

## ORIGINAL ARTICLE

# Testosterone is negatively associated with the severity of coronary atherosclerosis in men

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This study aimed to determine whether plasma testosterone is associated with the severity of coronary atherosclerosis in a group of 803 men who underwent elective coronary angiography. Testosterone levels were measured in 803 male patients who were categorized into three groups according to testosterone level tertiles. All patients underwent elective coronary angiography, and the severity of coronary artery disease (CAD) was determined by the Gensini score. Moreover, patients were classified into two groups according to Gensini scores (score  $\leq 26$  and score  $> 26$ ) using the median values as cutoff points. The plasma testosterone levels were measured by an ELISA kit. The level of testosterone was negatively associated with the Gensini score ( $r = -0.188$ ;  $P = 0.000$ ). A multiple linear regression analysis revealed that testosterone was an independent risk factor for the Gensini score ( $\beta = -0.110$ ;  $P = 0.002$ ) after adjusting for confounding covariates. In a multivariate logistic regression model, the severity of CAD was shown to be significantly lower in the third tertile (highest) of testosterone compared to the first tertile (lowest) of testosterone (odds ratio (OR) = 0.465; 95% confidence interval (CI): 0.327–0.662;  $P = 0.000$ ). In this study, patients with lower testosterone levels had higher Gensini scores in a group of 803 men who underwent elective coronary angiography. Additional studies are needed to clarify the direction of causality and possible underlying mechanisms.

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**Keywords:** coronary artery disease (CAD); Gensini score; testosterone

## INTRODUCTION

Cardiovascular disease remains the leading cause of death in most developed or developing countries,<sup>1</sup> and men are at higher risk for coronary artery disease (CAD) when compared to women,<sup>2</sup> despite the advanced prevention of known risk factors. Harman *et al.*<sup>3</sup> reported that low serum total testosterone is common in an ageing male population and has a prevalence of 30% in men over the age of 60 years. Phillips *et al.*<sup>4</sup> first reported an inverse relationship between free testosterone levels and the degree of CAD in a series of patients undergoing coronary angiography. However, epidemiological studies have historically found no association between physiologically elevated androgen levels and atherosclerosis.<sup>5,6</sup> Yeap *et al.*<sup>7</sup> reported that lower testosterone levels predicted cardiovascular events in older men and are associated with higher cardiovascular and overall mortality. Akishita *et al.*<sup>8</sup> indicated that a low testosterone level was an independent risk factor for cardiovascular disease events in middle-aged Japanese men with coronary risk factors. In addition, a similar relationship has been shown to exist between decreased testosterone concentrations and the extent and severity of coronary atheromas in men undergoing coronary angiography.<sup>9</sup> These evidences indicate that testosterone may be involved in the pathogenesis of CAD and may provide a protective role in the development of cardiovascular disease in men. The serum testosterone level has been shown to be decreased with advancing age

in men,<sup>10</sup> and testosterone supplementation might reduce morbidity, increase longevity and preserve health in ageing men.<sup>11</sup>

Prior studies had lower reliability and smaller quantities compared to our present study that determine the relationship between plasma testosterone and the severity of coronary atherosclerosis.

## MATERIALS AND METHODS

### Study subjects

The patients were admitted to the First Affiliated Hospital of Nanjing Medical University, Nanjing (China) between 4 March 2003 and 12 May 2006. A total of 803 consecutive patients, 28–83 years of age (mean 62 years) who were undergoing elective coronary angiography due to CAD were enrolled. Diabetes was diagnosed using the known features of diabetes, including a plasma glucose level of  $11.1 \text{ mmol l}^{-1}$ , a fasting plasma glucose concentration of  $7.0 \text{ mmol l}^{-1}$  after at least 8 h of fasting or a 2-h plasma glucose level of  $11.1 \text{ mmol l}^{-1}$  during an oral glucose tolerance test.<sup>12</sup> The patients were on pharmacological treatment prior to the coronary angiography.

The exclusion criteria were as follows: inflammatory disease (white blood cell count  $> 10.0 \times 10^9 \text{ l}^{-1}$ ; neutrophil percentage  $> 70\%$ ); pre-catheterisation heart failure (Killip class  $\geq 2$  after acute myocardial infarction); severe chronic heart failure (New York Heart Association functional class  $\geq \text{III}$ ); renal or thyroid dysfunction (serum creatinine

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**Table 1** Baseline, clinical and biochemical characteristics based on testosterone tertiles in men

Variable	Testosterone tertile (ng ml <sup>-1</sup> )			P
	0.002–3.391 (n=267)	3.392–4.382 (n=269)	4.383–19.002 (n=267)	
Age (year)	66.0 (57.0–72.0)	64.0 (55.0–71.0)	60.0 (51.0–69.0)	0.000
BMI (kg m <sup>-2</sup> )	25.5 (22.5–28.5)	24.8 (21.9–27.7)	24.6 (21.7–27.5)	0.001
Gensini score	40.5 (9.8–84.0)	20.0 (0.0–51.3)	16.0 (0.75–48.0)	0.000
Cholesterol (mmol l <sup>-1</sup> )	3.98 (3.45–4.63)	4.06 (3.37–4.57)	3.94 (3.31–4.41)	0.092
Creatine kinase (mmol l <sup>-1</sup> )	82.0 (55.8–151.3)	75.0 (52.8–118.5)	75.0 (52.8–97.0)	0.001
Triglycerides (mmol l <sup>-1</sup> )	1.37 (1.05–1.89)	1.34 (0.93–2.01)	1.38 (0.98–2.00)	0.022
HDL-C (mmol l <sup>-1</sup> )	0.93 (0.78–1.07)	0.96 (0.85–1.14)	0.95 (0.82–1.11)	0.124
Creatinine (μmol l <sup>-1</sup> )	81.8 (69.0–97.0)	79.0 (69.0–91.0)	75.3 (65.0–89.0)	0.007
LDL-C (mmol l <sup>-1</sup> )	2.42 (1.98–2.99)	2.30 (1.88–2.86)	2.32 (1.84–2.71)	0.062
Glucose (mmol l <sup>-1</sup> )	5.20 (4.51–6.32)	4.73 (4.34–5.36)	4.67 (4.21–5.09)	0.000
Red blood cells (10 <sup>9</sup> l <sup>-1</sup> )	4.46 (4.02–4.82)	4.50 (4.15–4.84)	4.56 (4.11–4.90)	0.354
Haemoglobin (g l <sup>-1</sup> )	138.0 (126.5–148.0)	139.5 (128.8–147.0)	139.5 (129.7–150.0)	0.163
Smoking (yes/no)	180/87	157/112	155/112	0.041
Diabetes mellitus (yes/no)	61/206	49/220	24/243	0.000

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

≥177 μmol l<sup>-1</sup> and thyroid-stimulating hormone ≤0.3 mIU l<sup>-1</sup> or ≥5 mIU l<sup>-1</sup>, respectively), end-stage hepatic, familial hypercholesterolaemia and immunological disease.

Written informed consent was obtained from all participants before angiography, and the project was approved by the Ethics Committees of the First Affiliated Hospital of Nanjing Medical University.

#### Laboratory measurements

Blood samples were collected immediately prior to coronary angiography between 8:00 a.m. and 9:00 a.m. after a 12-h fast. The total cholesterol (TCH, mmol l<sup>-1</sup>), triglycerides (TG, mmol l<sup>-1</sup>), fasting blood glucose (mmol l<sup>-1</sup>), high-density lipoprotein cholesterol (HDL-C, mmol l<sup>-1</sup>), low-density lipoprotein cholesterol (LDL-C, mmol l<sup>-1</sup>), creatine kinase (U l<sup>-1</sup>) and creatinine (μmol l<sup>-1</sup>) levels were determined by enzymatic procedures on an automated autoanalyser (AU 2700 Olympus; First Chemical Ltd, Tokyo, Japan) at the central clinical laboratory of the First Affiliated Hospital of Nanjing Medical University.

The red blood cell (RBC) count (10<sup>9</sup> l<sup>-1</sup>) and haemoglobin level (g l<sup>-1</sup>) were determined using an automated blood analyser (Bayer Diagnostics ADVIA120; Bayer, Leverkusen, Germany). The total testosterone level (ng ml<sup>-1</sup>) was measured by enzyme immunoassay in human plasma (11-TESHU-E01-PLAS; ALPCO, Salem, NH, USA). The reference range for testosterone was 0–20 ng ml<sup>-1</sup>.

#### Evaluation

Baseline data, including age, smoking status and drinking status, were recorded after hospital admission. Smoking habits were categorized as never smoking and smoking (including formerly smoking or currently smoking). Current and ex-smokers reported the number of cigarettes smoked per day, and those who reported smoking at least one cigarette per day during the preceding year were classified as current smokers. Height and weight were measured in the clinic with participants wearing light clothing and no shoes. The body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m<sup>2</sup>).

#### Gensini coronary score

The severity of coronary stenosis in patients was estimated by the Gensini coronary score.<sup>13</sup> The Gensini score is based on the number of stenotic coronary artery segments, including the degree of luminal narrowing and the localisation of the stenosis.<sup>14</sup> The Gensini system scores the narrowing of the coronary artery lumen as follows: 1%–25%

narrowing=1; 26%–50% narrowing=2; 51%–75% narrowing=4; 76%–90% narrowing=8; 91%–99% narrowing=16; and total occlusion=32. The score is then multiplied by a factor that incorporates the importance of the lesion position in the coronary arterial tree as follows: ×5 for the left main coronary artery; ×2.5 for the proximal left anterior descending or left circumflex coronary artery; ×1.5 for the mid-segment of the left anterior descending; ×1 for the distal left anterior descending, right coronary artery or mid-distal left circumflex; and ×0.5 for any other arteries.<sup>13</sup>

#### Statistical analysis

The data were analysed with the Statistical Package for the Social Sciences (version 16.0; SPSS Inc., Chicago, IL, USA). Statistical significance was defined as a *P* value <0.05. All data were tested using the Kolmogorov–Smirnov test and presented as the mean±standard deviation or median (quartile ranges). The Kruskal–Wallis test or analysis of variance–Scheffé's *F* test was used for comparisons among groups. Categorical variables were compared by  $\chi^2$  analysis. Based on the tertile of the testosterone level, patients were classified into three groups as follows: 0.002–3.391 (*n*=267); 3.392–4.382 (*n*=269); and 4.383–19.002 (*n*=267). In addition, patients were classified into two groups according to the Gensini score (score ≤26 and score >26) using the median value as a cutoff point.

The Spearman correlation coefficient (for non-normal distributions) was used to assess the relationship between plasma testosterone concentrations and Gensini score or other risk factors of CAD. To determine the odds ratios (ORs) of the Gensini score by testosterone level tertile, a logistic regression analysis was used, with tertile 1 serving as the reference. We assessed independent predictors of the Gensini score with a stepwise multiple linear regression analysis. All *P* values were two-tailed.

## RESULTS

### Baseline, clinical and biochemical characteristics by tertile of the testosterone level in men

Baseline, clinical and biochemical characteristics of the three groups according to the testosterone level (the tertile values that were used as cutoff points) are displayed in **Table 1**. Age, BMI, creatine kinase, TG, creatinine, glucose, the Gensini score, smoking and diabetes mellitus differed among the three groups (all *P*<0.05) of patients who underwent elective coronary angiography. However, the TCH, HDL-C, LDL-C, haemoglobin levels and RBC counts were similar among the three groups (*P*>0.05).

**Table 2 Spearman correlations between the testosterone level, Gensini score and CAD risk**

Variable	Testosterone (ng ml <sup>-1</sup> )	
	Correlation coefficient	P
Age (year)	-0.120	0.001
Gensini score	-0.188	0.000
BMI (kg m <sup>-2</sup> )	-0.088	0.013
Cholesterol (mmol l <sup>-1</sup> )	-0.089	0.013
Creatine kinase (mmol l <sup>-1</sup> )	-0.124	0.001
Triglycerides (mmol l <sup>-1</sup> )	-0.089	0.013
HDL-C (mmol l <sup>-1</sup> )	0.055	0.123
Creatinine (μmol l <sup>-1</sup> )	-0.104	0.004
LDL-C (mmol l <sup>-1</sup> )	-0.089	0.013
Glucose (mmol l <sup>-1</sup> )	-0.195	0.000
Red blood cells (10 <sup>9</sup> l <sup>-1</sup> )	0.050	0.158
Haemoglobin (g l <sup>-1</sup> )	0.070	0.047

Abbreviations: BMI, body mass index; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

**Spearman correlations between the testosterone level and Gensini score and the risk of CAD**

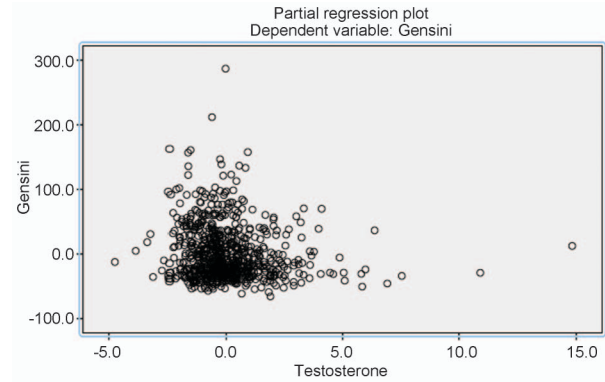
The corrections for the testosterone level and Gensini score and several cardiovascular disease risk factors are shown in **Table 2**. There was a negative association between the testosterone level and the Gensini score ( $r = -0.188$ ;  $P = 0.000$ ) based on the study population. The testosterone levels were also correlated with age ( $r = -0.120$ ;  $P = 0.000$ ), BMI ( $r = -0.088$ ;  $P = 0.013$ ), TCH ( $r = -0.089$ ;  $P = 0.013$ ), creatine kinase ( $r = -0.124$ ;  $P = 0.001$ ), TG ( $r = -0.089$ ;  $P = 0.013$ ), creatinine ( $r = -0.104$ ;  $P = 0.004$ ), LDL-C ( $r = -0.089$ ;  $P = 0.013$ ), glucose ( $r = -0.195$ ;  $P = 0.000$ ) and haemoglobin levels ( $r = 0.070$ ;  $P = 0.047$ ). No associations existed between the testosterone and HDL-C levels ( $r = 0.055$ ;  $P = 0.123$ ) or the RBC count ( $r = 0.050$ ;  $P = 0.158$ ) in men who underwent elective coronary angiography.

**A multiple linear regression analysis with the Gensini score as the dependent variable**

The Gensini score was used as the dependent variable, and the independent variables were age, BMI, RBC count, testosterone, creatine kinase, haemoglobin, glucose, LDL-C, HDL-C, creatinine, TCH, triglyceride levels and smoking. We showed that the testosterone, creatine kinase, haemoglobin, glucose, LDL-C and creatinine levels and age and smoking were independent predictors for the Gensini score (**Table 3**) in a stepwise regression. **Figure 1** presents the partial regression and more clearly shows the relationship between the Gensini score and the testosterone level.

**Determinants of the Gensini score in a multivariate logistic regression analysis**

The testosterone levels were analysed as tertiles, with tertile 1 serving as the reference, based on the study population. In a multivariate logistic regres-



**Figure 1** Multiple linear regression analysis with testosterone level as independent predictors for gensini score.

sion model (**Table 4**) adjusted for smoking, the severity of CAD, as defined by the Gensini score, was shown to be significantly lower in the third testosterone tertile (highest) compared to the first testosterone tertile (lowest) (OR=0.465; 95% confidence interval (CI): 0.327–0.662;  $P = 0.000$ ).

**DISCUSSION**

In this study, we demonstrated that the testosterone level was negatively associated with the Gensini score and was an independent predictor for the Gensini score. Thus, testosterone could affect the development of atherosclerotic coronary arteries. Our findings confirm a previous report of an association between the Gensini score and testosterone,<sup>14</sup> which involved 87 middle-aged male patients.

Similar results were confirmed thereafter by English *et al.*,<sup>5</sup> who observed lower levels of testosterone in men with CAD when compared to normal coronary angiography. Phillips *et al.*<sup>4</sup> first reported an inverse association between free testosterone levels and the severity of CAD in a series of subjects undergoing coronary angiography. Subsequently, Yeap *et al.*<sup>7</sup> and Akishita *et al.*<sup>8</sup> suggested that endogenous testosterone may have a protective effect against cardiovascular disease in men;<sup>16</sup> specifically, testosterone could benefit endothelial function,<sup>16</sup> elicit vasodilation and increase blood flow in men<sup>17</sup> and in animals.<sup>18</sup> An increased frequency of thromboembolic events has also been reported in androgen-deprived men.<sup>19,20</sup> These findings provide evidence for a role of endogenous testosterone in the severity of cardiovascular disease. However, Fallah *et al.*<sup>21</sup> reported that lower total testosterone has a preventive effect on CAD, whereas higher values increase the risk of CAD.

Dyslipidaemia also contributes to the pathogenesis of atherosclerosis. Recent epidemiological and observational studies have generally shown that low endogenous testosterone concentrations are independently associated with dyslipidaemia and an atherogenic lipid profile in men.<sup>22</sup> Positive associations have been shown between testosterone levels and HDL-C;<sup>23</sup> this is inconsistent with our research in which no such

**Table 3 The linear regression analysis with the Gensini score as the dependent variable in men**

Variable	Standardized coefficients (β)	95%CI	P
Age (year)	0.105	0.129–0.717	0.005
Haemoglobin (g l <sup>-1</sup> )	-0.186	(-0.678)–(-0.302)	0.000
Creatine kinase (mmol l <sup>-1</sup> )	0.111	0.003–0.011	0.002
Glucose (mmol l <sup>-1</sup> )	0.108	0.680–3.041	0.002
LDL-C (mmol l <sup>-1</sup> )	0.075	0.380–8.304	0.032
Creatinine (μmol l <sup>-1</sup> )	0.096	0.053–0.324	0.006
Testosterone (ng ml <sup>-1</sup> )	-0.110	(-4.785)–(-1.133)	0.002
Smoking	0.085	1.579–13.623	0.013

Abbreviations: CI, confidence interval; LDL-C, low-density lipoprotein cholesterol.

**Table 4** The determinants of the Gensini score in a multivariate logistic regression analysis in men

Variable	Gensini score		P	OR (95%CI)
	≤26 (n=403) frequency	>26 (n=400) frequency		
Testosterone 1 (lowest)	109	158	0.000	
Testosterone 2	138	131	0.021	0.660 (0.465–0.938)
Testosterone 3 (highest)	156	111	0.000	0.465 (0.327–0.662)

Abbreviations: CI, confidence interval; OR, odds ratio.

association existed. These discrepancies might be attributed to the sample size and differences in the population characteristics. Further studies should be conducted to explain the underlying mechanism. The observation that lower testosterone levels were also correlated with elevated TCH, TG, LDL-C and fasting glucose levels<sup>24</sup> is in agreement with previous reports.<sup>23,25,26</sup> Moreover, an inverse association between testosterone and creatine kinase or creatinine levels ( $r=-0.124$ ;  $P=0.001$  vs.  $r=-0.104$ ;  $P=0.004$ ) was shown in the current study.

The Massachusetts Male Aging study showed that decreased testosterone concentrations are associated with an increased risk of developing metabolic syndrome<sup>27</sup> in men with a BMI <25 kg m<sup>-2</sup>. Jockenhovel *et al.*<sup>28</sup> reported that obesity may also act as an inhibitor of the hypothalamic–pituitary–gonadal axis, possibly *via* agents such as leptin. In our study, we also found that testosterone was negatively correlated with BMI in men ( $r=-0.088$ ;  $P=0.013$ ), indicating that the testosterone concentration correlates with adiposity. However, there is no evidence to suggest the direction of possible causality.

We also found that increased testosterone levels were associated with elevated haemoglobin levels in males ( $r=0.07$ ;  $P=0.047$ ). This is in agreement with a previous study,<sup>29</sup> but no correlation was shown with the RBC count ( $r=0.050$ ;  $P=0.158$ ).

The precise mechanism underlying our findings and its clinical relevance require future elucidation. Oestrogen will be an added measurement in a follow-up study. In addition, there are a number of risk factors for CAD; however, we only analysed the most common risk factors in the current study.

In conclusion, men with lower testosterone levels had higher Gensini scores in a group of 803 men who underwent elective coronary angiography. Additional studies are needed to clarify the direction of causality and possible underlying mechanisms.

#### AUTHOR CONTRIBUTIONS

EZJ conceived and designed the research; LL and CYG collected data and performed the research; TBZ, LSW and KJC contributed new analytical tools and reagents; WZM and ZJY analysed the data; and LL performed the statistical analysis and drafted the manuscript.

#### COMPETING FINANCIAL INTERESTS

All authors declare that there are no competing financial interests.

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