The Association of Hypotestosteronemia With Coronary Artery Disease in Men

Gerald B. Phillips, Bruce H. Pinkernell, Tian-Yi Jing

Abstract Hyperestrogenemia and hypotestosteronemia have been observed in association with myocardial infarction (MI) and its risk factors. To determine whether these abnormalities may be prospective for MI, estradiol and testosterone, as well as risk factors for MI, were measured in 55 men undergoing angiography who had not previously had an MI. Testosterone \( r = -0.36, P = 0.008 \) and free testosterone \( r = -0.49, P < 0.001 \) correlated negatively with the degree of coronary artery disease after controlling for age and body mass index. When the patient group was successively reduced to a final study group of 34 men by excluding the patients with other major disorders, the testosterone and free testosterone correlations persisted \( r = -0.43, P < 0.02 \) and \( r = -0.62, P < 0.001 \), respectively. Neither estradiol nor the risk factors, except for high-density lipoprotein cholesterol, correlated with the degree of coronary artery disease in the final group. Testosterone correlated negatively with the risk factors fibrinogen, plasminogen activator inhibitor-1, and insulin and positively with high-density lipoprotein cholesterol. The correlations found in this study between testosterone and the degree of coronary artery disease and between testosterone and other risk factors for MI raise the possibility that in men hypotestosteronemia may be a risk factor for coronary atherosclerosis. (Arterioscler Thromb. 1994;14:701-706.)

Key Words • testosterone • estradiol • coronary artery disease • HDL • hemostatic risk factors • myocardial infarction • risk factors for coronary heart disease

The observations in men of hyperestrogenemia after myocardial infarction (MI), of an association of sex hormones with risk factors for MI, and of a concurrence of risk factors for MI in clinical states other than MI and in populations led to the hypothesis that an elevation in the estradiol-to-testosterone ratio or some closely related hormonal alteration may underlie risk factors and that hyperestrogenemia may lead to MI in men. Most laboratories studying sex hormones and MI in men have reported a high estradiol level after MI, both acutely and months to years later. Other laboratories have observed a low testosterone level, and yet others have observed both abnormalities after MI. Prospective studies for MI, however, have thus far failed to show an abnormality in the level of either estradiol or testosterone.

The present study investigated whether a hormonal abnormality might be prospective for MI by determining the sex hormone levels in relation to the degree of coronary artery disease (CAD) in men who had not had an MI. The serum estradiol and testosterone levels as well as the levels of risk factors for MI were measured in 55 men undergoing coronary angiography who had not had an MI.

Methods

Patients

Fifty-five male patients undergoing coronary angiography were studied. The patients had been referred to the Cardiac Catheterization Laboratory of Roosevelt Hospital for evaluation of chest pain syndromes and/or abnormal stress tests and were consecutive except that those with any previous episode of characteristic chest pain, electrocardiographic changes, and serum enzyme elevations of MI, or who gave a history of MI, were excluded from the study. The patients were separated into four groups for statistical analysis. Group 1 consisted of all 55 patients. Group 2 (53 patients) excluded the 2 patients whose testosterone values were outliers. Group 3 (46 patients) further excluded 2 of the 3 patients with insulin-dependent diabetes (the third was also one of the testosterone outliers) and the 3 patients with major medical disorders other than non-insulin-dependent diabetes or hypertension. Group 4 (34 patients) excluded, in addition to the above, the 8 patients with hypertension, the 2 with non-insulin-dependent diabetes, and the 2 with both disorders. All 55 patients were on medication, with an average of three drugs per patient (not including the diazepam or pentobarbital given before sampling). Group 4 patients took an average of two drugs per patient.

Coronary Angiography and Blood Sampling

Coronary angiography was performed via the femoral artery using preformed catheters, and angiograms were taken using the Judkins technique with multiple views. One of the authors (Dr Pinkernell) visually estimated the maximum percent reduction in luminal diameter of the main left, left anterior descending, left circumflex, and right coronary artery in each patient without knowledge of the laboratory results. The mean of these four values was used as the estimate of the degree of CAD for each patient in the statistical analyses.

Blood samples were obtained through the needle inserted in the femoral artery for angiography before heparin administration. All samples were taken before noon with the patient fasting. The methods for sampling, storage, and measurement of the plasma hemostatic factors, ie, fibrinogen, factor VII, and plasminogen activator inhibitor—1 (PAI-1), have been described. All other measurements were performed on serum that had been stored airtight at \(-20^\circ\text{C}\). Hormones were measured by radioimmunoassay (RIA). Estradiol and testosterone were measured on serum stored less than 7 months. Materials for the RIA of estradiol were obtained from ICN.
Biomedicals, Inc, and those for the RIA of testosterone, free testosterone (FT), insulin, and dehydroepiandrosterone sulfate (DHEAS) from Diagnostic Products Corp. Cholesterol was measured enzymatically, as was the cholesterol in the supernatant after phosphatungstic acid precipitation of serum in the measurement of high-density lipoprotein cholesterol (HDL-C) (Sherwood Medical Co).

Statistical Analysis

Means, SDs, Pearson and partial correlation coefficients, unpaired Student's t tests (for drug and smoking analyses), and outliers (using box plots) were calculated with SPSS programs on a Macintosh SE/30 computer.

Results

Although atherosclerosis of only a single vessel occurred in these 55 patients, the degree of occlusion in one vessel correlated with that in each of the other vessels \((r>.33, \ P<.01)\) and with the mean degree of occlusion \((r>.60, \ P<.001)\) of all four vessels. Thus, the mean percent occlusion of the four vessels appeared to be a representative measure of the degree of occlusion of the coronary system. The correlation between the percent occlusion of each of the four vessels with age \((r>.39, \ P<.003)\) and the strong degree of correlation between mean percent occlusion and age \((r=.60, \ P<.001)\) support the validity of the mean percent occlusion as a measure of the degree of atherosclerosis of the coronary system.

Because group 4 had the fewest confounding factors, the mean values with SDs and ranges of the variables measured are shown for this subset of 34 patients in Table 1.

Table 2 shows the correlation coefficients, controlled for age and body mass index (BMI), of the degree of CAD (mean percent occlusion) with hormone and risk factor levels in the four groups of patients. Testosterone correlated negatively with CAD in each of the four groups. FT correlated similarly but more strongly. The correlation of FT with CAD in groups 1 and 4 is depicted in Fig 1. The exclusion of the two testosterone outliers from group 1 (group 2) had almost no effect on the degree of any of the correlations. CAD correlated negatively with HDL-C (Fig 2) in all groups and positively with PAI-1 in groups 1 and 2. CAD did not correlate with estradiol, insulin, fibrinogen, factor VII, cholesterol, systolic blood pressure, diastolic blood pressure, or DHEAS. When the one testosterone outlier, who had no other disorders, was added back to groups 3 and 4, all of the significant correlations in groups 3 and 4 remained essentially unchanged.

Table 3 shows the correlation coefficients, controlled for age and BMI, between sex hormones and risk factors in group 4. Testosterone correlated negatively with fibrinogen and PAI-1; testosterone and FT correlated negatively with insulin. Testosterone correlated positively with HDL-C in group 4 as well as in groups 1 through 3 \((r>.48, \ P<.001)\); FT correlated positively with HDL-C in groups 1 through 3 \((r>.32, \ P<.02)\) and with marginal significance in group 4. The correlations of testosterone and FT with HDL-C are depicted in Fig 3 for group 1; after controlling for age and BMI, the correlation coefficients were .52 \((\ P<.001)\) and .38 \((\ P<.003)\), respectively.

Previously unreported correlations were observed between PAI-1 and fibrinogen \((r=.47, \ P<.007)\) and PAI-1 and HDL-C \((r=-.46, \ P<.008)\) (both controlled for age and BMI). Correlations controlled for age and BMI were also found between cholesterol and PAI-1 \((r=.43, \ P<.02)\) and HDL-C \((r=-.45, \ P=.01)\).

Patients taking calcium-channel blockers had a significantly lower mean HDL-C level than patients not taking them in groups 1 \((\ P<.008)\) and 2 \((\ P<.009)\); however, HDL-C correlated with CAD, testosterone, and FT more strongly in the patients not taking these drugs than in those taking them. Patients taking aspirin had a significantly higher mean fibrinogen level than patients not taking it in groups 1, 3, and 4 \((\ P<.05)\), but again, none of the correlations could be attributed to an aspirin effect in any of the groups. Where four or more patients on any one drug were compared with the patients not on that drug in groups 1 through 4, no significant effect of any drug on the level of estradiol, testosterone, FT, insulin, or PAI-1 could be demonstrated.

Comparing current smokers with nonsmokers or current plus past smokers with nonsmokers showed no significant difference in the mean levels of CAD, estradiol, testosterone, FT, insulin, PAI-1, or HDL-C in any of the groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.7</td>
<td>12.9</td>
<td>39-89</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.9</td>
<td>3.5</td>
<td>23.1-37.2</td>
</tr>
<tr>
<td>Estradiol, pg/mL</td>
<td>25.6</td>
<td>4.3</td>
<td>16.4-32.3</td>
</tr>
<tr>
<td>Testosterone, ng/mL</td>
<td>5.86</td>
<td>1.66</td>
<td>1.83-9.40</td>
</tr>
<tr>
<td>E/T</td>
<td>4.72</td>
<td>1.54</td>
<td>2.60-9.95</td>
</tr>
<tr>
<td>Free testosterone, pg/mL</td>
<td>17.5</td>
<td>5.2</td>
<td>5.2-31.5</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>15.1</td>
<td>8.0</td>
<td>5.4-42.2</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>292</td>
<td>104</td>
<td>132-610</td>
</tr>
<tr>
<td>Factor VII, %</td>
<td>104</td>
<td>36</td>
<td>48-176</td>
</tr>
<tr>
<td>PAI-1, AU/mL</td>
<td>12.9</td>
<td>4.5</td>
<td>4.4-23.0</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>230</td>
<td>53</td>
<td>157-392</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>29.3</td>
<td>6.5</td>
<td>20.4-47.1</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>134</td>
<td>22</td>
<td>100-190</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>74</td>
<td>14</td>
<td>50-110</td>
</tr>
<tr>
<td>DHEAS, μg/dL</td>
<td>123</td>
<td>83</td>
<td>20-420</td>
</tr>
<tr>
<td>Main, % occlusion</td>
<td>14</td>
<td>24</td>
<td>0-75</td>
</tr>
<tr>
<td>LAD, % occlusion</td>
<td>47</td>
<td>36</td>
<td>0-100</td>
</tr>
<tr>
<td>Circ, % occlusion</td>
<td>43</td>
<td>41</td>
<td>0-100</td>
</tr>
<tr>
<td>RCA, % occlusion</td>
<td>38</td>
<td>37</td>
<td>0-100</td>
</tr>
<tr>
<td>CAD, % occlusion</td>
<td>35</td>
<td>25</td>
<td>0-84</td>
</tr>
</tbody>
</table>

\(E/T\) indicates estradiol-to-testosterone ratio; \(PAI-1\), plasminogen activator inhibitor-1; \(AU\), arbitrary units; \(HDL-C\), high-density lipoprotein cholesterol; \(BP\), blood pressure; \(DHEAS\), dehydroepiandrosterone sulfate; \(Main\), main artery; \(LAD\), left anterior descending artery; \(Circ\), circumflex artery; \(RCA\), right coronary artery; and \(CAD\), coronary artery disease. Group 4 comprised the 34 men; see "Methods" for definition of groups.
TABLE 2. Correlation Coefficients Controlled for Age and Body Mass Index Between Variables and Degree of CAD in Men

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n=55)</th>
<th>Group 2 (n=53)</th>
<th>Group 3 (n=46)</th>
<th>Group 4 (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>-.03</td>
<td>.06</td>
<td>.10</td>
<td>-.07</td>
</tr>
<tr>
<td>Testosterone</td>
<td>-.36</td>
<td>-.36</td>
<td>-.32</td>
<td>-.43</td>
</tr>
<tr>
<td>E/T</td>
<td>.31</td>
<td>.34</td>
<td>.34</td>
<td>.30</td>
</tr>
<tr>
<td>FT</td>
<td>-.49</td>
<td>-.49</td>
<td>-.52</td>
<td>-.62</td>
</tr>
<tr>
<td>Insulin</td>
<td>-.06</td>
<td>-.06</td>
<td>-.20</td>
<td>.19</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>.08</td>
<td>.05</td>
<td>.04</td>
<td>.02</td>
</tr>
<tr>
<td>Factor VII</td>
<td>.06</td>
<td>.06</td>
<td>-.02</td>
<td>-.15</td>
</tr>
<tr>
<td>PAI-1</td>
<td>.31</td>
<td>.30</td>
<td>.21</td>
<td>.15</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>.11</td>
<td>.12</td>
<td>.07</td>
<td>.08</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-.50</td>
<td>-.49</td>
<td>-.46</td>
<td>-.37</td>
</tr>
<tr>
<td>SBP</td>
<td>.09</td>
<td>.07</td>
<td>.04</td>
<td>.07</td>
</tr>
<tr>
<td>DBP</td>
<td>.07</td>
<td>.08</td>
<td>.10</td>
<td>.27</td>
</tr>
<tr>
<td>DHEAS</td>
<td>-.04</td>
<td>-.04</td>
<td>.06</td>
<td>-.02</td>
</tr>
</tbody>
</table>

Note: CAD indicates coronary artery disease; E/T, estradiol-to-testosterone ratio; FT, free testosterone; PAI-1, plasminogen activator inhibitor—1; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; and DHEAS, dehydroepiandrosterone sulfate.

Discussion

The present study is the first to find a correlation between testosterone and a measure of the degree of CAD. This negative correlation was stronger with FT, which may be the biologically active form of testosterone. The correlations persisted after controlling both for age and BMI and could not be attributed to drug intake or smoking. Furthermore, the testosterone and FT correlations with CAD were found not only in the original group of 55 men but also after successively excluding the two patients whose testosterone values were outliers and then the patients with diabetes, hypertension, and other major disorders, which resulted in a final group of 34 men. Two previous studies measured testosterone in men with and without CAD were found not only in the original group of 55 men but also after successively excluding the two patients whose testosterone values were outliers and then the patients with diabetes, hypertension, and other major disorders, which resulted in a final group of 34 men. Two previous studies measured testosterone in men with and without CAD who had not had an MI; one found the mean level of testosterone low in the men with CAD and one found it normal. It appears that no previous studies have measured testosterone in relation to the degree of CAD in men who had not had an MI.

Because of the striking prevalence of MI in men, testosterone has heretofore been implicated as a causative factor. However, the finding of hypotestosteronemia in relation to CAD in men who had not had an MI suggests that hypotestosteronemia may be a prospective factor for MI. More importantly, that the relation of testosterone and FT levels to the degree of CAD found in the present study was continuous throughout the range of values suggests not only that a low testosterone level may be prospective for MI but also that it may lead to atherosclerosis and that testosterone, rather than being a causative factor, may protect against atherosclerosis in men. The declining testosterone level and increasing atherosclerosis with age in men is consistent with this concept. Of interest, administration of testosterone to men has been reported to decrease risk factors for MI. That the administration of testosterone may be protective for men while administration of estrogen appears to be protective for women against MI may seem contradictory. However, based on the differing relations in men and women of sex hormones to MI and its risk factors as well as other evidence, it has been suggested that sex hormones may have opposite effects in men and women.

The present study also showed correlations, controlled for age and BMI, between testosterone and risk factors for MI. These correlations further support the possibility that hypotestosteronemia may be a prospective factor for MI as well as the hypothesis that risk factors for MI may be linked by an underlying alteration in the sex hormone milieu. In the present study and as found previously, testosterone correlated negatively with PAI-1 and insulin and positively with HDL-
Testosterone also correlated negatively with the fibrinogen level. Associations between hypotestosteronemia and the risk factors diabetes, hyperglycemia, hypercholesterolemia, hypertriglyceridemia, hypertension, obesity, increased waist-to-hip ratio, and increased factor VII level in men who had not had an MI have been reported. Additionally, administration of testosterone to men has been reported to decrease risk factors for MI. Of particular interest are the negative correlations between testosterone and the hemostatic risk factors PAI-1, factor VII, and in this study fibrinogen as well, which suggest that hypotestosteronemia, if it does underlie these risk factors for MI, could be a factor leading to thrombosis in men.

Since these studies were carried out on men who were undergoing angiography and who had not had an MI, the results may not be representative of the population at large. For example, a possible explanation for the testosterone and CAD correlation is that a high testosterone level may induce angina (eg, through spasm or other mechanisms), and hence lead to angiography, before CAD develops. However, testosterone administration has not been reported to induce angina in men. Furthermore, the possibility of a low testosterone level leading to CAD is supported by the continuous correlation of testosterone with CAD throughout the range of values observed in the present study and by the negative correlations reported in men between testosterone and risk factors for MI.

The absence of a correlation between estradiol and CAD in the present study may indicate that hyperestrogenemia is not prospective for MI. However, none of the prospective factors for MI measured in this study correlated with CAD except HDL-C and PAI-1. Intervention may have confounded the correlations of estradiol and these prospective factors with CAD. It appears that no previous studies have measured the estradiol level in relation to the degree of CAD in men who had not had an MI. The association of hyperestrogenemia with diabetes, hypercholesterolemia, hypertriglyceridemia, hypertension, obesity, and smoking in men who had not had an MI, however, suggests that hyperestrogenemia may be prospective for MI. The possibility arises that hyperestrogenemia may lead to atherosclerosis (and perhaps thrombosis), while hyperestrogenemia may lead to thrombosis.

The only risk factors that correlated with CAD were HDL-C, which correlated in all of the groups, and PAI-1, which correlated in groups 1 and 2. Results of previous studies correlating HDL-C with the degree of CAD have been conflicting. The positive correlation of testosterone with HDL-C found in this study and previously suggests that testosterone might protect against atherosclerosis through an effect on lipoproteins. It is possible that certain risk factors may be related to CAD and/or MI only through correlations with sex hormones and may be incidental to their development. It is also possible that the sex hormones are related to the risk factors and to CAD and/or MI through another factor(s). One factor suggested as
leading to MI\(^{48}\) and recently offered as a possible link between risk factors and MI\(^{49,50}\), is hyperinsulinemia. The strong correlations observed of both testosterone and the estradiol-to-testosterone ratio with insulin\(^{22,28}\) may account for similar correlations of sex hormones and insulin with risk factors for MI. However, insulin did not correlate with CAD in the current study. Thus, the present findings that the serum testosterone and FT levels in men who had not had an MI correlated with the degree of CAD and for the reported correlations be-

References

6. Labropoulos B, Velonakis E, Oekonomakos P, Laskaris J, Katsimades D. Serum sex hormones in patients with coronary disease and their relationship to known factors causing athero-
13. Poggi UL, Arguelles AE, Rosner J, De Laborde NP, Cassini JH, Volmer MC. Plasma testosterone and serum lipids in male sur-
16. Lichtenstein MJ, Yarnell JWG, Ebwood PC, Bezwick AD, Sweet-
18. Mendoza SG, Zepra A, Carrasco H, Colmenares O, Ramel A, Gartside PS, Kashyap ML. Estradiol, testosterone, apolipo-
19. Aksut SV, Aksut G, Karamehmedoglu A, Oram E. The determina-
20. Sewdarsen M, Vythilingum S, Jialal I, Desai RK, Becker P. Abnor-
malities in sex hormones are a risk factor for premature manifes-
22. Barrett-Conner E, Khaw KT. Endogenous sex hormones and cardio-


The association of hypotestosteronemia with coronary artery disease in men.
G B Phillips, B H Pinkernell and T Y Jing

Arterioscler Thromb Vasc Biol. 1994;14:701-706
doi: 10.1161/01.ATV.14.5.701

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/14/5/701

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/