Concentrations of Sex-Hormone Binding Globulin and Corticosteroid Binding Globulin in Serum in Relation to Cardiovascular Risk Factors and to 12-Year Incidence of Cardiovascular Disease and Overall Mortality in Postmenopausal Women

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We determined sex-hormone binding globulin (SHBG) and corticosteroid binding globulin (CBG) by radioimmunoassay of serum samples from a group of 253 women, who were 54 or 60 years old when first studied in 1968–69. The SHBG concentration was highly significantly and inversely related to body mass, body mass index, waist-to-hip circumference ratio, and serum triglyceride concentration; CBG concentration was inversely related to body mass and body mass index. The concentration of neither protein was related to whether or not the subject smoked. Decrease in the concentration of SHBG, but not of CBG, was a significant risk factor for 12-year overall mortality. The plot of the 12-year incidence of myocardial infarction vs SHBG concentration was U-shaped. We recommend that SHBG be included when serum androgens or estrogens are being evaluated as risk factors for cardiovascular disease and death.

Additional Keyphrases: longitudinal study · myocardial infarction · abdominal adiposity · androgens · estrogens · proteins · metabolism · smoking

Evidence is accumulating that abdominal obesity is a risk factor for cardiovascular disease. As reviewed elsewhere (1, 2) this type of obesity is correlated with established risk factors; longitudinal studies in men (3) and women (4) have shown that abdominal obesity is associated with myocardial infarction, stroke, and early death. Prevention of this particular type of obesity is therefore a major challenge for preventive medicine and, in women, has led to a search for metabolic indicators of the tendency for such a development.

The link between abdominal adiposity—the accumulation of intra-abdominal fat (5)—and certain cardiovascular disorders might be an androgenic influence, either a male hormonal pattern or increased tissue sensitivity to male hormones. In the longitudinal study of postmenopausal women we report here, we determined the concentrations of sex-hormone binding globulin (SHBG) and corticosteroid binding globulin (CBG) in serum in an attempt to find a metabolic correlate to increased androgenicity. The former protein reflects the estrogen–androgen balance (6, 7) but is also affected by several other factors, mainly other hormones, certain drugs, and factors related to energy metabolism (food intake, obesity). The regulation of CBG concentration is less well known. Estrogens increase the amounts of CBG in circulation (as reviewed in ref. 8), whereas thyroid hormones seem to decrease them (9). A pronounced decrease in CBG, determined by a corticosteroid binding technique, has been observed in septic shock (10). We included CBG in the present study because of the possibility that the ratio between the concentrations of SHBG and this protein in serum might better indicate androgenicity than would SHBG concentration only (8). We evaluated our results for these proteins in relation to indices of body fat amount and distribution, to other cardiovascular risk factors, and to the outcome of a 12-year follow-up study of ischemic heart disease, stroke, and overall mortality in the original group. A preliminary account of some of these findings has been given (11).

Study Population and Methods

Subjects

The procedures we used in this longitudinal population study of randomly selected women have been recently summarized (12, for details see refs. 13–15). In brief, 1462 women (90.1% of those invited) in the age strata 38, 46, 50, 54, and 60 years were studied in Gothenburg, Sweden, in 1968–69 and six and 12 years later. The present study is confined to older postmenopausal women, i.e., women who were 54 and 60 years old in 1968–69. We obtained information from 96.9% of the women who participated in 1968–69 and were still living in 1980–81, and for all the women who died during the 12-year follow-up period. We had serum available for SHBG and CBG analysis from 172 of the 180 women who were 54 years old, and from all of the 81 women who were 60 years old.

By excluding women who had undergone bilateral oophorectomy, were premenopausal (as judged from questionnaire as well as from serum follitropin assay), or received estrogens, cortisone, thyroid hormones, or anticonvulsive drugs, we limited the statistical analysis to data only from those naturally postmenopausal women who did not receive drugs known to affect the homeostasis of SHBG or CBG (7, 8). Details of the characteristics of the 31 women who were excluded are available upon request from the authors or from the editorial office of this journal.
Moreover, as reported below, a few women were excluded from statistical analysis of risk because of evidence of the presence, already at the 1968–69 investigation, of the events investigated during the 12-year follow-up.

**Biochemical Methods**

We determined serum SHBG and CBG in 1985 by radio-immunooassay of the samples collected in 1968–69, with use of monospecific antisera prepared in rabbits in this laboratory. For raising antisera and for labeling purpose we purified the two steroid-binding proteins according to Fernlund and Laurell (17), with minor modifications. The two proteins were first adsorbed from human serum, collected in the 16–18th week of pregnancy, by filtration through an affinity-chromatographic column in which the adsorbent was the 21-hemisuccinyl derivative of cortisol coupled to aminohexyl-Sepharose 4B (Pharmacia Fine Chemicals, Uppsala, Sweden). This cortisol–Sepharose was prepared as detailed in ref. 17. About 800 mL of serum that had been treated with a charcoal suspension for 4 h at room temperature and overnight at 6°C was centrifuged. The supernatant fraction was adjusted to pH 5.5 with 1 mol/L HCl, then passed through a 1.6 × 21 cm column containing 15 g of cortisol-Sepharose in 25 mmol/L piperazine chloride buffer (pH 7.0, and containing 200 mmol of NaCl and 20 mmol of CaCl₂ per liter). We washed and eluted the column at 6°C at a flow rate of 50 mL/h; after washing first with the above-mentioned piperazine chloride buffer for one day, then with 100 mL of a solution of Triton X-100 (1.0 g/mL) in the buffer followed by 100 mL of buffer alone, we eluted the column with 100 mL of a solution of cortisol, about 3 mmol/L (1.0 g/L), in the piperazine buffer. We then passed the fractions containing SHBG and CBG through a 1.0 × 11 cm column of phenyl-Sepharose CL-4B (Pharmacia Fine Chemicals), which adsorbed SHBG but not CBG. We eluted the SHBG with ethylene glycol/piperazine buffer (2/3 by vol).

SHBG was radiolabeled by the Bolton–Hunter technique (18). As suggested by Fernlund (personal communication), this was carried out in two steps. First, 500 μg of protein in 500 μL of 1 mol/L Tris solution (pH 7.0) was incubated at 4°C with a suspension of about 1 mg of 3-(p-hydroxyphenyl)propionic acid N-hydroxysuccinimide ester (Sigma Chemical Co., St. Louis, MO) for five days. The product was purified by gel filtration through a 10-L column of Sephadex G-10 (Pharmacia Fine Chemicals) in 0.5 mol/L sodium phosphate buffer, pH 7.5. Fractions corresponding to the void volume were stored at −60°C in 25-μL aliquots (about 10 μg of protein). Then we labeled 3-(p-hydroxyphenyl)propionyl-SHBG (about 10 μg) with 1.0 mCi of Na₂¹²⁵I and 50 μg of Chloramine T for 60 s at room temperature (final volume, 45 μL), added Na₂SO₄ (62 μg in 25 μL), and then immediately added the reaction mixture to a 1.6 × 91 cm column of Ultrogel AcA-44 (LKB-Produkter, Stockholm, Sweden) (Figure 1). CBG was labeled with Chloramine T and purified by gel filtration as described for SHBG.

For both radioimmunoassays the serum samples were diluted 100-fold with a 10 mmol/L sodium phosphate buffer at pH 7.5, containing 20 g of bovine albumin (Boehringer Mannheim, F.R.G.), 0.15 mol of NaCl, and 15 mmol of NaN₃ per liter. We assayed SHBG in duplicate 100-μL diluted samples and CBG in duplicate 25-μL diluted samples, which were incubated overnight at 4°C in 12 × 57 mm polystyrene tubes with 200 μL of diluted antisera, containing 5 μmol of EDTA and 0.3 μL of normal rabbit serum, and 100 μL of radiolabeled protein (about 3 × 10⁴ counts/μL), after which we added 10 μL of swine anti-rabbit immunoglobulin G (Dako-Immunoglobulins a/s, Copenhagen, Denmark). After 3 h we added 2.0 mL of polyethylene glycol 6000 at 4°C (60 g/L in the above-mentioned phosphate buffer), let the mixture stand for 10 min, then centrifuged (2000 × g, 30 min, 4°C). We decanted the supernatant fractions and determined the remaining radioactivity in an LKB Wallac Rackgamma II counter (Model 1221; LKB, Stockholm, Sweden). Calculations were made by a logit-log procedure (19).

Calibrators were prepared from a pool of human serum. For the assay of SHBG we calibrated the serum pool by use of an immunoradiometric assay (IRMA) (Farmos Diagnostics, P.O. Box 425, SF-20101 Turku, Finland). For CBG we assigned a value of 1.00 arb. unit/L to the mean value found in the 222 women remaining after the exclusions described under Subjects.

Controls were prepared from pools of human serum, control 1 from male serum and control 2 from postmenopausal serum from 57-year-old women. We stored 1-mL aliquots of each control at −20°C in sealed, all-glass ampoules for 10–11 months before the present study in 1985. We used a new ampoule for each analytical run. In 12 consecutive runs the within-assay CV for our SHBG radioimmunoassay (calculated from the differences between duplicate assays for all samples) ranged from 2 to 5% in the concentration range 10–100 nmol/L; the total CV for control 1 was 4.7% (mean 33 nmol/L) and, for control 2, 3.5% (mean 62 nmol/L), calculated from the mean values for duplicate assays of the two controls.

For CBG the within-assay CV ranged from 1.2 to 3.2% in 19 consecutive analytical runs (concentration range 0–2 arb. units/L). The total CV in the 19 runs was 2.2% for control 1 (mean 0.92 arb. unit/L) and 1.9% for control 2 (mean 0.93 arb. unit/L).

We also used a dihydrotestosterone-binding assay for SHBG in serum samples that had been adsorbed with concanavalin A (bioMérieux, 69260 Charbonnières-les-Bains, France).

**Events Investigated during the Follow-up Period**

Elsewhere (20) we have summarized the criteria used for the following events: myocardial infarction (12 women),

![Fig. 1. Gel filtration pattern of radiolabeled material after iodination of SHBG](image-url)
angina pectoris (19 women), electrocardiographic changes indicating ischemic heart disease (18 women), and stroke (seven women). Thirty-two women died.*

Patients with findings positive for events at the initial examination were excluded when the risk for this event was assessed. This amounted to five women with angina pectoris and seven with electrocardiographic changes, but none had myocardial infarction or stroke.

Statistical Methods

Associations between graded or continuous variables were tested by means of Pitman’s nonparametric permutation test (21). In adjusting for confounding variables we used an extension of the Mantel–Haenszel procedure to permutation tests (22). Two-tailed tests were used. We considered p values <0.05 to indicate significant relationships.

Results

Method Comparison for Assay of SHBG in Stored Serum

When fresh human sera are used, the results of the radioimmunoassay we used for serum SHBG well agree with those by two other methods: an IRMA and a dihydrotestosterone-binding assay for concanavalin-A treated samples (“DHT capacity”). Assaying the samples from the 1968–69 study, however, gave the following results: present method, nmol/L = 0.70 mmol/L + 1.2 nmol/L (r = 0.98), and present method, nmol/L = 1.73 DHT capacity – 24 nmol/L (r = 0.98) (30 samples, concentration range by radioimmunoassay 9.7–121 nmol/L, mean 69 nmol/L). Despite the good correlation between methods, the differences in absolute values for SHBG were large.

Concentrations of SHBG and CBG in Serum

The concentrations of SHBG and CBG in serum ranged from 9.7 to 162 nmol/L and from 0.70 to 1.5 arb. unit/L, respectively (Figure 2). The concentrations of CBG after exclusions (see above) were distributed normally with a relative standard deviation (SD/mean) of 0.12. Median and mean (relative SD) concentrations of SHBG were 57 nmol/L and 62 (0.40) nmol/L, respectively. A recent sample of 57-year-old women (see Biochemical Methods) showed the same mean concentration of SHBG as these 16-year-old samples but a slightly lower (about 7%) concentration of CBG.

Linear regression analysis of the results from the 1968–69 study showed a significant correlation between the concentrations of the two proteins (r = 0.18, n = 222; p = 0.009, adjusted for age).

Relationship to Risk Factors

Table 1 shows the age-adjusted p-values for the nonparametric correlations between the binding globulin concentrations (and their ratio) and age, concentrations (during fasting) of serum triglycerides, serum cholesterol, and blood glucose, body mass, body mass index, waist-to-hip circumference ratio, smoking habits, and systolic blood pressure. The inverse relationships found between the concentration of SHBG and concentration of serum triglycerides (Figure 3), body mass, body mass index, and waist-to-hip circumference ratio (Figure 4) were significant. We then tested the possibility that the waist-to-hip circumference ratio was independently associated with the concentration of serum SHBG. The p value increased to 0.04 when body mass index was included as a potentially confounding variable for the relationship to waist-to-hip circumference ratio, whereas the level of significance was unchanged when the waist-to-hip circumference ratio was included as a background variable in the analysis of the relationship between SHBG concentration and body mass index. For the inverse relationship between concentrations of SHBG and serum triglycerides, the level of significance was unchanged when either body mass index or waist-to-hip circumference ratio was included as a background variable. Finally, the levels of significance for the inverse relationships between SHBG concentration and body mass index or waist-to-hip circumference ratio were unchanged when serum triglyceride concentration was included as a background variable.

Table 1 also shows the results from statistical analysis of the relationship between above-mentioned risk factors and concentration of CBG. There was a significant association (inverse relationship) with body mass and body mass index but not with waist-to-hip circumference ratio. No significant relationship was observed between the concentration of CBG in serum and the concentration of triglycerides in serum. The p-value for the inverse relationship between CBG concentration and body mass index decreased to 0.003 from 0.007 when serum triglyceride concentration was included as a background variable.

Levels of significance for SHBG alone vs other parameters were approximately the same as for the ratio between the two proteins (Table 1).

Relationship to Cardiovascular Events and Mortality

Table 2 shows the p-values for the nonparametric correlations between initial serum concentrations of binding globulins and the 12-year incidences of myocardial infarction and

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* Details of the characteristics of the 23 women who died during the 12-year follow-up are available upon request from the authors or from the editorial office of this journal.
Table 1. Age-Adjusted Nonparametric Correlations (p-Values) of Concentrations of SHBG and CBG, and SHBG/CBG Ratio, vs Selected Variables

<table>
<thead>
<tr>
<th></th>
<th>SHBG</th>
<th>CBG</th>
<th>SHBG/CBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.77*</td>
<td>0.88*</td>
<td>0.72*</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>&lt;0.0001*</td>
<td>0.35*</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>0.35*</td>
<td>0.47*</td>
<td>0.14*</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>&gt;0.05*</td>
<td>0.06</td>
<td>0.10*</td>
</tr>
<tr>
<td>Body mass index</td>
<td>&lt;0.0001*</td>
<td>0.0007*</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Waist/hip circumference ratio</td>
<td>&lt;0.0001*</td>
<td>0.85*</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>0.13</td>
<td>0.07</td>
<td>0.31</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.11*</td>
<td>0.22</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

*Weight/height² (kg/m²). Measured as described in ref. 4. As determined in a standardized interview (13). Measured with mercury manometer after subject was sitting for 5 min. *Inverse relationship.

Table 2. Nonparametric Correlations (p-Values) between initial SHBG and CBG Concentrations and 12-Year Incidence of Myocardial Infarction (MI) and Overall Mortality

<table>
<thead>
<tr>
<th>Background variable(s)</th>
<th>MI</th>
<th>Mortality</th>
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</thead>
<tbody>
<tr>
<td>SHBG</td>
<td>0.28*</td>
<td>0.03*</td>
</tr>
<tr>
<td>Age</td>
<td>0.05*</td>
<td>0.02*</td>
</tr>
<tr>
<td>Age + waist/hip ratio</td>
<td>0.47*</td>
<td>0.03*</td>
</tr>
<tr>
<td>CBG</td>
<td>0.06</td>
<td>0.58</td>
</tr>
<tr>
<td>Age + waist/hip ratio</td>
<td>0.49</td>
<td>0.58</td>
</tr>
<tr>
<td>Age + waist/hip ratio</td>
<td>0.03</td>
<td>0.80*</td>
</tr>
</tbody>
</table>

*Inverse relationship.

mass index, and waist-to-hip circumference ratio vs mortality and cardiovascular events showed significant correlations for body mass index and for waist-to-hip circumference ratio vs myocardial infarction (the age-adjusted p values were 0.013 and 0.007, respectively). For serum triglyceride concentration there was a significant correlation with mortality and with myocardial infarction (age-adjusted p values 0.004 and <0.001, respectively).

A plot of the 12-year age- adjusted incidence of myocardial infarction vs different centile intervals of serum concentration of SHBG indicated a U-shaped relationship (Figure 5). Also for CBG there appeared to be a U-shaped relationship to incidence of myocardial infarction, though with a less pronounced descending limb. Similar analysis for mortality revealed a linear type of relationship with SHBG concentra-

Fig. 3. Relationship between concentration of SHBG and triglycerides in serum

Samples were taken after an overnight fast in 1968-69 from 222 naturally postmenopausal women, ages 54 or 60 years, who did not receive drugs known to affect the serum concentration of SHBG. The equation for the linear regression line was y = -13x + 80 (r = 0.34)

Fig. 4. Relationship between concentration of SHBG (upper) and of CBG (lower) in serum and body mass, body mass index, and waist-to-hip circumference ratio

Study group as in Fig. 3; results from linear regression analyses are given by straight lines.

A low concentration of SHBG in serum was found to be a significant risk for mortality, also with the background variables waist-to-hip circumference ratio, serum triglyceride concentration (Table 2), and traditional risk factors for cardiovascular disease such as systolic blood pressure, smoking habits, body mass index, blood glucose concentration, and serum cholesterol concentration (data not shown). There was no correlation between SHBG concentration and subsequent angina pectoris, electrocardiographic changes indicating ischemic heart disease, or stroke. The concentration of CBG was not significantly associated with any of the events studied.

Analysis of possible relationships for body mass, body mortality. A low concentration of SHBG in serum was found to be a significant risk for mortality, also with the background variables waist-to-hip circumference ratio, serum triglyceride concentration (Table 2), and traditional risk factors for cardiovascular disease such as systolic blood pressure, smoking habits, body mass index, blood glucose concentration, and serum cholesterol concentration (data not shown). There was no correlation between SHBG concentration and subsequent angina pectoris, electrocardiographic changes indicating ischemic heart disease, or stroke. The concentration of CBG was not significantly associated with any of the events studied.

Fig. 5. Incidence of myocardial infarction during 12 years vs initial serum concentration of SHBG.

Solid lines indicate quintiles of SHBG concentration; broken lines indicate lowest decile.
tion, with a risk ratio of 6.0 between the lowest and the highest quintile (13% vs 2.2%). The ratio was 12 when we compared women in the lowest decile of the distribution with those in the highest quintile.

Characteristics of Nonsurvivors

There was no relationship between initial SHBG concentration and the interval between examination and death of the 23 women who died during the 12-year follow-up, i.e., a low concentration of SHBG was not an expression of a condition leading to death within the next few years.

Figure 6 shows the relationship between initial waist-to-hip circumference ratio and initial concentration of serum SHBG in women who died during the 12-year follow-up ($r = 0.64$, compared with 0.35 for the complete sample after exclusions).

Records of nonsurvivors from the 1968–69 study provided no evidence for previous gynecologic endocrine abnormality such as menstrual irregularity, infertility, or high prevalence of spontaneous abortions. However, the 1968–69 questionnaire did not include questions concerning abnormal hair growth on body or scalp. Clinical examination did not reveal any cases of gross hirsutism. Karyopyknotic indices (evaluated from light-microscopic examination of vaginal smears) were those normally found in postmenopausal women. Thus we found no clinical evidence for the presence, at the time of screening, of abnormal androgenic or estrogenic influence on the women who died during the 12-year follow-up.

Discussion

Myocardial infarction is more common, and the life-expectancy shorter, in men than in women. One must therefore consider the possibility that female sex hormones are protective or that male sex hormones are deleterious. We have here examined this problem by studying the concentration of SHBG, an indicator of inter alia the estrogen–androgen balance, in relation to cardiovascular and mortality risk in postmenopausal women.

Assay of SHBG

Several techniques have been used to determine serum SHBG, based on its biological or its antigenic properties. In the former case, unbound has been separated from bound ligand (usually labeled dihydrotestosterone) by use of two-phase systems (dialysis, gel filtration, immiscible solvents), by electrophoresis (agar, polyacrylamide), by adsorption (charcoal, silicates, specific antibodies), or by isolation of the ligand–protein complex (precipitation with ammonium sulfate, adsorption onto diethylaminoethyl-cellulose or concanavalin-A). Some of these methods are too laborious to be used in either large-scale studies or clinical routine, and several of them are poorly precise. Severalfold differences in estimates of health-associated reference limits occur (23), indicating bias problems, but, to our knowledge, the cause(s) for this bias has not been elucidated. Recently summarised (7), there are also several reports on immunochemical procedures for determination of this protein. These assays may offer higher precision and are less labor-intensive. There is, however, no universally accepted reference preparation for calibration purpose. Our results from analysis of the presently studied 16-year-old samples, which had been carefully protected from repeated freezing and thawing as well as from freeze-drying during storage, indicate that bias between different methods may occur, not only with binding-capacity assays but also between different immunochemical procedures. Possibly, therefore, special attention should be given to incubating conditions in future studies of this dimeric protein. With our assay we found no difference in results between a recent sample of 57-year-old females and the presently studied 54- and 60-year-old females, indicating that the method is valid for the present study. A special problem with radioimmunoassay of SHBG is the difficulty in labeling the protein with radioiodine by conventional procedures. Our results given in Figure 1 indicate satisfactory purity and antigenic properties of the material in our study.

A negative relationship between serum SHBG capacity and serum concentration of triglycerides has been found in males (24, 25) but not in premenopausal women (26, 27). It remains possible, however, that the stability of SHBG during the 16-year storage might be affected by sample triglyceride content, in view of its tendency for hydrophobic associations.

Smoking

A high concentration of ceruloplasmin has been found in serum of tobacco smokers (28), but the mechanism(s) involved are unknown. Of possible relevance for the relationship between smoking and cardiovascular disease is the fact that an increased ceruloplasmin concentration may occur as a result of estrogenic activity. However, the absence of an association between smoking habit and concentration of the presently studied estrogen-sensitive plasma proteins speaks against the presence of increased estrogenicity in smoking postmenopausal women as compared to nonsmokers.

Obesity

A number of factors govern the synthesis and/or elimination rates of SHBG (7). Our findings of an inverse relationship between body mass and body mass index, respectively, and the concentration of this protein in serum confirm early results by De Moor et al. (29) and Vermeulen et al. (30), and more recent reports from some other laboratories, that the concentration of this protein in serum decreases in obesity. The mechanism(s) involved are unknown. In our study the amount of body fat and the waist-to-hip circumference ratio, reflecting the male type of obesity, had independent effects.
Only obesity per se had an influence on the concentration of CBG. Interestingly, increased body mass index was associated with lower rather than with higher values—in postmenopausal women, obesity is commonly thought to be associated with increased estrogenicity. The ratio between the concentrations of the two steroid-binding proteins was not more informative than either measurement alone.

To our knowledge there are no previous studies from representative population samples on the concentration of serum SHBG vs abdominal obesity. A comprehensive study, carried out in 80 pre-menopausal women who had volunteered for a study of body fat topography (37), revealed a negative relationship between waist-to-hip circumference ratio and concentration of SHBG; the effect of the former parameter was independent of that of per cent ideal body weight. Of the serum steroid hormones studied, only the per cent free testosterone showed a significant association (positive relationship) with the waist-to-hip circumference ratio.

Myocardial Infarction and Mortality

We are not aware of any previous study considering serum SHBG or CBG as potential risk factors for cardiovascular disease or death. It is tempting to speculate that part of the women who died during follow-up (Figure 6) represent an "android" subgroup of postmenopausal women with increased sensitivity to androgens or increased circulating concentrations of metabolically active androgens, or both. Results of an androgenic influence would be low concentration of SHBG and a tendency for abdominal obesity. Increase in amount of body fat, in this case in intra-abdominal fat depots (5), then results in further decrease in the concentration of SHBG in the circulation. Whether the decreased concentration of this steroid binder in the circulation results in a change in availability of sex hormones to tissues is unclear (cf. refs. 8 and 31); normal women may differ in this respect from those with the polycystic ovary syndrome.

We did not find any linear relationship between the concentration of SHBG and subsequent myocardial infarction. However, there was a tendency towards a U-form type of relationship (Figure 5), which was also found for CBG concentration. We have not attempted any statistical analysis of these findings, because the number of subjects was low; their significance can be definitively evaluated only by independent studies of a similar type. They may, however, be relevant for the following reasons. Abdominal adiposity as well as male gender are established risk factors for myocardial infarction, as judged from epidemiological studies in humans. These factors would correspond to the descending limb in Figure 5. Possibly, estrogens are also risk factors for myocardial infarction (32, 33) and estrogenic influence would correspond to the ascending limb in Figure 5.

SHBG being a carrier protein for androgens and, to a lesser extent, for estrogens, its concentration will influence total hormone levels. One should therefore consider the need to determine serum SHBG in future studies of serum sex hormones as risk factors for myocardial infarction.

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