Association of testosterone and CRP with the severity of coronary artery disease among male patients: A case-control hospital-based study

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ABSTRACT

Epidemiological studies have found an inverse association between testosterone and coronary artery disease (CAD), while a positive association was observed between inflammation and CAD in men, but the relationships are inconsistent. The study aimed to investigate, whether serum levels of total testosterone (TT) and high sensitivity C-reactive protein (hs-CRP) differ in men with CAD from those without CAD and to evaluate the relationship of serum TT and hs-CRP with the severity of CAD.

Three hundred and nine males (103 patients with ST-elevation myocardial infarction (STEMI), 103 patients with angiographically-proven CAD, 103 controls without having a history of CAD) were recruited. Serum TT, hs-CRP, lipids, cardiac troponin I (cTnI) and plasma glucose were estimated. Three angiogram-based severity scores (Gensini, Leaman and vessel score) were used in the severity assessment of angiographically-proven CAD. Killip classes, TIMI (Thrombolysis In Myocardial Infarction), GRACE (Global Registry of Acute Coronary Events) and modified Sylvester ECG (electrocardiographic) QRS scores were used in assessing the severity of STEMI.

Mean basal serum TT in patients with CAD was significantly lower than controls ($p = 0.001$). Low TT level showed high adjusted (age, BMI, smoking) odds ratio as a risk factor for angiographically proven CAD ($p = 0.007$, OR = 3.4, CI = 1.41-8.61) and STEMI ($p = 0.001$, OR = 5.6, CI = 2.32-13.84). The mean basal hs-CRP concentration in patients with CAD was significantly higher compared to controls ($p = 0.001$). TT showed a significant negative correlation with hs-CRP and LDL-Ch, while a significant positive correlation was seen between TT and HDL-Ch. TT levels were not associated with the severity of angiographically-proven CAD, but hs-CRP levels were associated with the severity. TT level did not show a significant association with the severity of STEMI assessed by clinical risk scores, while hs-CRP level showed a significant positive association with the severity.

In conclusion, TT levels were low in patients with CAD compared to controls, while hs-CRP levels were higher in patients compared to controls. TT did not show a significant correlation with the severity of CAD, while hs-CRP did show a significant positive correlation. TT was negatively correlated with hs-CRP. Low levels of TT and inflammation reflected by high levels of hs-CRP play a role in the development of CAD.

Dr. Chandima Madhu Wickramatilake, Senior Lecturer, Department of Biochemistry, conducted her PhD research project on the title of "Association of testosterone and CRP with the severity of coronary artery disease among male patients: a case-control hospital-based study". She registered for her PhD at University of Ruhuna, Sri Lanka and the thesis was defended in May 2014. The results were published as 11 research papers in peer reviewed journals. Further, 20 abstracts were presented in national and international forums. Professor K Rajasooriya oration was delivered at the Annual Academic Sessions of Ceylon College of Physicians in 2015, based on the findings of the study. The publications of the study received awards such as best oral presentation at Annual Academic Sessions of Sri Lanka Heart Association 2014 and G. R. Handy Award offered by Sri Lanka Medical Association for best original article published in the field of Cardiovascular Medicine in 2014.

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Introduction

Sex hormones are known to have cardiovascular effects and epidemiological studies have identified an inverse association between testosterone and coronary artery disease (CAD) in men (1,2).

There are several studies that support the idea of the role of low testosterone as an independent risk factor of CAD (1). There are studies that have shown a relationship between low endogenous testosterone levels and risk factors of CAD, including haemostatic risk factors, obesity, hypertension, dyslipidaemia, diabetes mellitus and metabolic syndrome (3).

There are few studies, which investigated the association between testosterone and the severity of CAD. Some studies show a positive association between testosterone and atherosclerotic burden (1), while others do not (4). Therefore, the findings are inconsistent and need further evaluation.

Atherothrombosis of the coronary vessels is understood as a disorder of inflammation and lipid accumulation (5). High-sensitivity C-reactive protein (hs-CRP) proposed as a new coronary risk marker and may reflect either an acute or chronic inflammation. Hs-CRP has attracted increasing attention in recent years following epidemiologic studies, consistently showing hs-CRP as an independent predictor associated with risk of future cardiovascular events in those who are predisposed (6).

Furthermore, there is insufficient evidence supporting the association between hs-CRP and the atherosclerotic burden. These studies have reported conflicting results on the association of hs-CRP with the extent of atherosclerosis (7,8) and therefore need further evaluation.

The morbidity from non-communicable disease has increased globally. Therefore health and economic implications of caring for these patients are enormous. Hence, identification of novel risk factors which are modifiable is of immense importance in the primary prevention. The present study may potentially help to identify the relationship between testosterone, inflammation and CAD. In the local setting the association of testosterone with CAD has not been studied, although this relationship has been studied in Western population. Therefore our study would contribute in filling gaps in the knowledge of this association in the Sri Lankan population.

Therefore aims of the study were to investigate, whether serum levels of total testosterone (TT) and high sensitivity C-reactive protein (hs-CRP) differ in men with coronary artery disease from those without CAD and to evaluate the relationship of serum TT and hs-CRP with the severity of CAD.

Methods

This study was conducted as a case-control study. Three hundred and nine males (103 patients with ST-elevation myocardial infarction (STEMI), 103 patients with angiographically-proven CAD, 103 controls without having a history of CAD) were recruited. Morning serum total testosterone (TT) was estimated by enzyme immunoassay. Serum hs-CRP was estimated by turbidimetry. After a preliminary study done on patients with acute coronary syndrome, the optimal time to obtain blood for TT and hs-CRP was decided as on admission from patients with STEMI. STEMI patients who admitted in the morning before 10.00 hours were recruited. Serum fasting lipids (total cholesterol, triglycerides, HDL-Ch) were estimated by a spectrophotometry based test kit. Serum cardiac troponin I (cTnI) was estimated by enzyme labeled chemiluminescent immunometric assay. Fasting plasma glucose was estimated by spectrophotometry based test kit. Three angiogram-based severity scores such as Gensini, Leaman (9,10) and vessel score (11) were used in the severity assessment of angiographically proven CAD. Killip classes (12), TIMI (Thrombolysis In Myocardial Infarction) (13), GRACE (Global Registry of Acute Coronary Events) (14) and modified Sylvester ECG (electrocardiographic) QRS scores (15) were used in assessing the severity of In STEMI.

Data were analysed using appropriate statistical tools with Minitab version 15 for Windows. Categorical baseline data were displayed as frequencies and percentages and were analysed using Chi-squared test or Fisher's exact test. Numerical data were examined for normality and presented as mean ± SD. Adjusted means of hormone, lipid and plasma glucose levels were

calculated using multiple regressions models. Statistical significance was defined when $p < 0.05$. Multivariate logistic regression analysis was used in calculating the adjusted (for BMI, age, smoking) odds ratios for low testosterone as risk factors for CAD.

Coronary vessel score was divided into three groups as one, two and three vessel disease. Gensini and Leaman scores were categorised into quartiles and mean levels of biochemical variables in the respective groups were compared using ANOVA. Clinical risk scores (TIMI and GRACE) and ECG score were categorised into quartiles and the biochemical variables in the respective groups were compared using ANOVA

Ethical clearance was obtained from the Ethical Review Committee of Faculty of Medicine, University of Ruhuna, Galle. Informed written consent was obtained from all the participants.

Results

Baseline characteristics of the study groups are shown in Table 1 and 2.

Mean basal serum TT in patients with angiographically-proven CAD was significantly lower than controls and mean basal (on admission) serum TT in STEMI patients was significantly lower than controls. The difference remained statistically significant after adjustment for confounding variables.

Serum TT was found to be an independent predictor of both angiographically-proven CAD ($p = 0.001$, OR = 0.68, CI = 0.58-0.79) and STEMI ($p = 0.001$, OR = 0.75, CI = 0.66-0.85). Low testosterone level showed high adjusted (age, BMI, smoking) odds ratio as a risk factor for angiographically-proven CAD ($p = 0.007$, OR = 3.4, CI = 1.41-8.61) and STEMI ($p = 0.001$, OR = 5.6, CI = 2.32-13.84).

Total testosterone showed a significant negative correlation with hs-CRP and LDL-Ch, while a significant positive correlation was seen between TT and HDL-Ch (Table 3).

Table 1: Comparison of baseline characteristics between angiographically-proven CAD patients and controls

Measurements	Angiographically proven CAD patients n = 103 unadjusted	Controls n = 103 unadjusted	*p*
Age (years)	57 ± 8	52 ± 11	0.001
BMI (kgm^2)	23.9 ± 3	22.4 ± 5	0.001
TT (nmol/L)	11.4 ± 2.7	18.1 ± 7.2	0.001
hs-CRP (mg/L)	3.4 ± 1.62	1.7 ± 0.6	0.001
TGs (mmol/L)	2.5 ± 1.0	1.5 ± 0.8	0.001
TCh (mmol/L)	5.9 ± 2.8	5.2 ± 1.6	0.022
HDL-Ch (mmol/L)	1.1 ± 0.5	1.4 ± 0.6	0.001
LDL-Ch (mmol/L)	3.9 ± 1.2	3.1 ± 0.5	0.001
PG (mmol/L)	5.5 ± 1.4	5.1 ± 0.6	0.007

All values expressed as mean ± SD. *p*-Values stated calculated by two-sample *t*-test. Multiple regression model was used in adjusting 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), hs -CRP (Age, BMI, smoking, diabetes mellitus, statin and aspirin use) in the regression analysis. CAD = Coronary artery disease, TT = Total testosterone, hs-CRP = High sensitivity -C-reactive protein, TGs = Triglycerides, TCh = Total cholesterol, HDL-Ch = High density lipoprotein cholesterol, LDL -Ch = Low density lipoprotein cholesterol, PG = Plasma glucose.

Table 2: Comparison of baseline characteristics between STEMI patients and controls

Measurements	STEMI patients n = 103 unadjusted	Controls n = 103 unadjusted	*p*
Age (in years)	54 ± 8	52 ± 11	0.201
BMI (kgm^2)	21.2 ± 3.6	22.4 ± 5.1	0.055
TT (nmol/L)	11.4 ± 3.2	18.1 ± 7.2	0.001
hs-CRP (mg/L)	3.7 ± 0.84	1.7 ± 0.60	0.001
TGs (mmol/L)	2.1 ± 1.0	1.5 ± 0.8	0.001
TCh (mmol/L)	6.0 ± 2.4	5.1 ± 1.6	0.001
HDL-Ch (mmol/L)	1.1 ± 0.5	1.3 ± 0.6	0.001
LDL-Ch (mmol/L)	4.5 ± 2.4	3.1 ± 0.5	0.001
PG (mmol/L)	6.0 ± 2.06	5.0 ± 0.6	0.001

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

Total testosterone showed a significant negative correlation with hs-CRP and LDL-Ch, while a significant positive correlation was seen between TT and HDL-Ch (Table 3).

Table 3: Correlation between testosterone and other measurements in angiographically proven CAD patients

Measurement	*r*	*p*
Age	-0.711	0.001
BMI	-0.012	0.862
Waist circumference	-0.266	0.001
Hip circumference	-0.187	0.007
W/H ratio	-0.256	0.001
PG	-0.081	0.246
TCh	-0.071	0.313
TGs	-0.130	0.064
LDL-Ch	-0.333	0.001
HDL-Ch	0.490	0.001
hs-CRP	-0.598	0.001

Pearson correlation coefficient was used in calculating the *p*-Values.
hs-CRP = High sensitivity-C- reactive protein, TGs = Triglycerides,
TCh = Total cholesterol, HDL-Ch = High density lipoprotein cholesterol,
LDL-Ch = Low density lipoprotein cholesterol, PG = Plasma glucose.

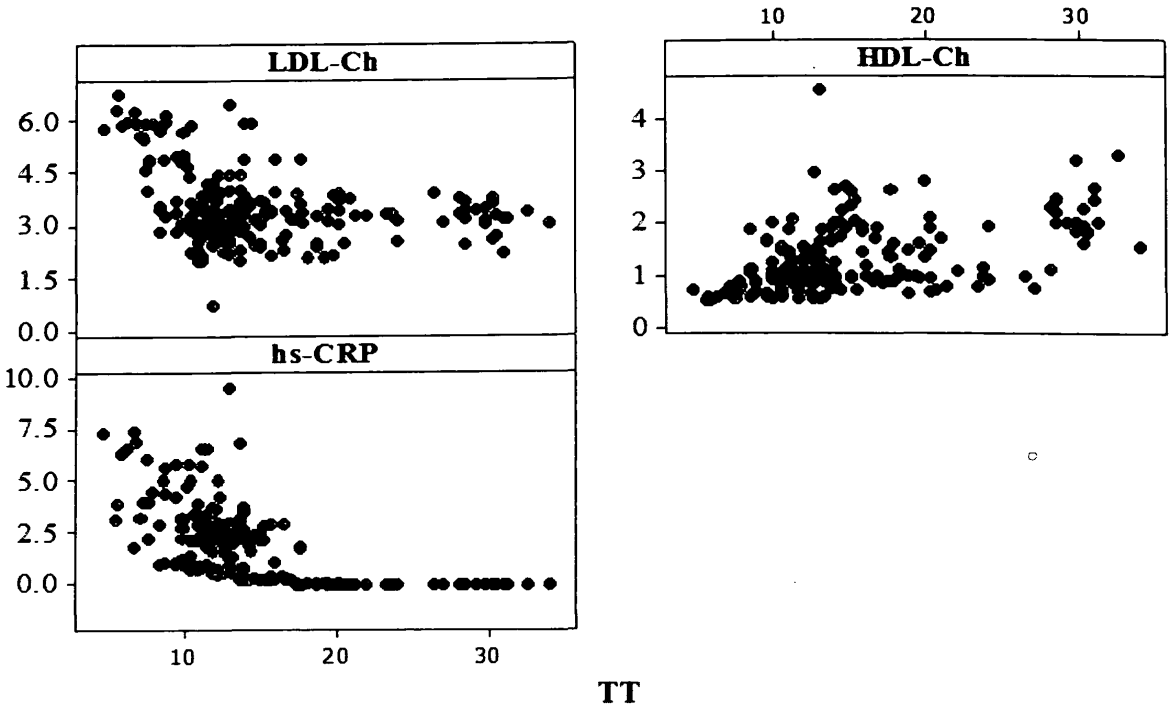

Figure 1: Scatter plot showing the correlation between serum total testosterone concentration and biochemical variables in angiographically proven CAD patients. TT = Total testosterone, LDL-Ch = Low density lipoprotein cholesterol, HDL-Ch = High density lipoprotein cholesterol, hs-CRP = High sensitivity C-reactive protein.

In angiographically proven CAD patients, the TT levels were not significantly different according to the severity categories of vessel score ($p = 0.373$), Leaman score ($p = 0.694$) and Gensini score ($p = 0.329$), but hs-CRP level showed a significant difference among the severity categories estimated by the respective scores ($p = 0.001$, $p = 0.028$, $p = 0.015$). In STEMI patients the TT level did not show a significant association with the severity of STEMI assessed by cTnI ($p = 0.129$), Killip classes ($p = 0.864$), TIMI ($p = 0.783$), GRACE ($p = 0.342$) and ECG score ($p = 0.659$), but it showed a significant association with left ventricular ejection fraction ($p = 0.049$). However, hs-CRP level showed a significant positive association with the severity assessed by Killip classes ($p = 0.025$), TIMI ($p = 0.017$), GRACE ($p = 0.002$) and ECG scores ($p = 0.044$).

Discussion

In the present study, we found that mean basal serum TT levels in patients with angiographically-proven CAD and mean basal serum TT levels (on admission) in patients with first STEMI were significantly lower than that in controls. These findings are consistent with several previous case-control studies (1,2) linking lower total testosterone levels to CAD. There is evidence suggesting that TT level is significantly lower in patients with myocardial infarction compared to controls (16).

Serum hs-CRP levels were significantly higher in patients compared to controls according to our study. This is in accord with the existing reports that have shown higher hs-CRP level in patients with unstable angina and acute myocardial infarction (1,17). This supports the hypothesis that hs-CRP is a marker of vascular inflammation and a risk factor of CAD (18). However, there are studies where no significant differences of hs-CRP levels have been found between patients with coronary artery disease and subjects with normal coronary arteries based on coronary angiograms (4).

The elevation of hs-CRP in the diseased group indicates enhanced systemic inflammatory process that may have caused atherosclerosis. One of the current concepts in the pathogenesis of atherosclerosis is the chronic inflammation, which is

initiated by various insults to the vascular endothelium and its dysfunction (19).

There was a significant difference in serum testosterone and lipid concentrations between both patient groups and control group which was consistent and remained unchanged following adjustments to the clinical covariates. There was a significant positive correlation between HDL-Ch and testosterone, while a significant negative correlation was elicited between LDL-Ch and testosterone. Total cholesterol and triglycerides showed a negative correlation with testosterone, although statistically not significant. The low testosterone level was found to be associated with adverse lipid profile and found to correlate positively with cardio-protective HDL-Ch (1). Few showed a negative correlation between testosterone and HDL-cholesterol (19). Previous reports suggested that atherogenic LDL-Ch was negatively correlated with testosterone (1).

The inverse relationship between serum total testosterone and hs-CRP may indicate that low levels of endogenous testosterone may encourage low-grade chronic inflammation and hence, atherogenic environment. Reports on the association of testosterone with hs-CRP are restricted to few, all showing negative correlation, but with variable strength relationships (1,4). However, the involvement of a third factor which influence the interplay between low testosterone, inflammation, elevated hs-CRP and CAD has not been excluded.

The severity of angiographically proven CAD assessed by the vessel score, Gensini and Leaman scores did not show a significant association with serum total testosterone concentration in our study. Several previous reports showed that the degree of CAD severity assessed by coronary angiogram was not correlated with serum testosterone levels (4,21). Yet, there are studies that have found a significant negative correlation between angiographically-assessed severities of CAD with serum testosterone levels (1,2).

Moreover, there is limited evidence on the association of hs-CRP with the atherosclerotic burden. These studies show variable associations between C-reactive protein concentration and the extent of atherosclerosis. Some studies have shown that serum hs-CRP concentrations are correlated with the severity of peripheral arterial disease assessed by ankle brachial pressure index (7), when others show a correlation with the extent and severity of CAD (22). Our study also shows a positive correlation between hs-CRP and CAD severity assessed by three types of scoring systems with a significant difference among the severity categories. In contrast, there are studies suggesting that hs-CRP is not associated with the severity of CAD assessed angiographically (8).

There are few studies which investigated the association of testosterone with the extent of myocardial infarction; some of which have shown inverse association of testosterone with the extent of myocardial infarction assessed by the magnitude of release of cardiac biomarkers or by the development of clinical complications (23) found a trend of correlation between changes in TT and the maximum myosin concentration, showing a relationship between the hormonal changes and the severity of the myocardial infarction (24) has shown an inverse correlation between peak CK (creatine kinase) and TT on day three of myocardial infarction. However, in our study cTnI levels at 20th hour from the onset of symptoms showed no significant correlation with testosterone. Left ventricular ejection fraction of two-dimensional echocardiography showed a significant positive correlation with testosterone.

Furthermore, in our study, we graded the severity of myocardial infarction using Killip classes and the clinical risk scores such as TIMI, GRACE and modified Sylvester QRS scoring system. It was found that serum TT concentration was not correlated with the severity assessed by these scores. There is almost no literature available on the relationship between testosterone and the severity of myocardial infarction graded by these clinical risks scores, although these scores have been used in the risk assessment in relation to myocardial injury.

Conclusions

In conclusion, TT levels were low in patients with angiographically-proven CAD and in patients with STEMI compared to controls, while hs-CRP levels were higher in both groups of patients compared to controls. Total testosterone did not show a

significant correlation with the angiographic severity of CAD, while hs-CRP did show a significant positive correlation. Severity of myocardial infarction graded by clinical risk scores and ECG score was not correlated with the testosterone concentration, but positively correlated with hs-CRP. Total testosterone was negatively correlated with hs-CRP. A significant positive association was found between testosterone and HDL-Ch, while a negative association was found between testosterone and LDL-Ch. Low levels of testosterone, inflammation reflected by high levels of hs-CRP and abnormal lipid profile play a role in the development of coronary artery disease. Further studies are required to understand the precise mechanisms underlying these observations and its clinical applications.

Acknowledgements

I wish to express my sincere gratitude to Prof. M. R. Mohideen, Senior Professor in Internal Medicine, International Medical University IMU Clinical School, Malaysia and Prof. Chitra Pathirana, Senior Professor of Biochemistry, Department of Biochemistry, Faculty of Medicine, University of Ruhuna, Galle for being my supervisors sparing their valuable time and giving me enormous guidance and encouragement. I extend my gratitude to Dr. B.P.S. Withanawasam, Cardiologist, Teaching Hospital, Kegalle, Sri Lanka for the valuable services rendered in interpreting the coronary angiograms and formulating the severity scores. I wish to express my gratitude to Mrs. D.A.B.N. Amerasekara (Statistician, Applied Statistic Association, Sri Lanka), Senior Lecturer, Department of Crop Science, Faculty of Agriculture, University of Ruhuna, Sri Lanka for providing statistical advice. I wish to acknowledge the University Grants Commission, Sri Lanka for the financial assistance provided for the project (Grant No: UGC/ICD/CRF/2009/2/47).

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