Adaptation to acute coronary syndrome-induced stress with lowering of testosterone: a possible survival factor

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Abstract

Objective: The objective of this study was to explore whether circulating testosterone (T) concentration is associated with the occurrence and risk for acute coronary syndromes (ACS).

Method: This case–control study included male patients with acute myocardial infarction (AMI) ($n=174$) or unstable angina pectoris (UAP) ($n=90$) and healthy controls ($n=238$). Patients gave serum samples during the acute ($n=264$) and recovery ($n=132$) phases after a median of 10.5 months after the incident event. Secondary events (ACS or cardiovascular death) were registered during the following 6 years.

Results: During the acute phase, AMI and UAP patients had similar significantly reduced concentrations of serum testosterone in comparison to controls. Testosterone associated inversely with weight, the degree of inflammation (i.e. C-reactive protein concentration) and signs of a chronic infection. In a multiadjusted Cox regression, when compared to testosterone concentrations considered high-normal (14.91–34.0 nmol/l), low-normal testosterone (9.26–14.90 nmol/l) in the acute phase predicted better prognosis for cardiovascular death rate with a hazard ratio (HR) of 0.17 (0.04–0.68, $P=0.012$). The increased testosterone concentrations after the recovery period did not associate with future cardiovascular disease events.

Conclusion: Low-normal testosterone levels in the acute phase of ACS predicted better survival. The observation may indicate better adaptation to stress in survivors and warrants further study.

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Introduction

Testosterone (T) replacement therapy has been recommended for men with coronary heart disease (1). However, recent findings suggest an association between testosterone treatment and increased risk for cardiovascular events (2, 3, 4, 5, 6). It remains a matter of debate whether low testosterone concentration is an actual risk factor or a consequence of coronary disease.

Reports on the role of circulating testosterone as a risk factor of ischemic heart disease are confusing. In patients with a previous history of cardiovascular disease (CVD) events, hypogonadism has been reported to associate with a reduced risk of new CVD events (6). On the other hand, low serum testosterone concentration has also been proposed to predict increased cardiovascular risk (7, 8).

We aimed to clarify the dynamics of serum testosterone concentrations in patients with acute coronary syndromes (ACS). Firstly, the association of testosterone concentration with ACS was analyzed in a cross-sectional case–control population. Secondly, the testosterone concentrations were compared in patients during the

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acute and recovery phases. Thirdly, the association of testosterone concentrations with subsequent CVD events was analyzed in the follow-up of the patients. The role of infections/inflammation as stressful agents possibly affecting the testosterone response was also addressed.

Methods

Study population and diagnoses

The inclusion criteria for the study population ($n=502$ men) were age under 80 years and no signs of cognitive intellectual disability. Cases consisted of 264 male patients, who were admitted for ACS to the CICU in Lund University Hospital between March 1999 and April 2002, as described in detail earlier (9). The 238 controls were selected from the same suburbs, as the patients and the groups were matched with age ± 2 years. Inclusion criteria of the controls were: i) no history of definite or suspected coronary heart disease or stroke; ii) no operations or chemotherapy within the previous 4 weeks; iii) no medication for diabetes, hypertension or dyslipidemia; and iv) no history of angina, i.e. chest pain, in any location related to exercise and relieved by rest.

The participants completed questionnaires on general background characteristics and demographic data including smoking, marital status, socio-economic data and the medical history of the family.

Of the patients, 21 died before they could be interviewed. Of the invited patients, 48 chose not to participate. After admission, 12 patients were excluded from the study with the following diagnoses: unspecified precordial pain (seven patients), atrial fibrillation, pericarditis, myocarditis, pulmonary embolism and aortic aneurysm. Of the participants, whose testosterone analyses were available, acute myocardial infarction (AMI) was diagnosed according to the prevailing criteria in 2002 in 174 individuals and unstable angina pectoris (UAP) in 90. AMI was diagnosed if two of the following criteria were fulfilled: i) typical chest pain lasting over 20 min; ii) ST elevations followed by testosterone wave inversion or new Q waves in the ECG; or iii) an increase in creatine kinase isoenzyme MB (CK-MB) to more than twice the upper limit of the normal range. UAP was diagnosed in patients with: i) continuous ischemic chest pain; ii) transient or persistent ST segment depression in the ECG (<1 mm); and/or iii) elevation of CK-MB ($5<$CK-MB<10 μg/l) or troponin testosterone (TnT) ($0.05<$TnT<0.10 μg/l). Coronary angiograms were done in 164 patients.

Recovery samples and follow-up

The recovery phase samples were taken from 132 males (50%) (84 with AMI and 48 with UAP) after the minimum recovery of 6 months (median 314, interquartile reage (IQR) 178–689 days). We followed 264 patients for up to a median 5.6 years (IQR 4.6–6.5) and recurrent ACS and cardiovascular deaths via the hospital records and population register. Follow-up samples were collected from all patients that were available and gave their consent.

Laboratory determinations

A research nurse made a visit to the control persons within 5 days. Blood samples were taken the first thing in the morning during the working hours of the nurses, usually around 0900 h and never after 1400 h. The mean (S.D.) testosterone concentration in the patient samples taken at 0700–1400, 1400–2200 and 2200–0700 h did not differ significantly, i.e. 13.3 (9.2), 17.3 (9.3) and 12.3 (6.1) nmol/l ($P=0.090$). During follow-up visits, the samples were taken beween 0900 and 1200 h. Blood samples for TnT and CK-MB samples were obtained on admission to the hospital and at 1000 and 2000 h. High-sensitivity serum C-reactive protein (CRP) was measured in patients and controls using nephelometry with polyclonal antibodies and calibrators (Behringwerke AG, Marburg, Germany).

The serum samples were stored at -20 °C until laboratory determinations. Testosterone was measured using Spectria RIA kits (Orion Diagnostica, Turku, Finland). The intra- and inter-assay coefficients of

Table 1 Characteristics of cases and controls. Data are presented as mean $\pm$S.D., geometric mean (1st and 3rd quartile) or as *n* (%).

	Cases	Controls	*P*[a]
n	264	238	
Age (years)	62.3±9.4	62.5±9.2	0.813
Weight (kg)	85.7±13.1	80.7±11.1	<0.001
Cholesterol (mmol/l)	5.27±1.29	5.66±0.97	<0.001
CRP (mg/l)[b]	9.66 (3.08–31.8)	1.57 (0.85–2.66)	<0.001
Testosterone (nmol/l)	10.9±5.6	14.3±6.3	<0.001
Porphyromonas gingivalis			
IgA (EU)[b]	2.43 (1.51–3.40)	2.24 (1.49–3.18)	0.331
IgG (EU)[b]	6.46 (4.52–8.79)	6.31 (4.64–8.84)	0.807
Current smokers	45 (17.0%)	43 (18.1%)	0.765[c]
Diabetes	35 (13.2%)	0	–

[a]*t*-test, variables with skewed distribution (CRP, *P. gingivalis* antibody levels) were log-transformed before analysis.
[b]Geometric mean (1st and 3rd quartile).
[c]χ^2-test.

variation were 4.6 and 6.5% respectively. The testosterone concentrations were divided into low (0.5–9.23 nmol/l), intermediate (9.26–14.90 nmol/l) and high (14.91–34.0 nmol/l) tertiles representing low, low-normal and high-normal levels.

The following viral and bacterial antibody titers, as reported in our earlier articles (9, 10), were used in statistical analyses: *Chlamydia pneumoniae*, *Helicobacter pylori*, cytomegalovirus, Herpes simplex virus, enterovirus (9), *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* (10).

Ethics approval

The ethical committee of the Lund University has approved this study. The study complies with the Declaration of Helsinki. A written informed consent was obtained from the subjects.

Statistics analysis

There was >80% statistical power (α 0.05) to detect a 1.5 nmol/l (S.D. 6.0 nmol/l) difference in the testosterone concentrations between the groups. Significance of the differences between the groups was analyzed with Student's *t*-test, ANOVA, paired sample *t*-test or χ^2 test. Association of the testosterone concentrations with CRP and antibody levels to multiple infectious agents was analyzed with linear regression models adjusted for age and case/control status. The appropriateness of these models was examined by defining residuals and examining residual plots. In the case–control setting, the association of ACS with testosterone tertiles was analyzed by logistic regression models adjusted for: i) age; ii) age, cholesterol and current smoking; and iii) age, cholesterol, current smoking, CRP and weight. Significance of the trend was examined with χ^2 test. In the follow-up study,

Table 2 Characteristics of cases and controls in testosterone tertiles. Data are presented as mean ±S.D., geometric mean (1st and 3rd quartile) or as *n* (%).

	Serum testosterone concentrations (nmol/l)			
	Normal–High (14.91–34.0)	Low–normal (9.26–14.90)	Low (0.5–9.23)	***P* values**
Cases (*n*)	68	81	115	
Age (years)	62.6±8.94	62.2±9.95	63.0±8.88	0.802[a]
Cholesterol (mmol/l)	5.29±1.20	5.28±1.73	5.27±0.96	0.997[a]
CRP (mg/l)	8.84 (2.41–29.8)[b]	9.28 (3.87–27.4)[b]	10.5 (2.50–36.8)[b]	0.748[a]
Weight (kg)	80.8±14.0	88.2±13.1	86.3±12.3	0.015[a]
BMI (kg/m^2)	19.3±11.9	21.3±12.1	24.9±9.4	0.003[a]
Blood pressure (mmHg)				
Systolic	140±19	145±21	139±15	0.717[a]
Diastolic	80±12	79±16	78±7	0.881[a]
Porphyromonas gingivalis				
IgA (EU)	2.32 (1.47–2.92)[b]	2.43 (1.67–3.61)[b]	2.50 (1.43–3.81)[b]	0.688[a]
IgG (EU)	5.92 (4.51–7.47)[b]	6.43 (4.48–9.46)[b]	6.80 (4.57–9.09)[b]	0.219[a]
Current smokers	14 (20.6%)	11 (13.6%)	20 (17.4%)	0.522[c]
Diabetes	10 (14.7%)	10 (12.3%)	16 (13.9%)	0.921[c]
Beta blockers	26 (38.2%)	31 (38.3%)	41 (35.7%)	0.842[c]
Calcium blockers	8 (11.8%)	17 (21.0%)	14 (12.2%)	0.154[c]
At follow-up				
Recurrent ACS	16 (23.5%)	23 (28.4%)	28 (24.3%)	0.750[c]
PTCA	29 (42.6%)	39 (48.1%)	43 (37.4%)	0.577[c]
CABG	8 (11.8%)	12 (14.8%)	21 (18.3%)	0.219[c]
CVD death	18 (26.5%)	13 (16.1%)	14 (12.1%)	0.692[c]
Controls (*n*)	98	87	53	
Age (years)	62.2±0.07	61.5±9.37	64.2±9.93	0.249[a]
Cholesterol (mmol/l)	5.82±0.97	5.61±1.03	5.45±0.85	0.078[a]
CRP (mg/l)	1.55(0.81–2.59)[b]	1.43 (0.76–2.60)[b]	1.88 (1.09–3.70)[b]	0.218[a]
Weight (kg)	78.7±9.80	80.7±11.1	84.5±12.8	0.021[a]
Porphyromonas gingivalis				
IgA (EU)	2.04 (1.43–4.21)[b]	2.10 (1.33–2.93)[b]	2.92 (1.59–5.30)[b]	0.002[a]
IgG (EU)	5.99 (4.75–8.27)[b]	6.05 (4.23–8.14)[b]	7.41 (5.28–11.4)[b]	0.02[a]
Current smokers	25 (25.5%)	14 (16.1%)	4 (7.5%)	0.017[c]

[a]ANOVA.
[b]lg10 tranformed (CRP, *Porphyromonas gingivalis* antibody levels) before testing; geometric mean (1st and 3rd quartile).
[c]χ^2-test.

Table 3 Association of CRP and *Porphyromonas gingivalis* antibody levels with the testosterone levels. Data are presented as standardized coefficient (*P* value).

	Cases	Controls	All[c]
n	264	238	502
P. gingivalis[a]			
IgA	−0.094 (0.166)	−0.134 (0.048)	−0.105 (0.021)
IgG	−0.129 (0.046)	−0.095 (0.164)	−0.114 (0.011)
CRP[b]	−0.127 (0.044)	−0.064 (0.342)	−0.109 (0.046)

Linear regression model for testosterone levels with logarithmically transformed independent variables adjusted for [a]age and CRP concentration or [b]age. [c]In the column 'All', the models are also adjusted for case/control status.

the association of recurrent ACS and CVD death with testosterone was analyzed in similar models by Cox regression. The variables' interactions with time were tested, and the proportional hazards assumption was not violated.The analyses were performed with PASW Statistics 18.

Results

Baseline

Characteristics of the cases and controls are presented in Table 1. ACS patients, when admitted to the coronary care unit, had lower mean (S.D.) serum testosterone concentrations than the controls; these differences were significant for both UAP and AMI patients ($P<0.001$), but did not differ significantly from each other, 11.3 (5.7) vs 10.8 (5.5) nmol/l ($P=0.494$). Testosterone tertiles correlated inversely with weight and BMI in cases and also with weight of controls (Table 2), but did not correlate with the sampling time, the time between appearance of cardiac symptoms and blood sampling or the degree of stenosing lesions in the coronary angiograms (results not shown). In multivariate linear regression models, testosterone associated inversely with CRP concentrations and IgA and IgG class antibody levels against *P. gingivalis* (Table 3). Other antibody levels did not associate with testosterone concentrations (not shown).

In a multivariate logistic regression model, ACS associated inversely with testosterone tertiles with an OR (95% CI) 1.22 (0.58–2.59) and 2.75 (1.31–5.80) in the low-normal and low tertiles with a significant *P* value for trend (0.015) (Table 4). Similar trends were seen for both UAP and AMI, but the significance was attenuated after adjusting for weight and CRP.

Follow-up

The mean testosterone concentrations in patients increased during the recovery period from 11.2 (5.77) to 16.6 (6.46) nmol/l ($P<0.001$), which did not differ from the values in controls (Fig. 1). This increase was evident in most of the patients (69.7% increase, 12.9% decrease, 17.4% no change within ± 2 nmol/l). The changes were similar in patients with AMI and UAP, 16.7 (6.77) vs 16.2 (5.90) nmol/l respectively. The difference between the acute and recovery phases testosterone levels correlated significantly with the time between the two samplings

Table 4 Association of testosterone concentrations with ACS in the case–control population. Data are presented as OR (95% CI).

	Serum testosterone concentrations (nmol/l)			
	Normal–High (14.91–34.0)	Low–normal (9.26–14.90)	Low (0.5–9.23)	***P* value**
ACS				
Case/control	68/98	81/87	115/53	
Model 1	1.00	1.34 (0.87–2.07)	3.13 (2.00–4.91)	<0.001
Model 2	1.00	1.34 (0.80–2.25)	3.18 (1.90–5.32)	<0.001
Model 3	1.00	1.22 (0.58–2.59)	2.75 (1.31–5.80)	0.015
UAP				
Case/control	23/98	24/87	43/53	
Model 1	1.00	1.17 (0.62–2.23)	3.46 (1.89–6.36)	<0.001
Model 2	1.00	1.14 (0.47–2.74)	4.15 (1.89–9.13)	<0.001
Model 3	1.00	1.43 (0.45–4.48)	3.51 (1.18–10.4)	0.050
AMI				
Case/control	45/98	57/87	72/53	
Model 1	1.00	1.43 (0.88–2.32)	2.97 (1.80–4.90)	<0.001
Model 2	1.00	1.41 (0.80–2.51)	2.76 (1.54–4.93)	0.001
Model 3	1.00	1.18 (0.49–2.86)	2.36 (0.97–5.75)	0.121

P value presented for the trend; Model 1: adjusted for age; Model 2: additionally, adjusted for cholesterol and current smoking; Model 3: additionally, adjusted for CRP and weight.

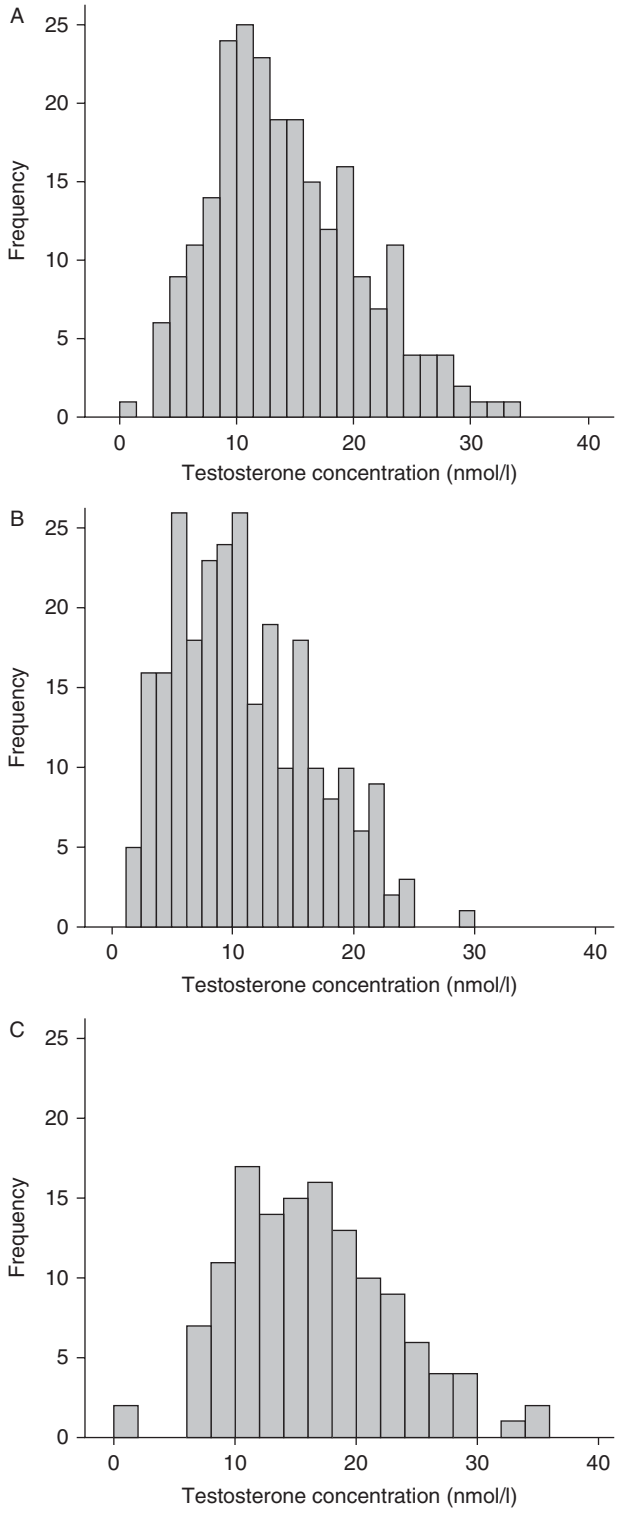

Figure 1
Histograms of the serum testosterone concentrations. The serum testosterone concentrations are shown for (A) healthy controls ($n=238$) and ACS (AMI and UAP) patients during (B) the acute phase ($n=264$) and (C) the recovery period ($n=132$).

($r=0.256$, $P=0.005$ for Δ testosterone (recovery and acute phases)), and the two levels correlated significantly with each other ($r=0.446$, $P<0.001$; Fig. 2).

In the follow-up study of the patients, neither the acute nor the recovery phase mean testosterone concentrations differed between those with or without a new event. However, in a Cox regression model compared to the high-normal testosterone levels, the low testosterone level in the acute phase associated with an increased risk of recurrent ACS with a HR 2.77 (1.18–6.52, $P=0.008$) when adjusted for age, cholesterol concentration and smoking, but the significance was abolished after adjusting for weight and CRP (Table 5). The lower tertiles of testosterone concentrations in the acute phase associated inversely with the risk of cardiovascular death ($P=0.025$ for trend). After all adjustments, the low-normal testosterone concentration remained inversely associated with the risk of death with a HR 0.17 (0.04–0.68, $P=0.012$) (Table 5). The predicted cumulative survival curves according to the Cox regression model for the testosterone levels with covariates age, smoking, cholesterol, CRP and weight are presented in Fig. 3. The result remained unchanged when the Cox regression model was adjusted for the medications when entering the hospital, TnT concentrations, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) performed during treatment or the antibody levels to *P. gingivalis*. Δ testosterone or the recovery phase did not associate with recurrent ACS or cardiovascular death.

Discussion

Low testosterone levels in the acute phase predict better survival

ACS was associateted with low-normal testosterone levels in the acute phase. After the acute phase, testosterone concentrations usually increased, but the recovery levels were not associated with future CVD events. The increase in the testosterone levels observed in the recovery phase supports a consequential, rather than causative, role of the low testosterone concentrations. Testosterone concentrations correlated inversely with CRP levels. The temporarily suppressed serum testosterone concentrations during ACS predicted improved prognosis: low-normal testosterone concentration during the acute phase decreased the incidence of CVD deaths in the follow-up of 6 year.

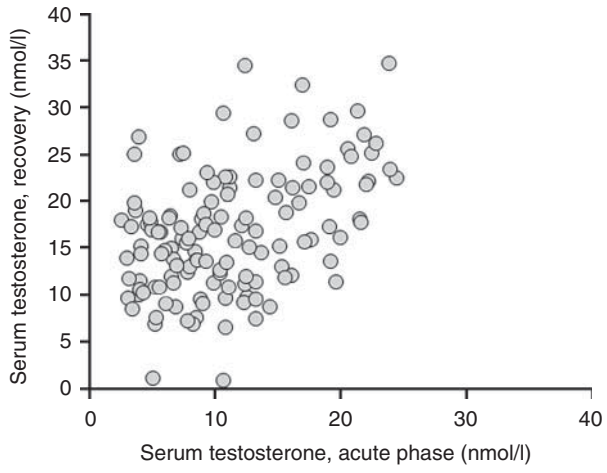

Figure 2

Serum testosterone concentrations during the acute and the recovery phases. The acute phase levels are shown on the *X*-axis and the recovery phase levels on the *Y*-axis ($n=132$). The mean levels of testosterone were significantly higher after 11 months' recovery period ($P<0.001$).

The controversy of testosterone and CVD

Cross-sectional observational studies suggest that low testosterone concentration is a risk factor for CVD. There is an inverse relationship between endogenous serum testosterone levels and coronary heart disease in males (8, 11, 12) although all studies cannot confirm this finding (6, 13, 14, 15, 16), and the direction of causality of the phenomenon remains unclear. Moreover, a decreased serum testosterone concentration has been shown to be associated with acute ischemic strokes, infarct size and mortality (17). These data suggest that normal testosterone levels may offer protection against the development of atherosclerosis in middle-aged men.

Optimal androgen levels seem to be a biomarker for survival because men with mid-range levels of testosterone and dihydro-testosterone were recently reported to have the lowest death rate from any cause (18). This was obvious also in the present study, where intermediate testosterone concentrations (9.26–14.90 nmol/l) considered as 'low-normal' were protective against CVD death in the follow-up of the patients, and the men with suppressed testosterone in the acute phase had increased risk of subsequent ACS in the follow-up of 6 years. Even if there is some supportive exprimental data (19), the causality between testosterone levels and CVD remains elusive. During the past 4 years, several independent studies, published in prestigious journals, have shown men treated with testosterone to have increased amount of cardiovascular symptoms (2, 3, 4, 5, 6), which has created heated debate around the testosterone vs CVD issue (20, 21).

Stress and clinical implications

The low testosterone concentrations in ACS patients might be caused by an acute stress even if chronic inflammation may play a contributory role. It is also possible that an acute decrease of testosterone was superimposed on a pre-existing lower testosterone. Suggestions in this direction are the negative association of serum testosterone with weight/BMI (a robust negative determinant of total testosterone in all situations also in healthy men) and the observed correlation between acute and recovery testosterone. However, also an acute suppression due to ACS is involved because of the subsequent increase of testosterone during recovery.

Table 5 Association of testosterone concentrations in the acute phase with recurrent ACS and CVD death in the follow-up of 6 years. Data are presented as HR (95% CI).

	Serum testosterone concentrations (nmol/l)			
	Normal–High (14.91–34.0)	Low–normal (9.26–14.90)	Low (0.5–9.23)	***P* values**
Recurrent ACS (67/193)[a]				
Model 1	1.00	1.64 (0.86–3.13)	2.81 (1.41–5.60)	0.011
Model 2	1.00	1.85 (0.83–4.15)	2.77 (1.18–6.52)	0.046
Model 3	1.00	1.33 (0.52–3.41)	2.39 (0.89–6.41)	0.171
CVD death (45/216)[a]				
Model 1	1.00	0.69 (0.34–1.39)	0.77 (0.36–1.64)	0.580
Model 2	1.00	0.27 (0.08–0.93)	0.43 (0.12–1.52)	0.098
Model 3	1.00	0.17 (0.04–0.68)	0.26 (0.06–1.02)	0.025

P value presented for the trend. Model 1: adjusted for age; Model 2: additionally, adjusted for current smoking and cholesterol; Model 3: additionally, adjusted for CRP and weight.
[a]Yes/no.

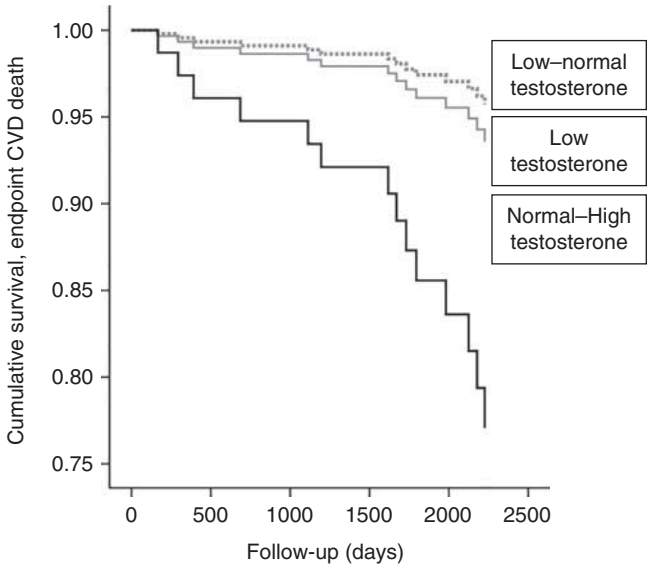

Figure 3

Predicted cumulative survival of the ACS patients from CVD death in the follow-up of 6 years. The Cox regression model for tertiles of serum testosterone concentration was performed for 261 men and adjusted for age, smoking, cholesterol, CRP and weight. The samples were taken during the acute phase.

Our study suggests that chronic stress in the form of infections may play a role in the 'low testosterone syndrome', since the antibody levels to the major periodontal pathogen, *P. gingivalis*, associated inversely with the testosterone levels both in patients and controls. Periodontitis is one of the most prevalent infectious diseases affecting as many as 75% of adult and elderly populations, and it eventually leads to loss of teeth. In earlier studies, the results on the association of sex steroids and periodontitis or tooth loss have been contradictory (22, 23), but the subject is rarely investigated.

Testosterone levels and survival

Paradoxically, although the decreased testosterone levels associated with an increased risk of recurrent ACS, they predicted better survival. This may involve better adaptation mechanisms of those with low testosterone concentrations to acute stress, to spare the energy of the body and to deviate it from redundant functions, such as reproduction and energy consumption (6). Therefore, the recent results by Corona *et al.* (6) suggesting that low testosterone concentration has a protective effect were confirmed in our study. The 'low testosterone syndrome' in these men would be analogous to the 'low T3 syndrome', a state of a suppressed thyroid function in connection with an acute disease, which is not recommended to be treated with thyroid hormone supplementation (24). Alternatevely, it could be analogous to the situation where mild hypothyroidism is associated with better survival in old age (25, 26). Besides the thyroid, also testicular hypofunction could be such a survival factor.

Potential study limitations

The limitations inherent in cross-sectional studies that a single sample of testosterone at a specific time point might not reflect the natural course of a disease are clearly shown in our study. Diurnal variation may decrease the reliability of the interpretations, although in the present study the time of the day did not correlate with the testosterone levels. In the morning, the testosterone levels may be on average 30–35% higher than the levels measured in the mid- to late afternoon. The observed difference between morning and afternoon declines with age dropping to ~10% at 70 years of age (27). In our patients, testosterone concentrations were measured immediately after the acute events. The follow-up values which have taken some months after the acute event might not reflect concentrations before the events, although they are probably closer to the individual's normal testosterone concentrations. The medication of the patients may conceal the effects on testosterone.

A good quality immunoassay was used for testosterone measurements; therefore, the hormone data can be considered reliable, although mass spectrometry was not used (28, 29). Only total testosterone was measured, because sex hormone-binding globulin (SHBG) levels were not available. Because the men in the highest testosterone tertile had the same age but were 5–10% lighter than the men with the lower testosterone levels, their SHBG levels were apparently higher (30). Our findings do not support the association of SHBG with a more favorable CVD risk in this older male population, as we have reported recently in healthy young men (16). Another limitation of the current study is the lack of gonadotropin and estradiol measurement.

Conclusion

Immediately after an acute coronary event, the testosterone concentrations are low, but usually increase thereafter. Stress is probably the cause of decreased serum testosterone concentrations during ACS even though

chronic inflammation might play a contributory role. These findings should be considered hypothesis generating. They suggest that individuals reacting to stress by lowering of testosterone have better prognosis, since the acutely low-normal testosterone levels have predicted better survival.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

All authors have participated in the planning of the study, analyzing the data and writing the article. E Pesonen is responsible for collecting the data, I Huhtaniemi for testosterone analyses and P Pussinen for statistical analyses.

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