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Plasma testosterone is associated with Framingham risk score

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***Introduction*: The Framingham risk score predicts a patient's 10-year risk of developing cardiovascular disease. Many risk factors included in its calculation influence or are influenced by circulating testosterone. To investigate the possible association between testosterone and cardiovascular risk, as defined by the Framingham score, a Veterans Affairs (VA) database was analyzed. *Methods*: A retrospective chart review was performed. Inclusion criteria were male sex and age ≥ 20 years. Exclusion criteria included pre-existing cardiovascular disease, stroke, and diabetes. Data were collected on veterans who had total plasma testosterone checked in the year 2008. *Results*: The study included 1,479 patients (mean age 61 years). Framingham score was negatively associated with both total testosterone ($p < 0.0001$) and free testosterone ($p = 0.0003$). There was a positive association between total testosterone and high-density lipoprotein and negative associations between total testosterone and body mass index (BMI), total cholesterol, triglycerides, and blood pressure medication use. Free testosterone was positively associated with total cholesterol, low-density lipoprotein, and current smoking status and negatively associated with age, BMI, and blood pressure medication use. The BMI was not associated with Framingham score. *Conclusions*: Lower plasma testosterone may suggest the presence of cardiovascular risk factors and potentially increased risk for heart disease.**

Keywords: Cardiovascular risk, Framingham score, hypogonadism, testosterone deficiency

Introduction

The Framingham Heart Study was started in 1948 to determine the cardiovascular risk factors. From these studies, a variety of scores have been formed to help predict one's risk of developing cardiovascular disease. The "hard" coronary heart disease risk score predicts a patient's 10-year risk of myocardial infarction or coronary death, taking into account age, sex, total cholesterol level, high-density lipoprotein (HDL) level, smoking status, and blood pressure. Many risk factors included in the score (i.e., age, total cholesterol, HDL, blood pressure) have been found to be associated with circulating testosterone [1–12]. Studies have also suggested a role for testosterone in cardiovascular health, with some evidence of an association between testosterone deficiency and cardiovascular disease [13–15]. To further investigate the possible association between testosterone and cardiovascular risk, as defined by the Framingham score, data from a Veterans Affairs (VA) database were analyzed.

Methods

This study involved a retrospective chart review of patients in the VA Northern California Health Care System (VANCHCS). Inclusion criteria for the study were male sex and age ≥20 years. Exclusion criteria included pre-existing coronary artery disease, diabetes, congestive heart failure, peripheral vascular disease, rheumatic heart disease, or cerebrovascular disease, as the Framingham score was not intended to calculate risk for patients with these pre-existing conditions. Patients who did not have data essential to calculate the Framingham score were also excluded. Testosterone supplements, antiandrogen therapy, antihypertensives, or lipid-lowering medications were not exclusion criteria but were factored in data analysis.

To determine gonadal status, plasma total testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), free testosterone, and sex hormone-binding globulin

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(SHBG) were collected. Both total and free testosterones were measured by immunoassay at VA laboratories. To determine cardiovascular risk, total cholesterol, triglyceride, low-density lipoprotein (LDL), HDL, smoking status, and systolic blood pressure were recorded. Additional demographic data included height, weight, body mass index (BMI), age, and ethnicity (White, Black, Latino, Asian/Pacific Islander, "Other"). Smoking status and ethnicity were patient-reported and obtained via chart review. Systolic blood pressure, height, and weight were recorded during clinic visits. Finally, the use of antihypertensive medications, lipid-lowering medications, testosterone supplementation, and androgen suppression was also determined from medication records in the chart.

Data were collected on those who had a total testosterone level checked between January 1, 2008 and December 31, 2008. In the case where more than one testosterone level was checked within the year, the first morning test (before 12:00 PM, if applicable) was used. One exception was when there were multiple morning tests, in which case the test drawn closest to the time the lipid panel was drawn was used. If a morning test was not available, the test drawn closest to the time of the lipid panel was used. Free testosterone, SHBG, LH, or FSH had to be drawn on the same day as the total testosterone to be recorded. All other data had to be checked within 1 year of the testosterone level. Framingham risk scores for developing hard coronary heart disease were calculated using the online tool provided by the National Heart Lung and Blood Institute at http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof.

Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Initial analysis of the data revealed outliers in the data set; for this reason, robust linear regression (a form of linear regression influenced less by outliers) was used to study the associations between total testosterone (as a predictor) and Framingham risk score (as a response variable). This analysis was first done using the entire population and then re-evaluated after exclusion of those on lipid-lowering medications, testosterone supplementation, or androgen suppression. The same analysis was also performed with free testosterone values in place of total testosterone. Because BMI is another possible confounder, the Spearman rank correlation coefficient was used to determine correlations between BMI and Framingham score; this analysis was also done first with the entire population and then with exclusion of those on lipid-lowering medications, testosterone supplementation, and androgen suppression.

Additional analysis of the relationship between total or free testosterone and Framingham score was performed after dividing the subjects into groups based on testosterone level or Framingham score. The two-sided Wilcoxon rank-sum test and linear regression compared Framingham score between patients with total testosterone ≤5.2 nmol/L and those with total testosterone >5.2 nmol/L. The two-sided Wilcoxon rank-sum test and linear regression were also used to compare Framingham score between those who had free testosterone ≤17.4 pmol/L and those who had free testosterone >17.4 pmol/L. These cutoffs were based on the lower limits of the reference ranges for the assays used. Logistic regression evaluated whether total or free testosterone predicted a patient's Framingham score as <10% or ≥10%.

The Spearman rank correlation coefficient evaluated the relationship between total or free testosterone and age, total cholesterol, triglycerides, LDL, HDL, systolic blood pressure, number of blood pressure medications, and BMI. Those on testosterone supplementation or androgen suppression were excluded for these analyses. Those on lipid-lowering medications were also not included in the analysis of the association between testosterone and total cholesterol, HDL, LDL, and triglycerides. Those on antihypertensive therapy were excluded in evaluating the relationship between testosterone and systolic blood pressure.

The two-sided Wilcoxon rank-sum test evaluated the relationship between total or free testosterone (response variable) and smoking status (grouped as current smoker or non-smoker). The Kruskal–Wallis test evaluated the relationship between total or free testosterone and ethnicity. Those on testosterone therapy or antiandrogen therapy were excluded from these analyses.

Post-hoc analysis was performed on 102 patients who had SHBG measured at the same time as total testosterone. The SHBG and total testosterone were used to calculate free testosterone using methods outlined by Vermeulen et al. [16], assuming an average albumin of 43 g/L. The Spearman rank correlation coefficient was used to explore the association between calculated free testosterone and Framingham score. The two-sided Wilcoxon rank-sum test was used to determine whether there was a difference in Framingham score between patients with calculated free testosterone ≤17.4 pmol/L and those with levels >17.4 pmol/L. A p value ≤0.05 was considered significant. The study was approved by the Human Studies Subcommittee of the VANCHCS.

Results

A total of 3,176 patients had total testosterone checked in the year 2008. Of those 3,176 subjects, 1,479 patients were included in the study after applying the inclusion and exclusion criteria. Of those, 983 (66.5%) were White, 347 (23.5%) were Black, 58 (3.9%) were Asian/Pacific Islander, 43 (2.9%) were Latino, and 48 (3.2%) were classified as "Other" (which included American Indians and those without identifiable ethnicity based on the medical records). This ethnic distribution is comparable to that of male veterans in our overall population. Summary statistics are illustrated in Tables I and II. The age distribution of our population is illustrated in Figure 1.

A statistically significant negative association was found between total testosterone and Framingham risk score ($p < 0.0001$; Table III). There was also a significant negative association between free testosterone and Framingham score ($p = 0.0003$; Table III). When patients on testosterone supplementation, antiandrogen therapy, or lipid-lowering medications were excluded, similar associations were also found for total testosterone ($p = 0.0031$; Table III) and free testosterone ($p = 0.015$; Table III).

Table I. Summary statistics of demographic and laboratory data.

	Number of values	Mean	Standard deviation	Median	Min	Max
Age (years)	1,479	61.27	11.98	61	22	96
BMI	1,475	28.83	5.30	28.21	12.45	60.55
Total testosterone (nmol/L)	1,479	12.98	8	11.98	0.35	115.2
Free testosterone (pmol/L)	703	29.43	17.45	27.41	1.73	183.91
Total cholesterol (mmol/L)	1,479	4.86	1.03	4.77	0.49	10.54
HDL (mmol/L)	1,479	1.15	0.36	1.09	0.39	3.42
LDL (mmol/L)	1,475	3	0.89	2.95	0.52	8.44
Triglycerides (mmol/L)	1,476	1.57	1.07	1.29	0.15	10.25
Systolic blood pressure (mm Hg)	1,479	131.75	17.93	131	84	238
Blood pressure medications	1,479	0.99	1.17	1	0	6

Table II. Proportion of population with certain characteristics.

	Proportion % (no.)
Current smoker	24.5 (362/1,479)
Non-smoker	75.5 (1,117/1,479)
On testosterone supplementation	9.3 (138/1,479)
On antiandrogen therapy	3.7 (55/1,479)
On lipid-lowering medications	30.3 (448/1,479)

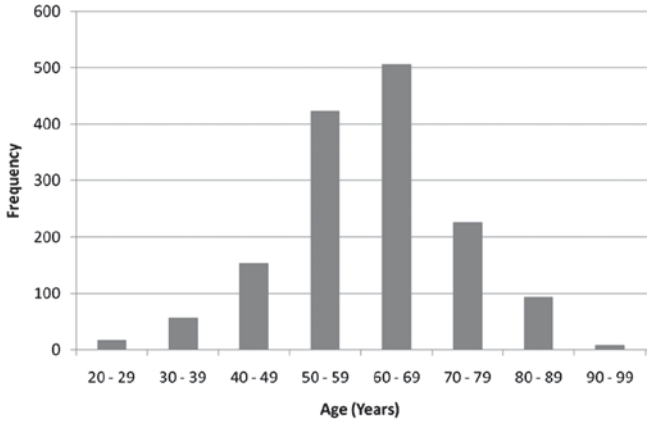

Figure 1. Age distribution by decade.

There were also statistically significant differences ($p < 0.01$) in Framingham risk scores between patients with total testosterone ≤5.2 nmol/L (mean 15.17) and patients with total testosterone >5.2 nmol/L (mean 13.32). This is illustrated in Figure 2.

When the subjects were divided into two groups based on Framingham score, a significant difference in total testosterone levels was seen. Mean total testosterone was 13.94 nmol/L for patients with Framingham score <10% and 12.5 nmol/L for patients with Framingham score ≥10% ($p < 0.01$). This is illustrated in Figure 3.

Dividing patients based on free testosterone also revealed a statistically significant difference ($p < 0.001$) in Framingham risk score; patients with free testosterone ≤17.4 pmol/L had a mean Framingham risk score of 16.19, while patients with free testosterone >17.4 pmol/L had a mean Framingham risk score of 13.68. Mean free testosterone was 31.3 pmol/L for patients with Framingham score <10% and 28.6 pmol/L for patients with Framingham score ≥10%, but this difference was not statistically significant ($p = 0.06$). Total testosterone was found to have a statistically significant positive association with HDL

Table III. Robust linear regression for studying the association between testosterone and Framingham score.

Parameter	Estimate	Standard error	95% CI	p value
All subjects				
Total testosterone	−0.0042	0.001	(−0.0063, −0.0022)	<0.0001
Free testosterone	−0.27	0.076	(−0.42, −0.13)	0.0003
Excluding those on testosterone supplements, antiandrogen therapy, or lipid-lowering medications				
Total testosterone	−0.0043	0.0015	(−0.0071, −0.0014)	0.0031
Free testosterone	−0.26	0.11	(−0.47, −0.05)	0.015

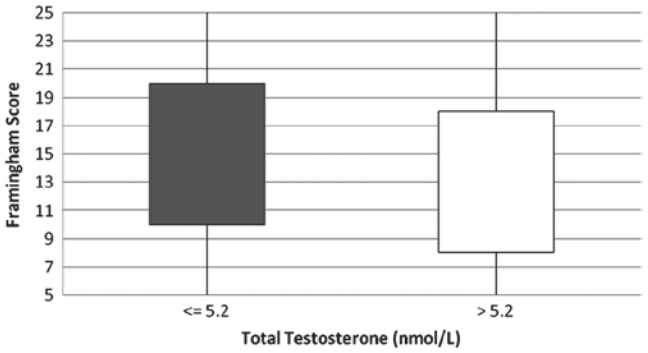

Figure 2. Comparison of Framingham score based on total testosterone level. Boxes encompass Framingham scores between the 25th and 75th percentiles.

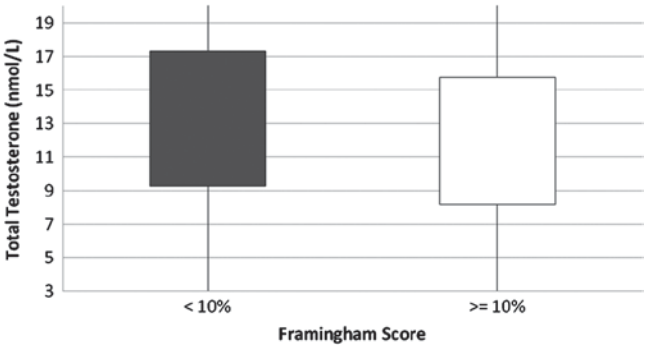

Figure 3. Comparison of total testosterone based on Framingham score. Boxes encompass total testosterone levels between the 25th and 75th percentiles.

($p < 0.0001$) and negative associations with BMI ($p < 0.0001$), total cholesterol ($p = 0.004$), triglycerides ($p < 0.0001$), and number of blood pressure medications ($p < 0.0001$). There

were no statistical associations between total testosterone and age, systolic blood pressure, or LDL. Free testosterone was found to have statistically significant positive associations with total cholesterol ($p < 0.0001$) and LDL ($p < 0.0001$) and negative associations with age ($p < 0.0001$), BMI ($p < 0.0001$), and number of blood pressure medications ($p = 0.0024$). There were no statistical associations between free testosterone and HDL, triglycerides, or systolic blood pressure. Analysis is summarized in Table IV.

There was no statistically significant difference ($p = 0.06$) in total testosterone between current smokers (mean 13.9 nmol/L) and non-smokers (mean 13.4 nmol/L), but there was a significant difference ($p = 0.02$) in free testosterone, which was higher in current smokers (mean 31.2 pmol/L) than in non-smokers (mean 29.5 pmol/L).

No significant differences were found between the ethnicities in regard to total testosterone ($p = 0.09$) or free testosterone ($p = 0.85$).

The BMI was not significantly associated with Framingham score, regardless of whether the entire population was included (Spearman rank correlation coefficient 0.0016, $p = 0.95$) or whether those on testosterone supplementation, antiandrogen therapy, or lipid-lowering medications were excluded (Spearman rank correlation coefficient 0.042, $p = 0.2$).

Post-hoc analysis using calculated free testosterone revealed a statistically significant negative correlation between calculated free testosterone and Framingham score (Spearman rank correlation coefficient −0.25, $p = 0.01$). Mean Framingham score was 15.95 among patients with calculated free testosterone ≤17.4 pmol/L and 13.28 among patients with calculated free testosterone >17.4 pmol/L. However, this difference was not statistically significant ($p = 0.07$).

Table IV. Spearman correlation coefficients for studying association between testosterone and the indicated parameters.

	Total testosterone	Free testosterone
Age[a]	−0.0039 ($p = 0.89$)	−0.25 ($p < 0.0001$)
BMI[a]	−0.32 ($p < 0.0001$)	−0.16 ($p < 0.0001$)
Total cholesterol[b]	−0.09 ($p = 0.004$)	0.18 ($p < 0.0001$)
HDL[b]	0.14 ($p < 0.0001$)	0.038 ($p = 0.41$)
LDL[b]	−0.014 ($p = 0.65$)	0.18 ($p < 0.0001$)
Triglycerides[b]	−0.31 ($p < 0.0001$)	0.013 ($p = 0.78$)
Systolic blood pressure[c]	−0.03 ($p = 0.44$)	−0.0059 ($p = 0.92$)
Number of blood pressure medications[a]	−0.13 ($p < 0.0001$)	−0.13 ($p = 0.0024$)

[a]Excluding those on testosterone supplementation or antiandrogen therapy.
[b]Excluding those on testosterone supplementation, antiandrogen therapy, or lipid-lowering medications.
[c]Excluding those on testosterone supplementation, antiandrogen therapy, or antihypertensive therapy.

Discussion

Many studies have found a potential link between testosterone and heart disease, although data are mixed overall. Low testosterone has been found to be associated with the incidence and severity of aortic atherosclerosis, coronary artery disease, carotid artery disease, and coronary heart disease mortality, even after controlling for age and BMI [17–20]. A systematic review of prospective studies on testosterone and cardiovascular conditions found a weak independent protective effect of total testosterone in elderly men (age > 70 years) but not younger men (age < 70 years) [21]. One reason for these findings may be the possible association between testosterone deficiency and various cardiovascular risk factors, including fibrinogen, plasminogen activator inhibitor-I, hypertension, hyperglycemia, diabetes, insulin resistance, hyperlipidemia, obesity, and intra-abdominal fat [1–7,11,17,22–27]. It is unclear whether there is a cause-and-effect relationship between testosterone deficiency and cardiovascular disease, although testosterone administration has been found to decrease exercise-induced ST segment depression, improve aerobic endurance, and relax coronary arteries and the aorta to improve coronary blood flow [28–36]. Testosterone administration has been found to reduce insulin resistance in hypogonadal men with type 2 diabetes or metabolic syndrome [10]. Testosterone may also improve cardiac healing after a heart attack and improve function in heart failure patients [37]. There may be a protective effect of estradiol produced from testosterone [38]. Alternatively, testosterone may not have a direct influence on cardiovascular health and instead simply be a biomarker of poor health or chronic disease. However, other studies have failed to find associations between testosterone and cardiovascular disease [11,12,39–41]. There might also be increased cardiovascular risk in older patients with chronic disease who take testosterone supplementation [42].

This study found a negative association between plasma testosterone levels and Framingham risk score. Of the components of the Framingham score, there were associations seen between testosterone and age, total cholesterol, HDL, and number of blood pressure medications. It is well known that testosterone decreases with advancing age, although only a statistically significant trend is seen when using free testosterone levels instead of total testosterone. This decrease in free testosterone is likely due to increase in SHBG with advanced age [43].

Various studies have found a positive association between testosterone and HDL and a negative association between testosterone and total cholesterol, LDL, and triglycerides [1–7]. Testosterone supplementation was also found to lower total cholesterol and LDL [8–10]. Similar to previous studies, HDL was found in this study to be positively associated with total testosterone and triglycerides to be negatively associated with total testosterone. However, contrary to these studies, a positive association between free testosterone and LDL was found, which would theoretically increase one's cardiovascular risk. There were also conflicting results regarding the association between testosterone and total cholesterol. Total cholesterol was negatively associated with total testosterone but positively associated with free testosterone.Of note, free testosterone was negatively associated with Framingham score despite a positive association between free testosterone and total cholesterol and the observation of high free testosterone in smokers compared to non-smokers. This suggests that the other factors (age and use of blood pressure medications) may have had a bigger influence in determining the difference in Framingham score. Review of the algorithm used to determine Framingham risk suggests that age is likely

the factor with the most influence. A few studies have found testosterone deficiency to be related to high blood pressure [1,11,12,44]. In this study, high free or total testosterone was related to fewer blood pressure medications being used, although there was no significant association between testosterone and systolic blood pressure in those who were not on antihypertensive therapy. A potential confounding factor is that of obesity, which can both increase cardiovascular risk and decrease testosterone [1]. While both total and free testosterone levels were negatively associated with BMI, BMI was not found to be associated with Framingham score.

There are many limitations to this study. One limitation is related to the use of immunoassay to measure free testosterone, which often measures levels lower than those measured by equilibrium dialysis or those calculated using SHBG and total testosterone [16]. For this reason, post-hoc analysis with calculated free testosterone was performed to determine whether similar trends could be seen. Although based on a smaller sample size, a statistically significant negative correlation was again seen between free testosterone and Framingham risk. When dividing the patients into two groups based on free testosterone, the differences in mean Framingham score between those with free testosterone ≤17.4 pmol/L and those with free testosterone >17.4 pmol/L were very similar: 15.95 versus 13.28 for calculated free testosterone and 16.19 versus 13.68 for measured free testosterone. This analysis would seem to confirm the relationships seen with measured free testosterone.

Testosterone levels can also be affected by time of day and acute/chronic illness, in addition to the limitations of the testosterone assay. An attempt was made to use morning measures of testosterone based on clinical practice guidelines, suggesting morning total testosterone as an effective initial test in identifying testosterone deficiency [45]. However, not all subjects had morning checks (407/1479, or 28%, had testosterone checked at noon or later). The possible random fluctuations in testosterone level as a result of the above may have decreased the ability to identify some associations, especially given the fact that single values were used. The use of single values is also notable because calculation of the Framingham score was intended for use with an average value of at least two measurements of total cholesterol and HDL. However, single values were used because of the plans to explore potential associations between the testosterone level and the cholesterol measurement.

Another limitation is that not all of the other patient data were collected at the same time as testosterone, which makes it possible that some data (i.e., lipid panels) may have been reflective of a different testosterone level than what was measured at another time of the year. Testosterone was measured on the same day as the other laboratories in 54% (805/1479) of patients.

Because patients were not randomly selected to have their testosterone checked (and most likely had testosterone checked because of specific symptoms or pre-existing conditions), there is a potential selection bias in our patient population. This may have resulted in selection of a population at higher risk for cardiovascular disease. For example, a common impetus for checking testosterone is the complaint of erectile dysfunction, which may be a common finding in a patient who has cardiovascular risk and who was checked for testosterone deficiency.

Finally, there are limitations inherent to retrospective studies. The associations found in this study cannot be concluded to be due to cause-and-effect relationships. It is very possible that testosterone was related to Framingham score because both are affected by another factor that independently affects both (i.e., the presence of other chronic diseases) or because testosterone acts as a biomarker of poor health.

In conclusion, patients with low plasma testosterone were found to have high Framingham risk scores, with findings of testosterone variation related to age, cholesterol levels, and blood pressure medication requirements. Lower plasma testosterone may suggest the presence of these more traditional cardiovascular risk factors and potentially increased risk for heart disease.

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