ORIGINAL ARTICLE

Serum testosterone and short-term mortality in men with acute myocardial infarction

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Abstract

Background: *A significant and independent association between testosterone levels and coronary events in men and women has not been confirmed in large prospective studies, although some reports have shown that endogenous testosterone concentrations in men are inversely related to cardiovascular and general mortality.*

Methods: *We aimed to assess the relationship between serum testosterone level and short--time (30-day) mortality in men with acute myocardial infarction.*

Results: *We included 126 consecutive male patients admitted with acute myocardial infarction. The mean age was 62 ± 13 years. We determined, at admission, serum free testosterone (T) level (using a chemoluminiscence assay), high sensitivity C-reactive protein, N-terminal pro--B-type natriuretic peptide, and glycated hemoglobin level. We analyzed the 30-day mortality.*

Conclusions: *The mean level of serum T was 4.1 ± 2.9 ng/mL. All non-survivors had T level ≤ 3 ng/mL. A low level of T was independently related to total short-term mortality.* (Cardiol J 2010; 17, 3: 249–253)

Key words: testosterone, myocardial infarction, mortality

Introduction

A significant and independent association between endogenous testosterone (T) levels and coronary events in men and women has not been confirmed in large prospective studies. There is some data suggesting that coronary artery disease is associated with low T level in men. Hypoandrogenemia was shown to be associated with visceral obesity, insulin resistance, low high-density lipoprotein (HDL) cholesterol and elevated triglycerides, low-density lipoprotein (LDL) cholesterol, and plasminogen activator type 1.

The effects of exogenous T on cardiovascular mortality or morbidity have not been extensively investigated in prospective controlled studies. Some data suggests there may be beneficial effects in men with coronary artery disease.

In animal experiments, exogenous testosterone had neutral or beneficial effects on the atherosclerosis process. Exogenous androgens decrease serum levels of HDL-cholesterol, plasminogen activator type 1, lipoprotein (a), fibrinogen, insulin, leptin, and visceral fat mass.

Exogenous testosterone, in high concentrations, produces vasodilation; at physiological concentrations, there are mixed effects on vascular reactivity.

Methods

Patients

We included 126 consecutive male patients admitted to the Craiova Cardiology Center between January and December 2008 with a diagnosis of acute myocardial infarction (MI), established based on current guidelines of the European Society of Cardiology.

Patients were excluded if they had been castrated as treatment for testicular or prostate cancer or if they were taking any medications known to affect sex hormone concentrations (e.g. antiandrogenic agents for prostate cancer). Approval for the study was obtained from the local Research Ethics Committee, and informed consent was obtained from all participants.

All patients/patient's family were contacted by phone 30 days after admission. The mortality data was based on the charts of the hospital or on information provided by the patient's family.

Evaluation

We determined, at admission, serum free testosterone level, high sensitivity C-reactive protein (hsCRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), glycemia and glycated hemoglobin level, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides. The blood sample was obtained at approximately the same hour in the morning.

Testosterone level was measured using a chemoluminiscence assay. Serum level of NT-proBNP was determined at admission using a commercially available assay device with a measuring range between 60–3,000 pg/mL.

A standard transthoracic echocardiography exam was performed in the 48 hours following admission; left ventricular ejection fraction (LVEF) was measured using the modified Simpson method.

Statistical analysis

Statistical analyses were performed using SPSS 15.0 for Windows. Student's t test was used to analyze differences between mean values, and ANOVA was used to analyze differences between multiple groups. Pearson's correlation coefficient was calculated to determine associations between continuous variables. A probability value of 0.05 or less was considered significant.

Results

The mean age of the patients included was 62 ± 13 years.

Table 1. Patient characterisics.

Age (years)	61.7 ± 12.9
ST segment elevation MI (%)	41.2
Arterial hypertension (%)	68.2
Diabetes mellitus (%)	33.3
Smokers (%)	65.8
Body mass index [kg/m^2]	26.7 ± 7.8
Baseline glycemia [mg/dL]	114.7 ± 41.7
Total cholesterol [mg/dL]	190.4 ± 50.5
Triglycerides [mg/dL]	183.0 ± 79.1
HDL [mg/dL]	41.8 ± 14.8
LDL [mg/dL]	118.3 ± 38.0
hsCRP [mg/L]	31.8 ± 25.4
Glycated hemoglobin (%)	6.3 ± 0.8
NT-proBNP [pg/mL]	1827.0 ± 983.1
Tesosterone [ng/mL]	4.1 ± 2.9
LVEF (%)	35.4 ± 10.6

MI — myocardial infarction; HDL — high-density lipoprotein cholesterol; LDL — low-density lipoprotein cholesterol; hsCRP — high sensitivity C-reactive protein; NT-proBNP — N-terminal pro-B-type natriuretic peptide; LVEF — left ventricular ejection fraction

Due to the relatively small number of patients, we decided to divide the group in relation to the type of myocardial infarction, into an ST segment elevation MI group and a non-ST segment elevation MI group.

The characteristics of the patients and the values (mean ± standard deviation) of the laboratory measurements are presented in Table 1.

The total 30 day mortality was 12.69% (16 patients). Based on the available medical data (hospital charts, death certificates), and on other information related to the mode of death, 12 patients died of cardiovascular causes and four of non-cardiovascular causes (including those with not witnessed sudden death).

The characteristics of survivors and non-survivors (mean ± standard deviation) and the statistical significance of the differences between the two groups are presented in Table 2.

The non-survivors were predominantly in the group of non-ST segment elevation MI (68.8% *vs* 51.3%, p < 0.01), and had a higher proportion of previously diagnosed diabetes mellitus (32.7% *vs* 37.5%, p = 0.043).

They had significantly lower HDL-cholesterol levels; hsCRP and NT-proBNP, which are known risk markers for cardiovascular mortality, were higher in non-survivors.

All non-survivors in our population had T level ≤ 3 ng/mL, and the mean value was significantly lower than in patients who survived (2.1 ± 0.8 *vs* 4.3 ± 3.3, p < 0.01).

Table 2. Characteristics of survivors and non-survivors.

	Survivors	Non-survivors	p
Age (years)	60.1 ± 12.1	64.4 ± 9.2	NS
ST segment elevation MI (%)	42.7	31.2	< 0.01
Arterial hypertension (%)	68.1	68.7	NS
Diabetes mellitus (%)	32.7	37.5	0.043
Smokers (%)	66.3	62.5	NS
Body mass index [kg/m^2]	26.4 ± 5.6	27.3 ± 4.3	NS
Baseline glycemia [mg/dL]	113.9 ± 53.1	116.4 ± 32.7	NS
Total cholesterol [mg/dL]	193.5 ± 44.7	188.3 ± 60.2	NS
Triglycerides [mg/dL]	180.5 ± 68.8	184.2 ± 85.4	NS
HDL [mg/dL]	43.2 ± 12.4	40.8 ± 6.8	0.037
LDL [mg/dL]	121.1 ± 41.3	116.3 ± 32.0	NS
hsCRP [mg/L]	28.5 ± 43.8	54.2 ± 74.4	< 0.01
Glycated hemoglobin (%)	6.2 ± 1.3	6.4 ± 0.4	NS
NT-proBNP [pg/mL]	524.0 ± 233.1	2314.1 ± 1381.7	< 0.01
Testosterone [ng/mL]	4.3 ± 3.3	2.1 ± 0.8	0.031
LVEF (%)	37.4 ± 9.8	32.6 ± 11.5	< 0.01

MI — myocardial infarction; HDL — high-density lipoprotein cholesterol; LDL — low-density lipoprotein cholesterol; hsCRP — high sensitivity C-reactive protein; NT-proBNP — N-terminal pro-B-type natriuretic peptide; LVEF — left ventricular ejection fraction; NS — not significant

Table 3. Distribution of variables by quartile group of serum testosterone level.

	Quartile groups of testosterone				p for trend
	1	2	3	4	
Age (years)	62.7 ± 10.9	61.7 ± 9.6	61.4 ± 11.6	60.3 ± 10.8	0.06
ST segment elevation MI (%)	42.2	40.4	41.6	39.4	0.08
Arterial hypertension (%)	69.4	68.2	69.3	70.1	0.2
Diabetes mellitus (%)	34.5	32.5	32.1	30.5	0.004
Smokers (%)	65.2	65.5	67.1	60.2	0.09
Body mass index [kg/m^2]	29.1 ± 6.7	27.7 ± 4.3	27.1 ± 3.2	25.4 ± 4.8	0.002
Baseline glycemia [mg/dL]	116.2 ± 32.7	113.7 ± 24.6	114.7 ± 45.8	115.1 ± 21.1	0.3
Total cholesterol [mg/dL]	193.8 ± 42.2	190.2 ± 30.2	187.4 ± 25.4	187.3 ± 32.6	0.003
Triglycerides [mg/dL]	186.3 ± 65.1	183.8 ± 43.6	180.8 ± 35.2	178.4 ± 29.1	0.004
HDL [mg/dL]	38.3 ± 12.2	38.9 ± 10.3	36.6 ± 14.6	35.2 ± 9.8	< 0.001
LDL [mg/dL]	115.6 ± 27.4	117.4 ± 30.2	117.9 ± 23.5	119.6 ± 34.1	< 0.001
hsCRP [mg/L]	33.2 ± 17.4	31.1 ± 23.1	29.5 ± 15.3	27.3 ± 8.9	< 0.001
Glycated hemoglobin (%)	6.3 ± 2.1	6.1 ± 0.9	6.2 ± 0.4	5.9 ± 0.9	0.4
NT-proBNP [pg/mL]	1814.0 ± 745.1	1809.2 ± 423.5	1832.2 ± 632.2	1756.5 ± 562.9	0.03
LVEF (%)	33.2 ± 9.3	34.7 ± 11.2	35.7 ± 6.8	35.9 ± 7.8	0.06

MI — myocardial infarction; HDL — high-density lipoprotein cholesterol; LDL — low-density lipoprotein cholesterol; hsCRP — high sensitivity C-reactive protein; NT-proBNP — N-terminal pro-B-type natriuretic peptide; LVEF — left ventricular ejection fraction

Table 3 shows the distribution of variables by quartile group of serum testosterone level. Testosterone concentrations were significantly inversely related to body mass index, triglycerides, prevalence of diabetes mellitus, and hsCRP, and were positively related to total cholesterol, LDL cholesterol, and HDL cholesterol concentrations.

Table 4 shows the odds ratio for all-cause mortality adjusted for age and the other covariates. Age-adjusted odds ratio for mortality due to all causes decreased significantly with increasing quartile

Table 4. Odds ratio (OR) of mortality due to all causes by quartile group of serum testosterone.

	Quartile groups of testosterone				p for trend
	1	**2**	**3**	**4**	
Age-adjusted OR	1	0.82 (0.67–1.03)	0.67 (0.52–0.86)	0.70 (0.56–0.89)	< 0.01
Age and covariate-adjusted OR	1	0.72 (0.51–1.00)	0.61 (0.43–0.81)	0.56 (0.40–0.83)	< 0.01

ORs were estimated with logistic regression. The p values for trend are based on χ^2 test. Covariates are age, body mass index, LDL and HDL cholesterol, tryglicerides, cigarette smoking, diabetes mellitus, history of hypertension, left ventricular ejection fraction, high sensitivity C-reactive protein and N-terminal pro-B-type natriuretic peptide levels.

group of testosterone, and strengthened slightly after multivariable adjustment for covariates. For total mortality, the odds ratio (95% confidence intervals) for increasing quartiles of endogenous total testosterone compared with the lowest quartile were 0.72 (0.51 to 1.00), 0.61 (0.43 to 0.81), and 0.56 (0.40 to 0.83), respectively, after adjustment for age, body mass index, total cholesterol, LDL and HDL cholesterol, tryglicerides, cigarette smoking, diabetes mellitus, history of hypertension, LVEF, hsCRP and NT-proBNP levels.

Discussion

Our study shows that men with acute MI 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, hsCRP and NT-proBNP levels.

Considering that, in our study, all non-survivors had T level ≤ 3 ng/mL, this cut-off value could be used as a marker of mortality risk in acute myocardial infarction. That remains to be validated with the further collection of data.

The level of testosterone was inversely related to that of hsCRP. We consider this to be an important finding that needs to be explored in future studies.

We also found a weak but significant positive correlation between T level and total serum cholesterol.

Several studies linked hypoandrogenemia with visceral obesity, insulin resistance, impaired lipid profile, and coagulation [1–4]. High T levels were found to be associated with high HDL-cholesterol levels, low LDL-cholesterol, and low triglyceride levels [5–7].

More cross-sectional studies have reported an association between hypotestosteronemia and cardiovascular morbidity [8, 9]. Several studies report that male survivors of MI have lower T levels than

controls, while others report an increased oestradiol to testosterone ratio which was mainly due to lower T levels rather than to increased oestrogen levels. Sewdarsen et al. [8] found significantly lower plasma levels of testosterone in men suffering an acute myocardial infarction.

Other studies suggest that although low T levels are associated with an increase in biochemical risk factors of cardiovascular disease, they are not associated with an increased risk of cardiovascular mortality or morbidity. Several cross-sectional and prospective studies have found no significant relationships between endogenous testosterone concentrations and cardiovascular disease events [10, 11].

In an analysis on the population of the European Prospective Investigation Into Cancer in Norfolk (EPIC-Norfolk) study [12] that included 11,606 men, the authors found that endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease, and that of all causes, and that a low testosterone level may be a predictive marker for cardiovascular disease. The risk of total mortality was 25% to 30% lower in the highest compared with the lowest quartile of testosterone level, and a 1-SD increase in testosterone level was associated with a 14% lower risk of total mortality. Testosterone concentrations were significantly associated with several cardiovascular risk factors (total, LDL and HDL cholesterol, triglycerides, body mass index, and diabetes prevalence).

The effects of exogenous T on cardiovascular mortality or morbidity have not been extensively investigated in prospective controlled studies [13].

Conclusions

Low endogenous testosterone level is independently associated with a higher short-term mortality in men with acute myocardial infarction. A serum level of testosterone lower than 3 ng/mL could be used as a marker of mortality risk in acute myocardial infarction.

Acknowledgements

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