Association of Sex Hormones and Adiposity with Plasma Levels of Fibrinogen and PAI-1 in Postmenopausal Women

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Blood levels of the clotting factor fibrinogen and tissue plasminogen activator inhibitor-1 (PAI-1), a primary inhibitor of fibrinolysis, have been positively linked to risk of coronary heart disease. The authors have reported previously that plasma fibrinogen appears to rise after menopause and to be reduced with use of postmenopausal hormonal therapy. There is also evidence to suggest that sex hormones may influence PAI-1. To examine whether plasma fibrinogen and PAI-1 antigen levels differ among older postmenopausal women according to use of hormone therapy and by blood level of estrogen and androgens, these variables were assessed among 277 healthy women aged 65–82 years, one half of whom were receiving therapy. The study population was drawn from the Study of Osteoporotic Fractures, Pittsburgh, Pennsylvania, during 1986–1988. Overall, results showed median PAI-1 levels to be lower on average with oral and transdermal use of hormone therapy (25.0 vs. 33.5 ng/ml, p < 0.01) and mean fibrinogen levels to be lower (279 vs. 295 mg/dl, p < 0.02) with use of oral estrogen (but not transdermal) therapy compared with women not receiving therapy. Among women not receiving therapy, PAI-1 and fibrinogen levels were not related to endogenous sex hormone levels, with the exception of a modest positive relation between PAI-1 and serum estrone concentrations ($r_s = 0.29$). In addition, a markedly higher PAI-1 level was found for women with a preponderance of upper body fat, independent of obesity. In sum, results showed that older women receiving postmenopausal hormone therapy had more favorable plasma levels of the hemostatic factors PAI-1 and fibrinogen than did those not receiving therapy, which can be explained in large part by differences between the two groups in obesity and body fat distribution. Am J Epidemiol 1996;143:159–66.

Blood coagulation; fibrinolysis; estrogens; obesity; plasminogen activator inhibitor 1; women

Plasminogen activator inhibitor-1 (PAI-1) is the dominant regulator of the fibrinolytic system binding with tissue plasminogen activator and thereby preventing the activation of plasmin, which is responsible for the degradation of fibrin, the central component of blood clots (1). Fibrin is formed from fibrinogen in the presence of thrombin. In addition, fibrinogen largely determines blood viscosity and therefore its flow properties (2).

Elevated plasma concentrations of fibrinogen and PAI-1 have been associated with coronary heart disease risk. Women enrolled in the Framingham Heart Study who had plasma fibrinogen levels in the highest tertile had about a twofold risk of coronary heart disease over a 12-year follow-up (3). Plasma PAI-1 activity level has been positively related to severity of angiographically determined coronary artery disease among men and women with angina pectoris (4) and has been found to be higher among young male and female (less than age 45 years) myocardial infarction cases compared with random controls (5).

Risk of coronary heart disease is also influenced by steroid hormone levels among women, as evidenced by the elevation in risk after premature surgical menopause, which is reduced by use of estrogen therapy (6).

Evidence that sex steroid hormones have an impact on hemostatic function comes from studies showing variation in hemostatic measures during the menstrual cycle (7–9), during pregnancy (10, 11), and with menopause (12–14). Studies of sex differences in PAI-1 have shown lower levels in females than in males at younger ages, with the difference diminishing with age (15) and disappearing altogether after orchidectomy in rats (16).
One potentially important component of the relation between coronary heart disease risk, sex hormones, and hemostatic factors is body fat distribution. Excess coronary heart disease risk has been noted for older women with a preponderance of upper body fat (17). Steroid hormones presumably influence body fat distribution, since men have more intra-abdominal fat than do women (18) and postmenopausal women have more intra-abdominal fat than do premenopausal women (19). Abdominal obesity in women has been linked to unfavorable plasma levels of hemostatic parameters (20), in particular, PAI-1.

The aim of this study was to improve our understanding of how hormone therapy and obesity may contribute to postmenopausal coronary heart disease risk via hemostatic mechanisms. Investigations of this sort are of obvious consequence, given that coronary heart disease is the major cause of death among postmenopausal women and that hormone therapy in the form of oral conjugated estrogen is the most frequently dispensed drug in the United States (21).

MATERIALS AND METHODS

Study population

This study, conducted during 1986–1988, was ancillary to the multicenter Study of Osteoporotic Fractures, a prospective study of risk factors for fractures in elderly women. To be eligible to participate in the parent study, women had to be nonblack, aged 65 years or older, living in the community, able to walk without the assistance of another person, and never to have had a bilateral hip replacement. A total of 2,401 white women living in a rural area near Pittsburgh, the Monongahela Valley, Pennsylvania, were enrolled in the Pittsburgh clinic of the study. Recruitment was primarily based on the response to mass mailing to all age-eligible women listed on the voter registration lists. The response to these mailings was about 8 percent.

There were 139 women aged 65–82 who reported receiving postmenopausal hormone therapy and who also had citrated plasma samples available at the baseline examination. An approximately equal number (n = 138) of women in the same age range who reported no use of hormone therapy and who had plasma available were randomly selected. Thus, by design, the number of women receiving hormone therapy was similar to the number who were not.

Clinic examination

Blood samples were drawn according to the protocol of the Study of Osteoporotic Fractures. Blood was drawn between the hours of 8:00 a.m. and 2:00 p.m. Individuals were not required to fast but were instructed to avoid fatty foods. For example, subjects could have coffee with skim milk but not 2 percent or whole milk. Blood was drawn after the participant had been seated for at least 10 minutes. The Vacutainer system, red-top, noncoated 10-ml tubes and blue-top 5 ml tubes with sodium citrate (Becton-Dickinson, Rutherford, New Jersey) were used. The red-top tubes were kept at room temperature for at least 60 minutes, but for not more than 120 minutes, and then refrigerated until centrifugation. The blue-top tubes were refrigerated immediately after blood was drawn and centrifuged within 120 minutes. After the serum and plasma were separated, they were transferred into tubes for storage at −20°C for 2–6 weeks and then frozen at −70°C. Samples were shipped on dry ice to the laboratory of one of the authors (J. P. G.) via overnight carrier for hormone determination and to another author (R. P. T.) for hemostatic measures. Laboratory personnel were unaware of subject characteristics, including use of hormone therapy.

Participants completed a questionnaire on demographics and health behaviors, including use of alcohol, cigarettes, and postmenopausal hormone therapy.

Body weight (in light indoor clothing) was measured by using a balance beam scale, and height was measured without shoes using a Harpenden stadiometer (Holtain Ltd. Dyved, United Kingdom). Body mass index was calculated using weight (kg) divided by height (m²). Waist and hip circumferences were measured using standardized methods (22). The waist: hip ratio was calculated as a measure of body fat distribution, with a higher ratio indicating greater upper body fat.

Laboratory

Fibrinogen was measured on a BBL Fibrometer (Becton-Dickinson, Cockeysville, Maryland) based on total clottable fibrinogen using a modified form of the Clauss technique (23). PAI-1 antigen was measured using an enzyme-linked immunosorbent assay (24) with intrassay and interassay coefficients of variation of 5.2 and 8.0 percent, respectively. The lower level of sensitivity is 2 ng/ml. This assay essentially measures the free PAI-1 and is far less sensitive to the tPA/PAI-1 complex.

Measurement of blood levels of sex hormones was limited to subjects who were not receiving postmenopausal therapy. Blood level of estrone was measured by highly specific methods involving an extraction step, a Sephadex LH-20 column chromatography (LKB Biotechnology, Piscataway, New Jersey), and a radioimmunoassay using a specific antibody to improve specificity. Total androstenedione and testosterone-
TABLE 1. Characteristics of study population according to use of hormone therapy, 273 women aged 65 years and over, Study of Osteoporotic Fractures, Pittsburgh, Pennsylvania, 1986–1988

<table>
<thead>
<tr>
<th>Use of hormone replacement therapy</th>
<th>Yes (n = 137)</th>
<th>No (n = 136)</th>
<th>Total</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50th percentile</td>
<td>Mean (SD)</td>
<td>50th percentile</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>PAI-1 (ng/ml)†</td>
<td>25.0</td>
<td>31.4 (20.0)</td>
<td>33.5</td>
<td>36.8 (18.0)*</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)‡</td>
<td>278</td>
<td>253 (46)</td>
<td>289</td>
<td>296 (60)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68</td>
<td>69.5 (4.3)</td>
<td>70</td>
<td>69.9 (3.3)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.5</td>
<td>26.0 (4.2)</td>
<td>27.1</td>
<td>27.3 (4.5)*</td>
</tr>
<tr>
<td>Waist:hip ratio (cm)</td>
<td>0.777</td>
<td>0.785 (0.07)</td>
<td>0.612</td>
<td>0.816 (0.06)*</td>
</tr>
<tr>
<td>Estrone (pg/ml) (n = 135)</td>
<td>—§</td>
<td>—§</td>
<td>—§</td>
<td>—§</td>
</tr>
<tr>
<td>Androstenedione (ng/dl) (n = 92)</td>
<td>—§</td>
<td>—§</td>
<td>—§</td>
<td>—§</td>
</tr>
<tr>
<td>Testosterone (ng/dl) (n = 84)</td>
<td>—§</td>
<td>—§</td>
<td>—§</td>
<td>—§</td>
</tr>
</tbody>
</table>

* p < 0.05, comparing users and nonusers of hormone therapy.
† SD, standard deviation.
‡ Two outliers deleted.
§ Not measured in hormone-users.

Statistical analyses

Of the total of 277 ancillary study subjects, 273 were included in the analyses, since four women with extreme values were excluded, two with plasma fibrinogen of greater than 550 mg/dl (99th percentile = 450 mg/dl) and two with PAI-1 values of greater than 195 ng/ml (99th percentile = 79 ng/ml). (Fibrinogen and PAI-1 can be elevated in response to acute inflammation or illness.) The fibrinogen values were normally distributed, and the PAI-1 values were log-normally distributed.

Unpaired t tests for continuous variables and chi-square tests for categorical variables were performed to compare women who were receiving estrogen therapy with those who were not except for the comparison of PAI-1, for which nonparametric analysis was used (table 1). Median values are presented for sex hormone levels and PAI-1 since the distributions were highly skewed. The nonparametric correlation coefficient (Spearman, r) was utilized to examine the relations among study variables (table 2). Multivariate linear analysis included variables for hormone therapy use (yes/no) and dummy variables comparing women in the upper two tertiles of body mass index and waist:hip ratio with those in the lowest tertile. Use of categories of body fatness avoided assumptions of linear relations between the dependent and independent variables.

RESULTS
Population

Overall, subjects were an average of 69 years old (range, 65–82 years) with a body mass index of 26.3 kg/m² and a waist:hip ratio of 0.796 cm; the range of values was wide for both measures of fatness (table 1). The serum estrone levels were clearly in the postmenopausal range, with a median of 37.3 pg/ml. Androgen levels, which do not decline postmenopausally to the same degree as do the estrogen levels (25), showed a median value of 77.0 ng/dl for androstenedione and 37.2 ng/dl for testosterone. A history of surgery...

plasma fibrinogen and PAI-1 in postmenopausal women.

TABLE 2. Spearman correlation between selected factors and PAI-1 and fibrinogen, 273 women aged 65 years and over, Study of Osteoporotic Fractures, Pittsburgh, Pennsylvania, 1986–1988

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>PAI-1† (ng/ml)</th>
<th>Fibrinogen (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of oral estrogen (mg/month)</td>
<td>92</td>
<td>-0.23**</td>
<td>-0.29**</td>
</tr>
<tr>
<td>Dose of progestin (mg/month)</td>
<td>14</td>
<td>0.10</td>
<td>0.48</td>
</tr>
<tr>
<td>Serum estrone (pg/ml)‡</td>
<td>135</td>
<td>0.29**</td>
<td>0.16</td>
</tr>
<tr>
<td>Serum testosterone (ng/dl)‡</td>
<td>84</td>
<td>-0.06</td>
<td>-0.17</td>
</tr>
<tr>
<td>Serum androstenedione (ng/dl)‡</td>
<td>92</td>
<td>0.12</td>
<td>-0.06</td>
</tr>
<tr>
<td>Age (years)</td>
<td>273</td>
<td>-0.05</td>
<td>0.12</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>273</td>
<td>0.36**</td>
<td>0.20**</td>
</tr>
<tr>
<td>Waist:hip ratio (cm)</td>
<td>273</td>
<td>0.28**</td>
<td>0.08</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01.
† PAI-1, plasminogen activator inhibitor-1.
‡ Subjects not receiving hormone therapy.
gical menopause was reported by 56 women, most \((n = 39)\) of whom reported use of hormone therapy.

Few women in this older cohort reported cigarette smoking (8 percent) or an alcohol intake of greater than 3 ounces (85.1 g) per week (about 3 percent).

**Use of hormone replacement therapy**

Oral estrogen was the most common form of postmenopausal therapy reported \((n = 92, 67\text{ percent})\), with 31 percent using estrogen cream \((n = 42)\) and two women reporting use of an estrogen patch. The monthly dose of oral estrogen ranged from 2.5 to 37.5 mg with a median of 13 mg; for reference, 0.625 Premarin (Wyeth-Ayerst, Philadelphia, Pennsylvania) per day for 25 days a month is equal to about 15 mg per month. Progestin therapy in combination with oral estrogen was reported by 13 women, and progestin alone was reported by one woman. Women who reported receiving postmenopausal hormone therapy differed from those not receiving therapy in that they were thinner (body mass index (BMI), 26.0 vs. 27.3, \(p = 0.01\)) and had a smaller waist:hip ratio (0.785 vs. 0.816, \(p = 0.0001\)) (table 1). There was no difference between the groups in age, smoking and drinking behavior, or proportion who were diabetic (not shown).

**Hemostatic factor levels**

The median plasma fibrinogen was 285 mg/dl, and the median PAI-1 was 30 ng/ml; both factors showed a wide range of values (table 1). Fibrinogen and PAI-1 were modestly related \((r_s = 0.14, p = 0.02)\). Neither factor was related to age in this sample of women aged 65 years and older.

**Hemostatic factors and hormone use**

As shown in table 1, women who reported receiving any form of postmenopausal hormone therapy compared with those not receiving therapy had on average a 12 mg/dl lower fibrinogen level \((p = 0.06)\) and a 5.4 ng/ml \((p < 0.01)\) lower PAI-1 level.

The form of administration of therapy, whether oral or transdermal, did not have an impact on PAI-1 level; median values were virtually the same for both forms (not shown). Mean fibrinogen level was 10 mg/dl lower on average with oral than with transdermal therapy \((p = 0.25)\). When use of hormone therapy was confined to oral estrogen, the difference in mean fibrinogen between users and nonusers was 16 mg/dl \((279\text{ vs. }295\text{ mg/dl, }p = 0.02)\). Thus, an effect of estrogen therapy on fibrinogen levels may be greater with oral as opposed to transdermal formulations. This observational study, however, with subjects using a variety of doses and formulations, could not address this question directly.

In addition, fibrinogen and PAI-1 (table 2) were lower with higher monthly oral doses of estrogen \((p < 0.05)\), and they tended to be positively but nonsignificantly \((p > 0.05)\) related to progestin dose. However, only 14 women used progestins. Neither estrogen nor progestin dose was correlated with BMI or with age (not shown).

**Hemostatic factors and endogenous hormone levels**

The endogenous blood levels of steroid hormones were not significantly correlated with plasma fibrinogen and PAI-1, with the exception of a positive relation between estrone and PAI-1 \((r_s = 0.29, p < 0.01)\) (table 2).

**Hemostatic factors and body fat**

Both hemostatic factors were significantly positively correlated \((r_s > 20)\) with body mass index, while only PAI-1 was correlated with the waist:hip ratio (table 2). Figure 1 shows that even nonobese women exhibited an increased PAI-1 concentration if they had greater upper body adiposity. A 5–10 ng/ml difference in PAI-1 was found for the smallest versus the largest waist:hip ratio tertiles within each of the three BMI groupings.

**Interrelation of hemostatic factors, hormone therapy use, and body fat**

Results of multiple linear regression analyses that included tertiles of body mass index, waist:hip ratio, and use of hormone replacement (yes/no) showed both obesity and fat distribution to be significantly positively associated with (log-transformed) PAI levels in this population of postmenopausal women (table 3). The percent difference between tertiles 2 versus 1 and 3 versus 1 of waist:hip ratio were estimated, using the antilog of the beta coefficient \((e^\beta - 1 \times 100 = \text{percent difference})\), as 27 and 34 percent, respectively. For BMI, the percent differences were 22 percent for tertiles 2 versus 1 and 39 percent for tertiles 3 versus 1 (not shown). The association with hormone therapy use was not significant by conventional standards after measures of fatness were accounted for \((p = 0.12)\), although the effect was in the predicted direction and the variation in PAI-1 associated with therapy use in this model was 6 percent \((r^2 = 0.06)\). The total variation "accounted for" by the model was 16 percent. Results were similar for the model with fibrinogen as the dependent variable. Hormone therapy use was marginally associated \((p = 0.09)\) with lower fibrino-
Gen level in this population, while women in the upper tertile of body mass index exhibited a 16 mg/dl higher fibrinogen than women in the lowest tertile ($p = 0.07$). The variance in fibrinogen accounted for by these variables overall, however, was only 2 percent ($r^2 = 0.02$). Including only those receiving oral estrogen in the multivariate analysis altered the results only slightly, yielding a 13.5 mg difference between those taking and those not taking estrogen ($p = 0.08$). Further, the multivariate analyses were also performed with BMI and waist:hip ratio as continuous, rather than categorical, variables that yielded virtually identical results. Cigarette smoking and alcohol intake (yes/no) were not significant in the multivariate analyses and were dropped from the final models. The prevalence of smoking and alcohol use was low in this population.

**DISCUSSION**

Results showed plasma fibrinogen and PAI-1 antigen concentrations to be lower, on average, among...
users of postmenopausal hormone therapy compared with nonusers. Moreover, the higher the dose of oral estrogen, the lower the plasma values of fibrinogen and PAI-1. However, the fact that women who took estrogen were thinner and had less abdominal fat (as measured by waist:hip ratio) appeared to largely account for the lower plasma levels of hemostatic factors. PAI-1 antigen levels, in particular, were positively related to upper body obesity. The very low endogenous steroid hormone levels among these older postmenopausal women were not related to fibrinogen or PAI-1 concentrations, with the exception of a positive relation between PAI-1 and estrone.

In spite of widespread use of postmenopausal therapy in the United States (21, 26), little is known about its impact on plasma levels of hemostatic factors. In particular, studies in older women, who are at greatest risk for coronary heart disease, have been scarce.

Mean fibrinogen level was higher (about 40 mg/dl) for this older group than for women aged 45–50 years in a previous report (13). In general, fibrinogen levels appear to increase with age, at least up to about age 70 years, resulting in relatively high values in older women (27). Older age has also been linked to an increase in PAI-1 levels, particularly for women (15). The age-related increase may be exacerbated by the onset of menopause since higher levels of fibrinogen (13, 28, 29) and PAI-1 (30, 31) have been reported among postmenopausal compared with premenopausal women.

Use of postmenopausal estrogen therapy in our study was associated with a modestly lower plasma level of the coagulation factor, fibrinogen, consistent with other population studies of generally younger postmenopausal women (13, 32, 33). For women taking progestin in addition to estrogen, there was no impact on the level of fibrinogen according to results from the Atherosclerosis Risk in Communities study (34). Exogenous estrogen may decrease fibrinogen via hepatic effects, since we observed a more marked association with oral than with transdermal estrogen therapy, consonant with an earlier report (35). However, a recent population study (14) found a plasma fibrinogen level that was about 10–15 mg/dl lower among users of both transdermal and oral postmenopausal therapies, although the number of users was small and results were not statistically significant. In addition, two small but carefully controlled experimental studies comparing effects of varying doses of transdermal estradiol and oral conjugated equine estrogens on hemostatic measures found very little impact for either preparation on fibrinogen (36, 37). Thus, while large population studies have reported lower plasma fibrinogen levels among women receiving postmenopausal hormone therapy, experimental studies do not consistently support this finding, nor have experimental results supported a differential impact of oral versus transdermal preparations. Studies comparing the effects of type of therapy preparation on hemostatic parameters have been very limited, however.

The few studies that examined the impact of sex hormone therapy on PAI-1 levels found lower plasma levels among hormone therapy users compared with nonusers. Two were observational studies that included relatively few women who took hormones (fewer than 40), with about one-half using transdermal forms (14, 30). A recent experimental study found PAI-1 to be lowered by oral but not by transdermal estrogen (38). Enhancement of fibrinolytic activity by vasoactive compounds has been reported (39), and exogenous estrogen is thought to have an effect on the function of vascular endothelial cells (40), which are a major source of PAI-1 (20).

Women who used therapy were thinner and had less upper body fat than did nonusers. The association of body fat distribution and PAI-1 levels is especially striking and is consistent with other reports of elevated PAI-1 levels among younger women with an androgenous body build (15). These findings point to a possibly adverse effect on hemostasis and fibrinolysis of not only obesity, but also a preponderance of upper body fat, even among normal-weight women. Results of this study are compatible with an increased risk of coronary heart disease among older women with a tendency toward upper body fat (17). Weight reduction among moderately obese women appears to reduce plasma levels of PAI-1, but not of fibrinogen (41). It should be noted that use of estrogen therapy may modify weight gain in middle-aged women but does not appear to alter increases in waist:hip ratio over time (42).

Corpulence also influences estrogen metabolism postmenopause when the primary source of estrone is aromatization in peripheral fat tissue; thus, fatter women tend to have higher levels of estrone, as was found for the present study population in which BMI and estrone level were positively correlated. The current study is unique in relating endogenous estrogen and androgen levels to plasma hemostatic factors among older women. Since subjects in our study were all well past menopause, their endogenous estrogen levels were quite low and, with the exception of estrone and PAI-1, showed little relation to hemostatic factor concentrations. A relation between PAI-1 and estrone may be mediated by obesity since PAI-1 levels among fatter women were higher among postmenopausal hormone therapy users compared with nonusers.
With regard to methodological considerations, it should be noted that taking only one measurement of fibrinogen and PAI-1, as was done in our study, is likely to produce weak relations because of the relatively high random within-person variability of hemostatic measures (43). In addition, handling of samples was not ideal for hemostatic measures. Suboptimal handling can increase PAI-1 values because of platelet release of PAI-1. However, sample-handling procedures did not differ according to hormone therapy use. Further, it is important to recognize that a cross-sectional study such as this one cannot exclude the possibility that findings may be due to bias. For example, it is possible that use of estrogen therapy is a marker for other (unmeasured) characteristics that lead to reduced fibrinogen and PAI-1 levels.

Overall, results of this study indicate that women older than 65 years who report using postmenopausal therapy exhibit more favorable plasma levels of fibrinogen and PAI-1, suggesting that they are potentially at lower risk of coronary heart disease than are women not receiving therapy. Women using therapy were thinner and had less abdominal fat (as measured by waist:hip ratio) than did nonusers, and this difference in adiposity appeared to account statistically for much of the association between use of hormone therapy and hemostatic factor levels. Nonetheless, an effect of exogenous estrogen was evidenced by a dose-response between oral estrogen and hemostatic measures. It is likely that adiposity, steroid hormones, and hemostatic function are interrelated in the pathophysiology of cardiovascular disease. In addition, perhaps this is particularly true for aging women, given the striking changes in steroid hormone metabolism at menopause. Considering the increasing number of postmenopausal women and the rapid rise in use of hormone therapy, an understanding of the impact of both endogenous and exogenous steroid hormones on hemostatic function as it relates to risk of cardiovascular disease in aging women is clearly of importance.

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