Sex Hormone Levels in Young Indian Patients with Myocardial Infarction

Mohan Sewdarsen, Ishwarlal Jialal, Shunmugam Vythilingum, and Rajesh Desai

The finding of abnormal levels of sex hormones in men with coronary artery disease has led to the hypothesis that alterations in sex hormones may represent an important risk factor for myocardial infarction. In this study, the sex hormone profile of 28 young men (aged < 40 years) with myocardial infarction was compared with 28 age- and weight-matched normal men. Although the mean total serum estradiol levels and the free estradiol index of the patients and controls were similar, the mean serum total testosterone level and the free testosterone index were significantly lowered in the patients with myocardial infarction (p < 0.01). The ratio of serum estradiol to testosterone was significantly increased in the patients (p = 0.0005) and correlated with serum cholesterol, triglycerides, and plasma glucose. A significant inverse correlation was also demonstrated between total testosterone and serum cholesterol and triglycerides. Hence, the results of this study support the hypothesis that low plasma testosterone and an increased estradiol-to-testosterone ratio may be important risk factors for myocardial infarction. (Arteriosclerosis 6:418-421, July/August 1986)

The possible role of sex hormones in the pathogenesis of coronary artery disease had not aroused interest until Phillips reported increased plasma estradiol and estrone levels in young male survivors of myocardial infarction.1,2 Subsequently, the results of numerous studies3-6 have confirmed the findings of increased estrogen levels in patients with coronary artery disease. Moreover, it has been postulated that hyperestrogenemia may constitute an important risk factor for myocardial infarction in men and that abnormalities in glucose tolerance insulin response, and serum lipid concentrations may be secondary to an elevated estradiol-to-testosterone ratio.2 However, the role of sex hormones in the pathogenesis of coronary artery disease is still a controversial one. Studies to date have produced conflicting results. Although most studies1-6 have demonstrated hyperestrogenemia in patients with coronary artery disease, some of these studies have not reported a significant difference in serum testosterone and the estradiol-to-testosterone ratio between patients and controls.2,3,6 One study7 suggested that the hyperestrogenemia demonstrated in some reports may have been due to the influence of smoking and body weight on plasma estrogen concentration. Accordingly, the present study was undertaken to investigate the sex hormone profile of 28 Indian men with myocardial infarction and 28 age- and weight-matched male controls.

Methods

Patients

Twenty-eight male patients between the ages of 25 and 40 years in whom myocardial infarction was documented were studied. All the patients satisfied the World Health Organization criteria for myocardial infarction.

Tests

The tests were carried out 6 to 30 months (mean, 15 months) after the acute episode of myocardial infarction. Patients were excluded from the study if they were left with any complication from the myocardial infarction or had any other serious disorder. Patients with well-known risk factors for myocardial infarction such as hyperlipidemia, diabetes mellitus, hypertension, or smoking were not excluded.

Selective coronary angiography was performed in all patients by using the percutaneous femoral technique of Judkins.8 Significant coronary artery disease was considered to be present when the occlusion of the lumen was greater than 70% in one or more of the three coronary vessels. Fifteen patients had single vessel disease, 11 patients had double vessel disease, and one had triple vessel disease.

The controls were male members of the hospital staff between the ages of 24 and 40 years who had no history of disease and were normal in a clinical examination. None were taking any drugs. The dietary histories of patients and controls as determined by a dietician were similar. Some of the patients with myocardial infarction were taking one or more of the following drugs: beta blockers, glyceryl trinitrate, nifedipine, and glibenamide. Blood samples for determination of glucose, HDL cholesterol, cholesterol, tri-
glycerides, testosterone, estradiol, cortisol, and sex-hormone binding globulin (SHBG) levels were obtained after a 14-hour fast. Thereafter 75 g of glucose was administered orally, and further samples for plasma glucose were taken 1 and 2 hours later. Details of the assay methods used have been described previously.10 Briefly, glucose cholesterol and triglycerides were assayed enzymatically in an automated system; high density lipoprotein (HDL) cholesterol was quantitated by the phosphotungstate-MgCl₂ method, and testosterone, SHBG, cortisol, and estradiol were assayed by radioimmunoassay. The intra- and interassay coefficients of variation for all assays were less than 10%. The free estradiol index and free testosterone index were calculated as follows: total estradiol or testosterone/sex-hormone binding globulin.

Height and weight were measured, and relative body weight was calculated by the Quetelet Index (weight (kg)/height (m)²). Statistical analyses included the Mann Whitney U test and the Spearman rank correlation test. All data are expressed as the means ± the standard error. Significance was defined as the 5% level.

The design of this study was approved by the hospital administration board, and informed consent was obtained from all participants.

Results

The clinical characteristics of the patients and the control group are shown in Table 1. These two groups of subjects were matched with respect to age and body weight. Although the patients smoked more cigarettes per day than the controls, the difference was not statistically significant.

Table 1. Clinical Characteristics of Patients and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 28)</th>
<th>Controls (n = 28)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>34.57 ± 0.71</td>
<td>33.61 ± 0.92</td>
<td>0.21</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.82 ± 0.37</td>
<td>23.64 ± 0.48</td>
<td>0.39</td>
</tr>
<tr>
<td>Smoking (cigarettes/day)</td>
<td>16.70 ± 2.40</td>
<td>13.10 ± 1.20</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Data are means ± SEM.

Table 2. Plasma Hormone Levels in Patients with Myocardial Infarction and in Control Subjects

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Patients</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total estradiol (pmol/liter)</td>
<td>114.10 ± 5.8</td>
<td>107.80 ± 5.2</td>
<td>0.21</td>
</tr>
<tr>
<td>Free estradiol index (x 10⁻³)</td>
<td>2.72 ± 0.13</td>
<td>2.62 ± 0.18</td>
<td>0.31</td>
</tr>
<tr>
<td>Total testosterone (nmol/liter)</td>
<td>14.90 ± 0.7</td>
<td>19.90 ± 1.1</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Free testosterone index (x 10⁻³)</td>
<td>0.35 ± 0.02</td>
<td>0.46 ± 0.03</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Serum cortisol (nmol/liter)</td>
<td>433.70 ± 22.8</td>
<td>371.43 ± 28.81</td>
<td>0.09</td>
</tr>
<tr>
<td>Estradiol/testosterone ratio (x 10⁻³)</td>
<td>8.04 ± 0.39</td>
<td>6.08 ± 0.38</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Sex-hormone-binding globulin (nmol/liter)</td>
<td>43.50 ± 2.8</td>
<td>46.70 ± 3.7</td>
<td>0.31</td>
</tr>
</tbody>
</table>

The hormone values of the patients as compared to the controls are presented in Table 2, and the scattergram of estradiol and testosterone levels is shown in Figure 1. The mean total testosterone (14.9 ± 0.7 nmol/liter) and the free testosterone index (0.35 ± 0.02 × 10⁻³) was significantly lower in the patients than the controls (p < 0.002 and p < 0.005, respectively). However, the mean total estradiol level and the free estradiol index were similar in the two groups. There were no significant differences in hormonal levels between the patients on medication (13) and those on no drug therapy (15): serum testosterone 15.2 ± 0.9 and 14.6 ± 1.0 nmol/liter, p = 0.34; serum estradiol 122.3 ± 8.5 and 110 ± 7.7 pmol/liter, p = 0.128, respectively. The serum sex-hormone-binding globulin and cortisol levels of the patients and controls were similar. The estradiol-to-testosterone ratio of the patients (6.08 ± 0.38 × 10⁻³) was significantly elevated compared to that of the controls (6.08 ± 0.38 × 10⁻³; p < 0.0005).

The estradiol-to-testosterone ratio and the total testosterone in the patients were correlated with the lipids and the 2-hour glucose level in the glucose tolerance test (Table 3). The estradiol-to-testosterone ratio correlated significantly with serum cholesterol (r = 0.65; p < 0.001), triglycerides (r = 0.46; p < 0.01), and plasma glucose (r = 0.35; p < 0.05), but not with HDL cholesterol. A significant inverse correlation was demonstrated between total testosterone and serum cholesterol and triglycerides (r = 0.37; p < 0.05 and r = 0.39; p < 0.05, respectively). Table 3 depicts the correlation matrix in which many of the interrelationships between the measured variables can be seen. There was a significant positive correlation between estradiol and testosterone for the entire group (r = 0.35; p < 0.005).

Table 3. Correlation Coefficients

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Patients</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/T ratio</td>
<td>0.65†</td>
<td>0.46†</td>
<td>−0.04§</td>
</tr>
<tr>
<td>Testosterone</td>
<td>−0.37*</td>
<td>−0.39*</td>
<td>0.03§</td>
</tr>
</tbody>
</table>

The glucose value represents the plasma glucose level 2 hours following 75 g of oral glucose. HDL-C = high density lipoprotein cholesterol; E/T = estradiol/testosterone ratio.

* p < 0.05.
† p < 0.01.
‡ p < 0.001.
§ p > 0.05.
Conclusions

The results of this study indicate that the ratio of estradiol to testosterone is significantly elevated in men with myocardial infarction. This difference is due to a significantly lowered plasma testosterone in the patients since the estradiol levels were similar in patients and controls.

Previous reports have indicated that plasma estrogen levels are significantly increased in men with myocardial infarction while testosterone levels when measured were shown to be similar to that obtained in controls. However, incomplete characterization of patients and controls in some of the reports does not rule out the possibility of exogenous factors influencing the results. Both smoking and obesity have been associated with high levels of estrogen. Another factor that may influence estrogen levels is physical and mental stress. Investigators have observed increased estrogen levels in men during the acute phase of myocardial infarction.

In this study, attempts were made to minimize the influence of these exogenous factors. The patients were studied at a mean interval of 15 months after the acute episode of myocardial infarction. None of the patients was left with any complication of the myocardial infarction or had any serious disorders. They were closely matched to controls with respect to age, body weight, and history of smoking. Furthermore, serum cortisol, which is readily influenced by stress, was similar in both the patients and controls. Although nearly half of the patients were on drug therapy, this did not affect their plasma estradiol or their testosterone levels. A change to a high-complex-carbohydrate, low-fat, low-cholesterol diet has been shown to significantly reduce serum estradiol levels. However, the dietary intake of the patients and controls was essentially the same in this study.

The finding of an increased ratio of estradiol to testosterone in patients with myocardial infarction agrees with some authors who have demonstrated an elevated estradiol to testosterone ratio in patients with coronary artery disease. In addition, Phillips demonstrated that the estradiol-to-testosterone ratio correlated significantly with cholesterol, serum glucose area, insulin area, and the ratio of insulin area to glucose area in the glucose tolerance test. The present study confirms these findings inasmuch as it found a significant positive correlation in the estradiol-to-testosterone ratio and plasma cholesterol, triglycerides, and glucose levels. Plasma estradiol levels in the patients with myocardial infarction were similar to those in the control group. Since there is a positive correlation between estradiol and testosterone, a possible reason for the failure to demonstrate increased estradiol levels in the patients is the fact that the major precursor for estradiol, serum testosterone, was decreased in the patients and hence masked any increase in estradiol concentration. Hence, previous reports of higher estradiol levels in men with myocardial infarction as compared to controls cannot be confirmed.

The majority of studies have reported that the testosterone levels in patients with coronary artery disease was similar to that obtained in control subjects. However, low plasma testosterone in patients with angiographically proven coronary artery disease have been reported. Plasma testosterone and the free testosterone index were found to be significantly lower in our patients.

The causes for the low testosterone levels in the patients are not known and this aspect is presently being investigated. Of interest are two recent reports in which low plasma...
testosterone was associated with impaired post-heparin lipoprotein lipase activity in patients with angiographically assessed coronary artery disease. Furthermore, plasma testosterone was positively correlated with plasma HDL cholesterol and negatively with plasma triglycerides. In addition to the impaired lipoprotein lipase activity that was reported in patients with coronary artery disease, a positive association between lipoprotein lipase activity and plasma HDL cholesterol and a negative association between lipoprotein lipase and the severity of coronary artery disease have also been demonstrated. Our hypothesis is that low plasma testosterone results in impaired lipoprotein lipase activity, which predisposes to secondary lipid abnormalities. In the present study, testosterone was inversely related to both cholesterol and triglycerides but not to HDL cholesterol.

The significance of the increased estradiol-to-testosterone ratio is not clear. Phillips postulated that in men with coronary artery disease, abnormalities in glucose tolerance and insulin response, and increases in serum cholesterol and triglyceride concentrations were all part of the same underlying defect and that this glucose-insulin-lipid defect was secondary to an elevated estradiol-to-testosterone ratio. The findings in the present study appear to support this hypothesis, as evidenced by the significant positive correlation between the estradiol-to-testosterone ratio and the serum cholesterol, triglycerides, and plasma glucose. Although insulin was not measured in this study, it has previously been reported that hyperinsulinaemia occurs in Indian men with myocardial infarction and that this appears to be secondary to increased blood glucose levels.

This study confirms that the risk factors for coronary artery disease may be related to an elevated estradiol-to-testosterone ratio; however, the data do not support either the hypothesis that hyperoestrogenemia may be a major predisposing factor for myocardial infarction in men or that the increased estradiol-to-testosterone ratio is due to the hyperoestrogenemia. An association between HDL cholesterol and either plasma testosterone levels or estradiol-to-testosterone ratio could not be confirmed.

In conclusion, this study has shown that Indian men with myocardial infarction have low plasma testosterone and an elevated ratio of estradiol to testosterone. The significance of this hormonal disturbance, however, remains a subject for further study.

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