor *et al.,* in 1988 the investigators found no significant association between total testosterone at baseline and the prevalence or development of cardiovascular disease[9]. The Caerphilly Heart Study in 1993 did not find testosterone level to be a primary risk factor for CAD mortality[10]. All these studies have limitations: particularly, Barrett-Connor et al.,[9] did not examine free testosterone levels, and the population in the Caerphilly Heart Study[10] was relatively young (aged 45-59 years) and followed for only 5 years. Stronger evidence might have been produced had the study been extended for a longer period.

***Corresponding Author:**
Dr. Sumit Kumar,
Sr. Resident,
Department of Medicine,
GGS Medical College & Hospital,
Faridkot, Punjab, India.

A study by Constantin Militaru *et al.,* in 2009 concluded that low endogenous testosterone level was independently associated with a higher short-term mortality in men with acute myocardial infarction[11]. Chris J Malkin *et al.,* in 2010 studied the correlation between serum testosterone and mortality in men with coronary heart disease and found that low serum testosterone was associated with increased mortality[12]. The present study was designed to evaluate the correlation of serum testosterone levels with the short-term (30 days) mortality in acute myocardial infarction. One study from India was reported long time back in 1998 by Tripathi *et al.,*[13]. The present study was planned to see the effect of testosterone level on short term mortality after acute MI in north Indian patients because of paucity of any further research in India on this subject after the pioneer work of Tripathi *et al.,*

1. To assess the relationship between serum testosterone level and short-term (30-day) mortality in men with acute MI within first 24 hours.
2. To correlate level of testosterone with hs-CRP levels in fresh myocardial infarction.
3. To assess the association between levels of testosterone and lipid profile in case of fresh myocardial infarction.

MATERIALS AND METHODS

The study was conducted in 100 male patients of acute MI, both STEMI and NSTEMI admitted in various Medical wards of Government Medical College and Guru Nanak Hospital, Amritsar. The diagnosis of acute MI was established as per current guidelines of American College of Cardiology. The informed consent for study was taken from the patient's family. Only those patients having age more than 40 years was included in the study. The observation period for the study was upto 30 days after admission and telephonic contact with the family was maintained for any morbidity or mortality parameter during this period.

Inclusion criteria

1. Men with age more than 40 years presenting with AMI for the first time.
2. Presentation during the first 24 hours of infarction.

Exclusion criteria

1. Female patients; male patients aged less than 40 years.
2. Patients with previous history of AMI or CABG.
3. Patients on anti-androgenic agents for prostrate and testicular cancer.
4. Patients on prolonged use of anabolic steroids or indigenous drugs.
5. Patients not willing for informed consent.

During the course of admission serum free testosterone level, total cholesterol, HDL-cholesterol, LDL-cholesterol triglycerides and hs-CRP was determined within the first 24 hours. The serum testosterone level was measured with commercial kit manufactured by WELDON BIOTECH. Trans thoracic Echocardiography was done in every case whenever the case was stable. All cases whether thrombolysed or not; diabetic or non-diabetic; hypertensive or hypertensive were studied.

Statistical Analysis

Statistical analysis was performed by student t-test to analyze the differences between mean values as per standard protocol. The results were tabulated and compared at the end of study.

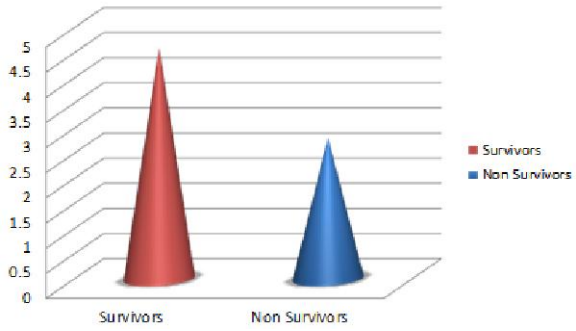
RESULTS

The mean serum testosterone in survivors was 4.598±1.392 ng/ml, whereas in non- survivors it was 2.801±0.498 ng/ml (Table 1, Figure 1). P value was highly significant (p<0.001).

Table 1: Showing mean serum testosterone value for surviors and non-survivors

	Survivors	Non survivors	P-Value
S. Testosterone (Mean ± SD)	4.598 ± 1.392	2.801 ± 0.498	< 0.001

Figure I: showing mean serum testosterone value for survivors and non-survivors



Testosterone was classified according to the increasing level into 4 quartile groups as A,B,C and D. Group A has mean of hsCRP as 4.13±0.43, Group B has mean as 3.41±.57, Group C as 2.48±0.55, Group D as 2.57±0.68 (Table 2). P-value was found to be highly significant (p<0.001).

Table 2: showing mean serum hs-CRP between serum testosterone groups

Group	S. Testosterone	S. hsCRP (mg/l)		P-Value
		No. of patients	Mean ± SD	
A	≤ 3	24	4.13 ± 0.43	< 0.001
B	3-5	47	3.41 ± 0.57	
C	5-7	25	2.48 ± 0.55	
D	> 7	4	2.57 ± 0.68	

Mean cholesterol in Group A was 213.83±29.78 mg/dl, in Group B it was 207.40±26.44 mg/dl, Group C mean Cholesterol was 206.92±41.28 mg/dl, Group D showed mean Cholesterol level as 192.00±30.11 mg/dl (Table 3). P value was found to be non–significant (p=0.600)

Table 3: Showing relationship between serum cholesterol and serum testosterone

Group	S. Testosterone	S. Cholesterol (mg/dl)		
		No. of patients	Mean ± SD	P-Value
A	≤ 3	24	213.83 ± 29.78	0.600
B	3-5	47	207.40 ± 26.44	
C	5-7	25	206.92 ± 41.28	
D	> 7	4	192.00 ± 30.11	

Mean serum LDL in Group A was found to be 138.16±26.25mg/dl, Group B as 131.42 ±26.94mg/dl, Group C serum LDL as 128.68±36.45mg/dl, Group D showed mean LDL to be 117.25±24.51 mg/dl (Table 4). P value was non-significant (p=0.498).

Table 4: Showing relationship between serum LDL and serum testosterone

Group	S. Testosterone	S. LDL (mg/dl)		
		No. of patients	Mean ± SD	P-Value
A	≤ 3	24	138.16 ± 26.25	0.498
B	3-5	47	131.42 ± 26.94	
C	5-7	25	128.68 ± 36.45	
D	> 7	4	117.25 ± 24.51	

Mean serum TG level in Group A was 181.87±36.96 mg/dl, group B mean level as 167.76±29.88 mg/dl, Group C mean TG level was found to be 168.88±36.40 mg/dl, and in Group D it was 174.60±41.73 mg/dl (Table 5). P-value was found to be non-significant (p=0.349)

Table 5: showing relationship between serum TG and serum testosterone

Group	S. Testosterone	S. TG (mg/dl)		
		No. of patients	Mean ± SD	P-Value
A	**≤ 3**	24	181.87 ± 36.96	0.349
B	**3-5**	47	167.76 ± 29.88	
C	**5-7**	25	168.88± 36.40	
D	**> 7**	4	174.60± 41.73	

In Group A mean serum HDL was 41.92 ±4.04 mg/dl, Group B mean was 43.12±4.81 mg/dl, Group C it was 46.36±4.04 mg/dl, Group D showed mean to be 42.50±3.41 mg/dl (Table 6). This data has significant P value as 0.004.

Table 6: Showing Relationship between Serum HDL and Serum Testosterone

Group	S. Testosterone	S. HDL (mg/dl)		
		No. of patients	Mean ± SD	P-Value
A	≤ 3	24	41.92 ± 4.04	0.004
B	3-5	47	43.12 ± 4.81	
C	5-7	25	46.36 ± 4.04	
D	> 7	4	42.50 ± 3.41	

In Group A mean LVEF was 36.38± 9.31%, Group B it was 39.43± 5.17 %, Group C showed mean as 42.36± 7.97%, Group D as 43.75±10.53% (Table 7). P-value obtained was significant (P=0.026).

Table 7: showing relationship between LVEF and serum testosterone

Group	S. Testosterone	LVEF (%)		
		No. of patients	Mean ± SD	P-Value
A	**≤ 3**	24	36.38 ± 9.31	0.026
B	**3-5**	47	39.43 ± 5.17	
C	**5-7**	25	42.36 ± 7.97	
D	**> 7**	4	43.75 ± 10.53	

DISCUSSION

The present study mainly focused on serum testosterone and whether its absolute value is responsible for short term (<30 day) mortality in patients with AMI.

Mean age of survivors in our study was found to be 57.96 ± 8.98 years which was significantly lower than that of non-survivors (63.04±10.77) with p-value of 0.026. This signifies that increasing age is by itself an independent risk factor for mortality in patients of acute coronary syndrome.

In our study, mean serum testosterone was found to be 4.185ng/ml, thus reflecting that decrease in serum testosterone in an important risk factor responsible for AMI. In our study, it was observed that mean value of serum testosterone of survivors was higher as compared to non-survivors (4.598 ± 1.392 vs 2.801 ± 0.498; p<0.0001) which was in comparison to study by Constantin Militaru *et al.*, which also showed somewhat similar results (4.3 ± 3.3 vs 2.1 ± 0.8; p=0.031). Similar findings were observed from the study conducted in 2010 by Malkin *et al.*,[14] Thus as the above mentioned studies show that decrease in serum testosterone is an important indicator of short term (<30 days) mortality in patients with AMI and hence in predicting the outcome of patients.

Lipid profile is known to be an independent risk factor for coronary artery disease .Our study showed higher mean total cholesterol and LDL cholesterol levels than recommended, with mean total cholesterol and LDL cholesterol found to be 208.21 mg/dl and 131.79 mg/dl respectively. Many prospective studies showed higher serum concentration of LDL cholesterol and total cholesterol as a major risk factor for coronary heart disease. Hence, by the Asian guidelines, total cholesterol level recommended should be <160 mg/dl and the recommended LDL levels is <70 mg/dl.

When we compared serum testosterone and lipid profile parameters, we found that with decrease in serum testosterone there was increase in serum total cholesterol, LDL cholesterol and serum triglycerides and decrease in serum HDL cholesterol. But statistical significance was met only in case of serum HDL with p-value=0.004 and not in other parameters. This finding of ours was also observed in study conducted by Tang Y. J *et al.,* and R. F Hellar *et al.,*[15] Similar results were also seen in study done by Makinen Ji *et al.,* with p-value for HDL <0.001.[16] Not much comparison data was found of association of total cholesterol and LDL cholesterol with serum testosterone levels, however little work that was found showed weak correlation. Thus, serum HDL values seem to be more important than isolated total cholesterol or LDL cholesterol.

Lipid profile parameters are an independent risk factor in describing mortality in patients with AMI and it was found in our study also. HDL value was found to be highly significant which was found to be similar when compared with study done by Constantin Militaru *et al.,* and Berge *et al.,* (p=0.029). But while comparing total cholesterol, LDL, TG's our findings with these parameters, which also met statistical significance, were not in accordance with those obtained by Militaru *et al.,* But in one of the study done by M G Binu *et al.,* he compared lipid profile with prognosis of AMI and in it death was one of the parameters and results were found to be highly significant.

hsCRP levels are raised in acute coronary syndrome, reflecting the inflammatory component of atherosclerotic plaques. Our study also observed mean levels of hs-CRP of survivors was significantly lower as compared to non-survivors (2.054 ± 1.392 vs 3.213 ± 0.498; p<0.0001) and was in correlation with Militaru *et al.,* which observed similar results (28.5 ± 43.8 vs 54.2 ± 74.4; p<0.01) and ToshihisaAnzai *et al.,*[17] So it is found that hsCRP inversely related to serum testosterone level and directly related to mortality in AMI as a biomarker.

One of the important complications of AMI is congestive cardiac failure which leads to fall in left ventricular ejection fraction. In our study it was observed that LVEF falls to 39.6±7.52% in AMI which was comparable to study done by Militaru *et al.,* in which LVEF was found to be 35.4±10.6 .It was also observed in our study that LVEF falls with decrease in serum testosterone levels with p-value (0.026) found to be significant. Our findings were found to be in accordance with the studies of Militaru *et al.,* (p<0.0001) and Gholamreza Davoodi *et al.,* (p<0.05)[18]

It was further observed that LVEF had direct correlation with short term mortality (p<0.001) and our results were similar to work done by RJ burns *et al.,* (p<0.001) and Militaru *et al.,* (p<001). So a decrease in serum testosterone increases congestive cardiac failure which further leads to increase mortality due to AMI.

Thus serum testosterone was found to be an important predictor of short term mortality in patients of AMI, and this was found to be independent of other risk factors. The results of this small study of short duration warrant further investigation in large, long-term studies.

It was observed that the present study had more or less similar findings in comparison with Militaru *et al.,* that men with AMI and a low endogenous testosterone level have a higher risk of short-term (30-day) mortality. Serum testosterone was significantly related to mortality, independent of age, body mass index, lipid profile, cigarette smoking, diabetes mellitus, history of hypertension, LVEF and hsCRP levels.

There were some differences from the previous studies because in the present study, short term mortality was taken, and moreover it has been studied in Indian population as compared to other studies done in western countries.

CONCLUSIONS

Serum testosterone is inversely proportional to short term mortality with p-value < 0.001. Serum testosterone is inversely related to hs-CRP. We consider this to be an important finding that needs to be explored in further studies. Direct co-relation of hs-CRP with mortality was observed. There is significant relationship between serum testosterone and HDL (p=0.004), but no significant relationship with LDL, TGs. Serum testosterone has direct co-relation with LVEF (p=0.026). Serum testosterone is significantly related to mortality independent of age, lipid profile, cigarette smoking, LVEF, hs-CRP, diabetes mellitus and hypertension. Thus, we conclude that low endogenous testosterone level is independently associated with high short term mortality in AMI. A serum testosterone level of <3.2 ng/ml could be used as a marker of mortality risk in AMI.

REFERENCES

1. Anderson RN. U.S. Decennial Life Tables for 1989–91: Eliminating Certain Causes of Death. National Health Statistics. 1999; 57:156-61.

2. Lopez AD, Mathers CD, Ezzati M. Global Burden of Disease and Risk Factors. Oxford, England: Oxford University Press. Washington, DC. 2006; 36:561-9.

3. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet. 1997; 349:1269–76.

4. Gupta R, Joshi P, Mohan V, Reddy KS, Yusuf S. Epidemiology and causation of coronary heart disease and stroke in India. Heart 2008; 94:16-26.

5. Aksut SV, Aksut G, Karamehmetoglu A, Oram E. The determination of serum estradiol, testosterone and progesterone in acute myocardial infarction. Jpn Heart. 1986; 27:825-37.

6. Chute CG, Baron JA, Plymate SR, Kiel DP, Pavia AT, Lozner EC, *et al.,* Sex hormones and coronary artery disease. Am J Med. 1987; 83:853-9.

7. Philips GB, Pinkernell BH, Jing TY. The association of hypotestosteronaemia with coronary artery disease in men Arterioscler Thromb Vase Biol 1994; 14(5):701-6.

8. Anderson RA, Ludlam CA, Wu FC. Haemostatic effects of supraphysiological levels of testosterone in normal men. Thromb Haemostas. 1995; 74(2):693-7.

9. Barrett CE, Khaw KT. Endogenous sex hormones and cardiovascular disease in men. A prospective population based study. Circulation. 1988; 78:539-45.

10. Yarnell JW, Beswick AD, Sweetnam PM, Riad-Fahmy D. Endogenous sex hormones and ischaemic heart disease in men. The Caerphilly Heart Study. Arterioscler Thromb Vase Biol. 1993; 13(4):517-20.

11. Militaru C, Donoiu I, Dracea O, Ionescu D. Serum testosterone and short-term mortality in men with acute myocardial infarction. Cardiology Journal. 2010; 17:234-8.

12. Malkin CJ, Pugh PJ, Morris PD, Asif S, Jones TH, Channer KS. Heart. 2010; 96(22):1821-5.

13. Tripathi Y, Hegde BM. Serum estradiol and testosterone levels following acute myocardial infarction in men. Indian J Physiol Pharmacol. 1998; 42:291–4.

14. Malkin CJ, Pugh PJ, Morris PD, Asif S, Jones TH, Channer KS. Heart. 2010;96(22):1821-25

15. Tang YJ, Lee WJ, Chen YT, Liu PH, Lee MC, Sheu WH. Serum testosterone level and related metabolic factors in men over 70 years old. .J Endocrinol Invest. 2007; Jun 30(6):451-58.

16. Mäkinen JI, Perheentupa A, Irjala K, Pöllänen P, Mäkinen J, Huhtaniemi I, *et al.,* Endogenous testosterone and serum lipids in middle-aged men. Atherosclerosis. 2008 Apr;197(2):688-93

17. ToshihisaAnzai, Tsutomu Yoshikawa, HirotoShiraki, Yasushi Asakura, Makoto Akaishi, Hideo Mitamura, *et al.,* C-Reactive Protein as a Predictor of Infarct Expansion and Cardiac Rupture After a First Q-Wave Acute Myocardial Infarction. Circulation. 1997; 96:778-84.

18. Gholamreza Davoodi, Alireza Amirzadegan, Mohammad Ali Boroumand, Maria Raissi Dehkordi, Ali Kazemi Saeid, Ahmad Yamini Sharif, *et al.,* Association between Androgenic Hormone Levels and Left Ventricular Ejection Fraction. J TehUniv Heart Ctr. 2010; 141-45.

Source of support: Nil
Conflict of interest: None Declared