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ASSOCIATION OF SERUM TESTOSTERONE WITH THE COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Objective: The objectives of the study were to assess (1) if serum levels of testosterone differ between men with and those without ST-elevation myocardial infarction, and (2) to determine the association of testosterone with the outcome of ST-elevation myocardial infarction (STEMI).

Methodology: This was hospital based case control study, conducted at Coronary Care Unit of Teaching Hospital, Karapitiya, Galle, Sri Lanka from January 2010 to December 2011. Two hundred and six males (103 patients with STEMI and 103 controls without a history of CAD) were studied. They were followed up for one year for the occurrence of clinically significant adverse cardiovascular events. Serum total testosterone, lipids and plasma glucose were estimated.

Results: The basal serum total testosterone in patients was significantly lower compared to controls (11.47 ± 3.3 vs. 18.15 ± 7.2 nmol/L, P = 0.001). The results showed that total testosterone (P = 0.001; OR = 0.75; 95 % CI = 0.66 - 0.85) was a significant independent predictor of STEMI and it was a significant independent predictors of in-hospital complications (P = 0.003, OR = 1.68, 95 % CI = 1.2 - 2.36).

Conclusion: Men with STEMI have significantly lower basal serum total testosterone compared to controls. Low testosterone is a risk factor of STEMI. Testosterone was independently related to the development of in-hospital complications of STEMI.

Key Words: Myocardial Infarction, Complications, Testosterone

INTRODUCTION

The association between testosterone and ST-elevation myocardial infarction (STEMI) is an area of current interest. There is evidence that the testosterone level is significantly lower in new myocardial infarction patients compared to controls.[1-3] Furthermore, endogenous testosterone concentrations in men are inversely related to cardiovascular disease mortality and all-cause mortality.[4-5] A prospective study conducted on a larger group of patients referred for coronary angiography showed that low levels of free testosterone (FT) were independently associated with the congestive cardiac failure mortality however, no significant associations of FT were found with other cardiovascular and cancer related mortality.[6,7]

Identification of existence of novel risk factors in STEMI patients which is of immense importance in primary prevention as well as in secondary prevention. In the local setting, the association of testosterone with STEMI, in relation to the development of complication has not been studied. Therefore our study would contribute in filling the gaps in knowledge in the Sri Lankan population.

The objectives of the study were to assess (1) if serum levels of testosterone differ between men with and without ST-elevation myocardial infarction and (2) to determine the association of testosterone with the complications of ST-elevation myocardial infarction.

METHODOLOGY

A hospital-based case-control study was conducted from January 2010 to December 2011. Patients with STEMI were followed up prospectively for one year (2011 to 2012).

The common exclusion criteria for both case and control groups were history of recent surgery or major trauma within three months or a history of acute coronary syndrome in the past three months, malignancy, chronic inflammatory disorders, current acute severe infections, dementia or any structural damage to the central nervous system, renal dysfunction, chronic liver disease, alcohol dependency based on the CAGE questions.[8] Those on current therapy with drugs that may alter serum testosterone level were also excluded. Patients with endocrine disorders, past history of orchidectomy, thyroidectomy, coronary artery bypass graft and testicular problems (testicular injury, tumour or infection, undescended testes) were not recruited to the study.

Group 1 comprised of 103 consecutive male patients (age range of between 30-70 yrs) admitted to the Coronary Care Unit of Teaching Hospital, Karapitiya, Galle, Sri Lanka with the first episode of ST – elevation myocardial infarction (STEMI; n = 103). The diagnosis of STEMI was made on a typical history and electrocardiographic changes and all recruited patients fulfilled the Universal guidelines for myocardial infarction.[9] The patients who were admitted in the morning before 10:00 hours of the day were recruited to overcome the effect of diurnal variation on testosterone.[10] Patients presenting 24 hours after chest pain were excluded.

Group 2 comprised of 103 controls (age range of between 30-70 yrs) selected from patients awaiting minor surgery in the surgical units of the same hospital and without clinically manifested coronary artery disease. The patients with abnormal electrocardiograms (presence of pathological Q waves in leads without ST- elevation is suggestive of old or silent myocardial infarction) were not included as controls.

Details were extracted from the hospital and personal health records, through interview and clinical examination. Anthropometric measurements (weight, height, waist circumference, hip circumference) were obtained and body mass index (BMI) and waist to hip ratio were calculated. Two-dimensional echocardiography was done in all patients during the hospital stay and left ventricular ejection fraction (LVEF) was determined by the modified Simpson's method.

Physical activity was defined as regular (daily) when physical activity was done daily for $\geqslant$ 30 minutes. Smoking was assessed as "Yes" if subject smokes at least one cigarette per day and "No"- if never smoked or ex smoker for more than one year at the time of recruitment to the study. Diabetes mellitus was diagnosed if the patient had fasting blood glucose of $\geqslant$ 7 mmol/L or if the patient was already on treatment for diabetes mellitus.[11] Hypertension was defined if the patient was already on antihypertensive therapy and if the blood pressure readings exceeded systolic blood pressure $\geqslant$ 140 mmHg or diastolic blood pressure $\geqslant$ 90 mmHg.[12] Hypercholesterolaemia was defined according to National Cholesterol Education Programme guidelines.[13] Premature coronary artery disease in males was defined by the upper age limit of $\leqslant$ 45 years.[14] Body mass index categories were defined according to the guidelines laid for Asian adults.[15]

Blood from STEMI patients was drawn at a mean of 6.3 hours from the onset of symptoms (patients presenting 24 hours after chest pain were excluded) and enrolled patients were restricted to morning admissions before 10:00 hours to avoid the effect of diurnal variation on testosterone level.[10] Plasma glucose estimation was done on the pre-discharge fasting sample. A sample of venous blood was collected in the morning from controls to measure the biochemical variables following an overnight fast (10-12 hours).

Plasma glucose was estimated by a colourimetry based method (ProDia International, UAE). Serum total cholesterol (TCh), triglycerides (TGs) and high-density lipoprotein cholesterol (HDL-Ch) were estimated by a colourimetric method (ProDia International, UAE). Low-density lipoprotein cholesterol (LDL-Ch) level was calculated using the

Friedewald formula except when TGs exceed 4.5 mmol/L.[16] Serum total testosterone concentration was estimated by an enzyme immunoassay kit (PATHOZYME TESTOSTERONE OD 497, OMEGA DIAGNOSTICS LTD, Omega House, UK; Star Fax 1000). In STEMI patients, serum cardiac troponin I (cTnI) was analyzed using an enzyme-labeled chemiluminescent immunometric assay (IMMULITE 1000 Troponin I). The cTnI concentration more than 1.0 ng/mL was considered as positive.

The follow up periods were determined on local clinic practices where the patients are followed up 1 month after the event and thereafter 3-monthly unless they develop complications or have special needs. Therefore patients were followed up for one year for the occurrence of clinically significant adverse cardiovascular events at specific time intervals as 30 days (short-term), > 1-3 months, > 3-6 months (medium-term) and > 6 months to one year (long-term) from the first STEMI.[5,17] Development of heart failure, unstable angina, myocardial infarction and death were considered as adverse cardiovascular events. The diagnosis of unstable angina and myocardial infarction was based on clinical history, electrocardiographic changes and cardiac biomarker changes.[9,18] Heart failure was defined according to the guidelines of European Society of Cardiology.[19]

Information on follow up was obtained at the clinic visits of patients. The cause of death was determined on scrutiny of hospital notes and death certificates. No postmortems were done in the two deaths that occurred during follow up. The cause of death was classified as death due to cardiovascular and non-cardiovascular causes. Cardiovascular death was further categorized into sudden cardiac death, fatal myocardial infarction, death due to congestive heart failure, and other cardiac deaths. Sudden cardiac death was defined as sudden unexpected death either within 1 h of symptom onset or within 24 h of having been observed alive and symptom free.

The research project was approved by the local Ethical Review Committee and conducted according to the ethical guidelines outlined in the Declaration of Helsinki. Permission was obtained from all necessary local authorities to conduct the study. Informed written consent was obtained by all the participants.

Data were analyzed using appropriate statistical tests. Categorical data were analyzed using the Chi-squared test or Fisher's exact test. Comparison between cases and controls was done using two sample t-tests for independent samples assuming unequal variance. Age, BMI, smoking, diabetes mellitus and physical activity were used as independent predictor variables for adjusted means of testosterone while age, BMI, smoking, diabetes mellitus, physical activity and use of statin were used as independent variables for lipids. Age, BMI, physical activity and use of hypoglycaemic agents were used as clinical covariates for the regression model to determine the adjusted plasma glucose. Pearson correlation coefficient was used to assess the relationship between serum testosterone concentrations and other parameters. Statistical significance was defined when $p<0.05$. Multivariate logistic regression was used in calculating the odds ratios. Predictors of STEMI related complications were analyzed by binary logistic regression analysis.

RESULTS

The mean age, body mass index (BMI), waist circumference, hip circumference and waist-hip ratio were not significantly different between the two groups (all $p > 0.05$). However, systolic and diastolic blood pressure measurements were significantly higher in the patient group than the controls. Not surprisingly, the presence of cardiovascular risk factors was high in the case group compared to controls (Table 1). In the STEMI group BMI ranged from 13.0 to 33.4 kgm^{-2}. According to the proposed new classification for adult Asians 26 (25.2 %), 52 (50.5 %), 13 (12.6 %) and 12 (11.7 %) of STEMI patients were in underweight, normal, overweight and obesity categories respectively. In the control group, BMI ranged from 13.8 to 46.3 kgm^{-2} and according to the new proposed classification for Asian adults, 17 (16.5 %), 45 (43.7 %), 20 (19.4 %), 21 (20.4 %) were in the underweight, normal, overweight and obese BMI categories respectively. The prevalence of BMI categories were not significantly different between the two groups ($p = 0.198$).

In the STEMI group, waist circumference (WC) ranged from 52.5 to 104.3 cm, 9 (8.7 %) of them had WC above 90 cm, which indicated the central obesity. In the control group, WC ranged from 58.8 cm to 104.1 cm, 9 (8.7 %) of them also had WC above 90 cm. Hip circumference varied from 45 to 109 cm and waist-hip ratio ranged from 0.77 to 1.17, 29 (28.2 %) of them were having waist to hip ratio above 0.9 in STEMI patients. Among the controls the hip circumference varied from 69.1 cm to 105.5 cm and the waist to hip ratio ranged from 0.74 to 1.08, 46 (44.6 %) of them had waist to hip ratio above 0.9.

Fasting plasma glucose levels and lipids were higher in STEMI group compared to control group and statistical significance was observed ($p=0.001$). Serum total testosterone concentration showed significantly low levels in the patient group compared to controls ($p = 0.001$) which remained significant ($p = 0.001$) after the adjustment for the clinical covariates (Table 2). Following adjustment to the clinical covariates also difference of significance remained between the two groups.

When lower cut off level of total testosterone was considered as 10.4 nmol/L according to the laboratory cut off and the American College of Endocrinologists guidelines,

Table 1: Baseline Characteristics in STEMI Cases vs. Controls

Characteristics	STEMI Group (n = 103)	Control Group (n = 103)	P-value
Age (in years)	54 ± 8	52 ± 11	0.201
Weight (kg)	56.3 ± 11.1	57.4 ± 11.8	0.486
BMI (kgm^{-2})	21.2 ± 3.6	22.4 ± 5.1	0.055
Waist circumference (cm)	76.9 ± 9.9	75.9 ± 10.1	0.462
Hip (cm)	84.4 ± 8.1	83.3 ± 7.6	0.300
Waist-hip-ratio	0.91 ± 0.06	0.91 ± 0.07	0.997
SBP mmHg	136 ± 26.5	125 ±13	0.001
DBP mmHg	87 ± 18	79 ± 8	0.001
Regular physical activity	14 (13.6 %)	15 (14.6 %)	0.433
LVEF (%)	48.6 ± 11	Not done	-
Diabetes mellitus	14 (13.6 %)	Not present	-
Hypertension	20 (19.4 %)	Not present	-
Cerebrovascular disease	2 (1.9 %)	Not present	-
Family history of premature CAD	2 (1.9 %)	Not present	-
Smoking	59 (57.3 %)	Not present	-
Obesity	12 (11.7 %)	21 (20.4 %)	0.270
Statin treatment	5 (4.8 %)	Not used	-
Aspirin treatment	22 (21.4 %)	Not used	-

STEMI=ST-elevation myocardial infarction, BMI=body mass index, CAD=coronary artery disease, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, LVEF=Left ventricular ejection fraction. All values expressed as mean ± SD, Frequencies or percentages. P-Values stated calculated by two-sample t-test, Chi-square test or Fisher's exact test.

the crude odds ratio of low testosterone for CAD was 5.4 (p = 0.001, 95 % CI = 2.42 - 11.92).[20] The individuals with total testosterone levels lower than 10.4 nmol/L had an adjusted (for BMI, age, smoking) odds ratio indicating 5.6 times risk for developing STEMI (p = 0.001; OR = 5.66; 95 % CI = 2.32 - 13.84) compared to those above the cut off value. The results showed that total testosterone, plasma glucose, total cholesterol, LDL-Ch and triglycerides were significant independent biochemical predictors of STEMI (Table 3).

Cardiac troponin I was elevated in all patients. During the hospital stay 50 (48.5%) patients developed complications, but no deaths were reported. Heart failure 34 (33.0%) was the most common in-hospital complication. The majority of patients 91(88.3%) were treated with thrombolysis (streptokinase), except for 12 patients (11.7%) who had one or more contraindications for its use.

The duration of hospital stay varied from day three to five. The clinical development of adverse events were observed, during the first 30 days (short-term), > 1-3 months, > 3-6 months (medium term) and > 6 months to one year (long-term) in 6 (5.8 %), 6 (5.8 %), 2 (1.9 %) and 5 (4.8 %) patients respectively. There were 2 (1.7%) deaths, 7 (5.8%) recurrent myocardial infarctions and 30 (25%) patients with unstable angina. Only 7 (5.8%) needed interventional treatment, while the rest of the patients were managed medically. There were no new events of symptomatic heart failure that required admission were reported during the follow up. The two deaths were due to a fatal myocardial infarction and due to a non-cardiac cause.

The left ventricular ejection fraction during hospital stay, serum cardiac troponin I and total testosterone were significant independent predictors of in-hospital complications (Table 4), but none of the other measurements were significantly related to the major in-

Table 2: Comparison of Biochemical Measurements

Measurements	Patients (n = 103) Unadjusted	Controls (n = 103) Unadjusted	P-value	Patient (n =103) Adjusted*	Controls (n =103) Adjusted*	P-value
TT (nmol/L)	11.47 ± 3.3	18.15 ± 7.2	0.001	11.49 ± 0.69	18.12 ± 6.80	0.001
TCh (mmol/L)	6.0 ± 2.3	5.1 ± 1.6	0.001	6.0 ± 0.7	5.1 ± 0.2	0.001
HDL-Ch (mmol/L)	1.1± 0.5	1.3 ± 0.6	0.001	1.1 ± 0.1	1.3 ± 0.2	0.001
LDL-Ch (mmol/L)	4.5 ± 2.3	3.1 ± 0.5	0.001	4.5 ± 0.8	3.1 ± 0.1	0.001
TGs (mmol/L)	2.1 ± 1.0	1.5 ± 0.8	0.001	2.1 ± 0.4	1.5 ± 0.1	0.001
PG (mmol/L)	6.0 ± 2.0	5.0 ± 0.6	0.001	6.0 ± 0.8	5.0 ± 0.1	0.001

TT = Total testosterone, TGs = Triglycerides, TCh = Total cholesterol, HDL-Ch = High density lipoprotein cholesterol, LDL-Ch = Low density lipoprotein cholesterol, PG = Plasma glucose. All values expressed as mean ± SD. p-Values stated calculated by two-sample t-test.* the measurements are adjusted for clinical covariates ; TT(Age, BMI, smoking and diabetes mellitus, physical activity), Lipids (Age, BMI, smoking, diabetes mellitus, physical activity and use of statin), PG (Age, BMI, physical activity and use of hypoglycaemic agents) in the regression analysis.

Table 3: Independent Biochemical Predictors of STEMI

Predictors	P-value	Odds ratio
TT	0.001	0.75
Tch	0.004	0.52
LDL-Ch	0.001	2.49
Tgs	0.001	3.33
PG	0.049	1.63

Results of the multivariate logistic regression analysis presented as odds ratio (OR) and confidence interval (CI). (Patient = 103, Controls = 103). TT = Total testosterone, TGs = Triglycerides, TCh = Total cholesterol, LDL-Ch = Low density lipoprotein cholesterol, PG = Plasma glucose

Table 4: Predictors of in-Hospital Complications

Predictors	P-value	Odds Ratio	95 % CI
LVEF %	0.001	0.90	0.85 - 0.95
Creatinine	0.222	0.99	0.97 - 1.01
cTnI	0.030	1.01	1.00 - 1.02
TT	0.003	1.68	1.20 - 2.36
Tch	0.720	0.77	0.19 - 3.13
LDL-Ch	0.606	1.44	0.36 - 5.68
Tgs	0.696	0.88	0.46 - 1.68
PG	0.549	0.93	0.72 - 1.19

Results of the logistic regression analysis are presented as odds ratio (OR) and confidence intervals (CI). TT = Total testosterone, TGs = Triglycerides, Tch = Total cholesterol, LDL-Ch = Low density lipoprotein cholesterol, PG = Plasma glucose, cTnI = Cardiac troponin I, LV EF - Left ventricular ejection fraction.

hospital complications. However, none of the above predictors showed significant association with the adverse cardiovascular events developed following discharge from hospital.

DISCUSSION

In the present study, it was found that basal serum total testosterone levels (on admission) in patients with first STEMI were significantly lower than that in controls. Findings of our study are consistent with the existing epidemiological studies which have identified an inverse association between testosterone and CAD in men.[21-23] Moreover there are studies that link reduced testosterone concentrations to premature CAD.[14] Further, there is evidence suggesting that the testosterone level is significantly lower in patients with new acute myocardial infarction patients.[1-3] Pugh et al, (2002) revealed low levels of baseline (on admission) total and bio-available testosterone in patients with MI compared to controls.[2] Mohamad, et al, (2007) showed that both total and free testosterone level were significantly lower in patients with acute myocardial infarction compared to old MI patients and patients with normal coronary angiograms.[3]

Our study revealed that plasma glucose, lipid measurements and blood pressure were significantly higher in the patients compared to controls. Recent studies showed that low endogenous testosterone was related to cardiovascular disease and its risk factors, including hypertension, dyslipidaemia, and diabetes mellitus.[24-26] However, in our study the anthropometric measurements and the prevalence of obesity among the cases were not significantly different from the controls in contrast to prior evidence.[27]

The anti-atherogenic mechanism of sex hormones is largely unknown, but several hypotheses have been proposed to explain that recently. Population studies have shown that systolic and diastolic blood pressures are inversely correlated with testosterone implying vasodilatory effect of testosterone.[28] The conversion of testosterone to oestrogens occurs locally by the action of aromatase enzyme. Oestrogen is now considered to be beneficial to the vascular system in men by different mechanisms.[29] Sex hormones influence lipid profile by direct effect on lipoprotein production, degradation and secretion. Effect of testosterone on lipid profile may be explained by different mechanisms. Testosterone may directly relate with HDL-Ch levels, perhaps by regulating the activities of enzymes involved in HDL-Ch metabolism such as hepatic lipase.[30] Alternatively, the relationship of testosterone with lipids may be due to peripheral conversion of testosterone to 17β-oestradiol.[31] Conversion of testosterone to oestradiol by aromatization appears fundamental for the vascular protective effects in males. It is like castration, aromatization inhibition causes a substantial increase in fatty streaks in vessel walls.[32]

Our study showed a high odds ratio for low testosterone as a risk factor for STEMI. Therefore our results also support the hypothesis that hypotestosteronaemia is likely to increase the risk of CAD which is in accord with prior reports.[14] Findings of our study are consistent with prior reports where total testosterone has been introduced as an independent predictor of CAD.[14,23] Therefore it could be further hypothesized that low testosterone levels may be a risk factor leading to CAD. Moreover, in an Asian study it was revealed that low plasma testosterone level was associated with cardiovascular events in middle-aged men independent of other risk factors indicating that a low testosterone level is an independent risk factor for cardiovascular disease events.[33] The results of our study are keeping with these results, confirming that that a low testosterone level may be a risk factor of STEMI. However, one other study found that no independent association between androgens (TT and FT) and CAD.[34]

Moreover, our findings suggested that total cholesterol, LDL-Ch, triglycerides and plasma glucose were independent predictors of STEMI. Turhan et al, (2007) demonstrated diabetes mellitus as a risk factor of premature CAD.[14] In addition, Davoodig, et al, (2007) suggested total cholesterol and LDL-cholesterol as independent predictors of CAD and Turhan, et al, (2007) showed hyperlipdaemia as an independent predictor of premature CAD.[14,34]

It was known that endogenous testosterone was associated with cardiovascular mortality and all-cause mortality independent of age.[4] It has been shown in the Tromso study that men with lowest free testosterone had increased risk of all-cause mortality.[35] Another investigator has recently evaluated the association between serum testosterone levels and 30-day mortality in patients with acute myocardial infarction and showed that a low level of testosterone was independently related to total short-term mortality.[36] Furthermore a prospective study conducted on a larger group of patients referred for coronary angiography showed that low levels of free testosterone (FT) were independently associated with the congestive cardiac failure mortality however, no significant associations were observed between FT and other cardiovascular and cancer related mortality.[6,7] The degree of association reflected by the odds ratios (OR) of predictors of complications of STEMI was marginally raised in our study, although statistical significance was observed. The OR of 1.68 for testosterone indicates an effect of testosterone on complications of myocardial infarction. However, our results showed that testosterone was not associated with the morbidity beyond the acute period. According to the results of our study, only 7 (5.8%) needed interventional treatment, while the rest of the patients were managed medically. A low rate of intervention may be due to limited facilities available for revascularization procedures for acute myocardial infarction. Therefore patients have wait for a considerably long time to get the procedure done in the state sector hospitals.

Our study included patients with acute STEMI which is a subset of coronary artery diseases where the association between testosterone has not been well studied as other subsets (e.g. angiographically-proven coronary artery disease). Furthermore, the study also has follow up information up to one year. Hence, this study contributes to improved understanding of this association. Therefore it requires further proof using a larger cohort of patients. However, further investigations are required to understand the precise mechanism underlying our observation and its clinical applications.

Limitations

Estimation of sex hormone binding globulin, free testosterone, bio-available testosterone and oestradiol could not be performed due to limited facilities and financial constraints.

CONCLUSION

In conclusion, men with ST-elevation myocardial infarction have significantly lower concentrations of basal (on-admission) serum total testosterone compared to controls. Total testosterone was an independent predictor of STEMI and low testosterone level may be a risk factor of STEMI. Testosterone was independently related to the development of in-hospital complications, but not beyond this period.

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REFERENCES

1. Tripathi Y, Hegde BM. Serum estradiol and testosterone levels following acute myocardial infarction in men. Indian J Physiol Pharmacol 1998;42:291-4.
2. 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;28:161-73.
3. Mohamad MJ, Mohamad MA, Karayyem M, Hairi A, Hader AA. Serum levels of sex hormones in men with acute myocardial infarction. Neuro Endocrinol Lett 2007;28:182-6.
4. Khaw KT, Dowsett M, Folkerd E, Bingham S, , Luben R, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. Circulation 2007;116:2694-701.
5. Militaru C, Donoiu I, Dracea O, Ionescu DD. Serum testosterone and short-term mortality in men with acute myocardial infarction. Cardiol J 2010;17:249-53.
6. Wehr E, Pilz S, Boehm BO, März W, Grammer T, Obermayer-Pietsch B. Low free testosterone is associated with heart failure mortality in older men referred for coronary angiography. Eur J Heart Fail 2011;13:482-8.
7. Wehr E, Pilz S, Boehm BO, März W, Grammer TB, Obermayer-Pietsch B. Sex steroids and mortality in men referred for coronary angiography. Clin Endocrinol

(Oxf) 2010;73:613-21.

8. Dhalla S, Kopec JA. The CAGE questionnaire for alcohol misuse: a review of reliability and validity studies. Clin Invest Med 2007;30:33-41.
9. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third Universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581-98.
10. The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1598-660.
11. Brambilla DJ, Matsumoto AM, Araujo AB, McKinlay JB. The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. J Clin Endocrinol Metab 2009;94:907-13.
12. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Report of WHO/IDF Consultation. Geneva: WHO; 2006.
13. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo J L, et al. National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.
14. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2286-497.
15. Turhan S, Tulunay C, Gulec S, Ozdol C, Kilickap M, Altin T, et al. The association between androgen levels and premature coronary artery disease in men. Coron Artery Dis 2007;18:159-62.
16. International Association for the Study of Obesity (IASO) and International Obesity Task Force (IOTF). The Asia Pacific perspective: redefining obesity and its treatment. Philippines: WHO Western Pacific Region; 2000.
17. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low- density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
18. James SK, Lindahl B, Timmer JR, , Siegbahn A, Stridsberg M, et al. Usefulness of biomarkers for predicting long-term mortality in patients with diabetes mellitus and non-ST-elevation acute coronary syndromes (a GUSTO IV sub study). Am J Cardiol 2006;97:167-72.
19. McMurray JJ1, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847.
20. Petak SM, Nankin HR, Spark RF, Swerdloff RS, Rodriguez-Rigau LJ. American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients--2002 update. Endocr Pract 2002;8:440-56.
21. English KM, Mandour O, Steeds RP, Diver MJ, Jones TH, Channer KS. Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. Eur Heart J 2000;21:890-4.
22. Rosano GMC, 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;19:176-82.
23. Hu X, Rui L, Zhu T, Xia H, Yang X, Wang X, et al. Low testosterone level in middle-aged male patients with coronary artery disease. Eur J Intern Med 2011; 22:e133-e6.
24. Vikan T, Schirmer H, Njølstad I, Svartberg J. Low testosterone and sex hormone-binding globulin levels and high estradiol levels are independent predictors of type 2 diabetes in men. Eur J Endocrinol 2010;162:747-54.
25. Allan CA, McLachlan RI. Androgens and obesity. Curr Opin Endocrinol Diabetes Obes 2010;17:224-32.
26. Muraleedharan V, Jones TH. Testosterone and the metabolic syndrome. Ther Adv Endocrinol Metab 2010;1:207-23.
27. Glueck CJ, Glueck HI, Stroop D, Spiers J, Hamer T, Tracy T. Endogenous testosterone, fibrinolysis and coronary heart disease risk in hyperlipidaemic men. J Lab Clin Med 1993;122:412-20.
28. Jones RD, Pugh PJ, Jones TH, Channer KS. The vasodilatory action of testosterone: a potassium-channel opening or a calcium antagonistic action? Br J Pharmacol 2003;138:733-44.
29. Collins P. Vascular effects of hormones. Maturitas 2001;38:45-50.

30. Zambon A, Bertocco S, , Polentarutti V, , Crepaldi G. Relevance of hepatic lipase to the metabolism of triacylglycerol-rich lipoproteins. Biochem Soc Trans 2003;31:1070-4.

31. Longcope C, Pratt JH, Schneider SH, Fineberg SE. Aromatization of androgens by muscle and adipose tissue in vivo. J Clin Endocrinol Metab 1978;46:146-52.

32. Nathan L, Shi W, Dinh H, Mukherjee TK, Wang X, Lusis AJ, et al. Testosterone inhibits early atherogenesis by conversion to estradiol: critical role of aromatase. Proc Natl Acad Sci USA 2001;98:3589-93.

33. Akishita M, Hashimoto M, Ohike Y, Qgawa S, Iijima K, Eto M, et al. Low testosterone level as a predictor of cardiovascular events in Japanese men with coronary risk factors. Atherosclerosis 2010;210:232-6.

34. Davoodig G, Amirezadegan A, Borumand MA, Dehkordimr MR, Kazemisaeid A, Yaminisharif A. The relationship between level of androgenic hormones and coronary artery disease in men. Cardiovasc J Afr 2007;18:362-6.

35. Vikan T, Schirmer H, Njolstad I, Svartberg J. Endogenous sex hormones and the prospective association with cardiovascular disease and mortality in men: the Tromso Study. Eur J Endocrinol 2009;161:435-42.