Plasma Fibrinogen Levels in Healthy Postmenopausal Women: Physical Activity and Hormone Replacement Status

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Background. Fibrinogen is a major component of the coagulation system and a powerful independent risk factor for cardiovascular disease in postmenopausal women. Regular physical activity has been recommended as an effective clinical approach to lowering plasma fibrinogen levels; currently, however, there are little or no data to support a relationship between habitual exercise status and plasma fibrinogen levels in healthy postmenopausal women who either use or do not use hormone replacement therapy (HRT).

Methods. Plasma fibrinogen levels were measured in 20 physically active (56 ± 1 yr) and 31 sedentary (58 ± 1 yr) healthy postmenopausal women. Nine (45%) physically active and 15 (48%) sedentary women had been using HRT for > 1 year; the others were nonusers of HRT.

Results. Plasma fibrinogen levels were ~15% lower (p = .001) in the physically active women (2.48 ± .08 g/L) than the sedentary controls (2.92 ± .06 g/L). Moreover, the lower (0.4 g/L) plasma fibrinogen levels associated with regular physical activity were evident in both the users (2.39 ± .11 vs 2.80 ± .08 g/L, p = .001) and nonusers (2.56 ± .11 vs 3.03 ± .08 g/L, p = .006) of HRT. Stepwise multiple regression analysis revealed that percent body fat was the primary determinant of plasma fibrinogen levels, accounting for 30% of the variability.

Conclusions. Regular physical activity is associated with lower plasma fibrinogen levels in postmenopausal women; the lower plasma fibrinogen levels associated with regular physical activity are evident in both users and nonusers of HRT; and plasma fibrinogen levels are positively related to percent body fat in postmenopausal women differing in physical activity and HRT status. Lower plasma fibrinogen levels in physically active postmenopausal women may contribute to their lower risk of cardiovascular disease.

The risk of cardiovascular diseases (CVD), atherosclerotic vascular diseases in particular, increases markedly in women after menopause (1). One of the proposed mechanisms for the increased risk of both CVD and atherothrombotic events among postmenopausal women is higher plasma fibrinogen levels (2). Fibrinogen is an important component of the coagulation system and a powerful independent risk factor for CVD in postmenopausal women (2,3).

Physically active postmenopausal women have a lower prevalence of CVD-related morbidity compared to their sedentary peers (4). It has been suggested that the lower CVD risk observed in physically active postmenopausal women is likely due, in part, to their more favorable risk factor profile (e.g., lower lipid and lipoprotein levels). Plasma fibrinogen levels, however, have been reported to be either lower (5) or not significantly different (6) in physically active versus sedentary postmenopausal women. Thus, it is currently unclear whether lower plasma fibrinogen levels could also contribute to the lower CVD risk in physically active postmenopausal women.

Postmenopausal women who chronically use hormone replacement therapy (HRT) demonstrate lower CVD risk versus nonusers (7). Plasma fibrinogen levels have been reported to be lower in users versus nonusers of HRT (8), and thus may play a role in their reduced risk of both CVD and atherothrombotic events. Because plasma fibrinogen levels are already lower in postmenopausal women taking HRT, it is possible that a favorable effect of physical activity on plasma fibrinogen levels is not observed in HRT users. However, no information is currently available on this issue.

Accordingly, the purpose of the present investigation was to test the hypotheses that: (a) physically active postmenopausal women have lower resting plasma fibrinogen levels compared to their age-matched healthy sedentary peers; and (b) the lower plasma fibrinogen levels associated with regular physical activity are evident in both users and nonusers of HRT. To accomplish these aims, we used a cross-sectional model in which plasma fibrinogen levels were measured at rest in healthy physically active and sedentary postmenopausal women who were either taking or not taking hormone replacement.
EXERCISE AND PLASMA FIBRINOGEN LEVELS IN WOMEN

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METHODS

Subjects. — Fifty-one healthy postmenopausal women ranging in age from 49 to 70 years volunteered to participate in this study; 20 women were physically active and 31 women served as age-matched sedentary controls. The postmenopausal physically active women had been performing regular endurance exercise (distance running) for an average of 50 ± 3 km/wk (27 to 77 km/wk). The sedentary women performed no regular physical activity. All of the women were at least one year postmenopausal (7.7 ± 0.8 yrs, 1 to 23 yrs). Among the 51 postmenopausal women, 24 were users of HRT (9 physically active and 15 sedentary), and 27 were nonusers (11 physically active and 16 sedentary). The majority (20 of 24) of the users of HRT were on an oral regimen of conjugated estrogen (Premarin, .625-1.0 mg/d) in combination with medroxyprogesterone acetate (Provera, 2.5 mg/d); the remaining HRT users were taking either estrogen (transdermally), Premarin, or Provera only. All subjects were free of overt disease as assessed by medical history, physical examination, and by resting and exercise electrocardiograms. None of the subjects smoked or were on any other medications. All of the subjects had the research study and its potential risks and benefits explained fully before providing written informed consent according to the guidelines of the University of Colorado at Boulder.

Body composition. — Body weight was measured to the nearest 0.1 kg using a medical beam balance (Detecto, Webb City, MO). Percent body fat was estimated from the sum of skinfolds measured at five body sites (9). All skinfold measurements were made by the same investigator while the subject was in a standing position. In our laboratory, similar levels of body fat percentage are obtained from skinfold measurements compared with hydrodensiometry in postmenopausal women (r = .89, unpublished observations). The waist-to-hip ratio (WHR) was calculated as the ratio of the minimal waist circumference to the circumference of the maximal gluteal protuberance. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared.

Maximal oxygen consumption (VO₂ max). — VO₂ max was assessed using an on-line computer-assisted open-circuit spirometry during incremental exercise on a motorized treadmill, as previously described (10). A valid VO₂ max was accepted when at least three of the following criteria were met: (a) a plateau in VO₂ with increasing work rate (<1 ml/kg/min or <100 ml/min); (b) a respiratory exchange ratio at maximal exercise >1.10; (c) achievement of age-predicted maximal heart rate (220-age); and (d) a rating of perceived exertion >17 (Borg Scale) (11).

Metabolic measurements. — Blood samples for the determination of plasma lipid and lipoprotein levels were collected into tubes containing EDTA (1 mg/mL blood) after a 12-hour overnight fast. Plasma total cholesterol and triglyceride (TG) concentrations were measured using conventional enzymatic methods (12). Because no subject had a plasma TG > 4.5 mmol/L, high-density lipoprotein cholesterol (HDL-C) and HDL₃-C were determined using the sulfate dextran precipitation technique (13). HDL₃-C was calculated as the arithmetic difference between HDL-C and HDL₃-C. Low-density lipoprotein cholesterol (LDL-C) was calculated as LDL-C = total cholesterol – (TG/5 ± HDL-C). Plasma glucose was determined in duplicate using a glucose hexokinase method (Gillford 203-S, Oberlin, OH), and insulin was determined by radioimmunoassay (14).

Measurement of fibrinogen. — Blood samples for the determination of plasma fibrinogen levels were collected into tubes containing sodium citrate after a 12-hour overnight fast with minimal venostasis. The Clauss method was used to measure plasma fibrinogen levels (15).

Statistical analysis. — Differences between the physically active and sedentary groups and users and nonusers of HRT for all selected variables were determined by a multifactor analysis of variance (ANOVA) (training status × HRT status). When indicated by a significant main effect, specific mean comparisons were performed to identify significant differences within each group. Simple and forward stepwise multiple regression analyses and partial correlation coefficients were calculated to determine relationships between fibrinogen and anthropometric, hemodynamic, and metabolic variables. All data are expressed as mean ± SEM. Statistical significance was set at p < .05.

RESULTS

Subjects. — There were no significant differences in age or resting blood pressure between the physically active and sedentary women. However, body weight, percent body fat, BMI, and WHR were lower (p = .001) and VO₂max was higher (p = .001) in the physically active women (Table 1). There were no differences in any of these subject characteristics in the users versus nonusers of HRT.

Metabolic characteristics. — The physically active women had significantly lower plasma total cholesterol, HDL-C, HDL₃-C, TG, glucose, and insulin concentrations compared to the sedentary controls (Table 2). The only difference in the users versus nonusers of HRT was the lower (p = .01) plasma insulin levels in the users of HRT (30.0 ± 1.8 vs 38.4 ± 3.0 pmol/L). However, there was no significant interaction between training status and hormone replacement on plasma insulin levels.

Plasma fibrinogen. — Plasma fibrinogen levels were ~15% lower (p = .001) in the physically active women compared to their healthy sedentary peers, and ~7% lower (p = .04) in the users versus nonusers of HRT. Moreover, the lower plasma fibrinogen levels in the physically active women were evident in both the users (p = .006) and nonusers (p = .001) of HRT (Table 3). There was no significant interaction between training status and HRT use.

Correlation analysis. — Univariate analysis on the pooled data revealed positive correlations between plasma
Table 1. Physical Characteristics of the Subjects Grouped by Physical Activity Status and Subgrouped by Hormone Replacement (HRT) Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Physically Active</th>
<th>Sedentary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRT Users (n = 9)</td>
<td>Nonusers (n = 11)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>56 ± 1</td>
<td>56 ± 2</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>57.9 ± 1.6</td>
<td>56.5 ± 1.6</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>21.0 ± 1.7</td>
<td>16.2 ± 1.3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>20.9 ± 0.4</td>
<td>20.3 ± 0.2</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.74 ± 0.01</td>
<td>0.75 ± 0.01</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>109 ± 3</td>
<td>109 ± 2</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>73 ± 1</td>
<td>75 ± 3</td>
</tr>
<tr>
<td>VO₂max, ml/kg/min</td>
<td>40.8 ± 2.4</td>
<td>45.7 ± 2.7</td>
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</tbody>
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Notes: SBP = systolic blood pressure; DBP = diastolic blood pressure. Values are mean ± SEM. *p < .01 vs the sedentary group.

Table 2: Metabolic Characteristics of the Subjects Grouped by Physical Activity Status and Subgrouped by Hormone Replacement (HRT) Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Physically Active</th>
<th>Sedentary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRT Users (n = 9)</td>
<td>Nonusers (n = 11)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.5 ± 0.2</td>
<td>4.9 ± 0.2</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.89 ± 0.12</td>
<td>1.75 ± 0.13</td>
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<tr>
<td>HDL2-C, mmol/L</td>
<td>0.59 ± 0.09</td>
<td>0.44 ± 0.09</td>
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<tr>
<td>HDL3-C, mmol/L</td>
<td>1.34 ± 0.05</td>
<td>1.31 ± 0.07</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.17 ± 0.18</td>
<td>2.66 ± 0.22</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.9 ± 0.1</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.0 ± 0.2</td>
<td>4.8 ± 0.2</td>
</tr>
<tr>
<td>Insulin, pmol/L</td>
<td>24.0 ± 1.9</td>
<td>27.3 ± 1.9</td>
</tr>
</tbody>
</table>

Notes: HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol. Values are mean ± SEM. *p < .05 vs the sedentary group.

Table 3: Plasma Fibrinogen Concentrations of the Subjects Grouped by Physical Activity Status and Subgrouped by Hormone Replacement (HRT) Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Physically Active</th>
<th>Sedentary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRT Users (n = 9)</td>
<td>Nonusers (n = 11)</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>2.39 ± 0.11*</td>
<td>2.56 ± 0.11*</td>
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*p < .01 vs the sedentary group.

fibrinogen levels and age (r = .28, p = .05), body weight (r = .41, p = .003), BMI (r = .39, p = .005), waist circumference (r = .44, p = .001), percent body fat (r = .54, p = .001), VO₂max (r = .49, p = .007), and plasma glucose (r = .31, p = .03), and insulin (r = .33, p = .02) concentrations. When multiple regression was applied for assessment of the independence of the observed relationships, only percent body fat was significantly associated with fibrinogen (R² = .30) (Figure 1).

DISCUSSION

The primary findings of the present study are that: (a) physically active postmenopausal women exhibit lower plasma fibrinogen levels than their less active peers; and (b) the lower plasma fibrinogen levels in the physically active postmenopausal women are evident in both users and nonusers of hormone replacement therapy.

Physically active postmenopausal women are at a lower risk of developing coronary heart disease (CHD) and subsequent atherothrombosis (4). Although the precise mechanisms responsible for the reduced risk of CHD in physically active postmenopausal women have not been completely elucidated, we (6) and others (16,17) have shown that physically active postmenopausal women exhibit a more favorable risk profile (e.g., lower body fatness, lower fasting plasma glucose and insulin concentrations, and a superior plasma...
lipid and lipoprotein profile) which may contribute to their lower incidence of CHD. In this context, the results of the present investigation complement and extend our previous findings by demonstrating that physically active postmenopausal women also have lower plasma fibrinogen levels compared to their sedentary counterparts. The lower (0.4 g/L) plasma fibrinogen levels observed in the physically active postmenopausal women in the present study are consistent with that reported in previous studies involving men (18). Most importantly, the lower levels in the active postmenopausal women would appear to be associated with a considerable reduction in CHD risk. Based on data from the Northwich Park Heart Study, in which 0.1 g/L difference in plasma fibrinogen concentration corresponded to a 15% reduction in CHD risk, Ernst (19) has suggested that a decrease of 0.4 g/L could potentially reduce the risk of CHD by as much as 60%. It is noteworthy that, although obesity has been shown to be an independent determinant of plasma fibrinogen levels (31), the mechanisms by which changes in body fat may affect fibrinogen are unknown (22). In addition, the biological mechanisms responsible for the fibrinogen lowering effect of HRT (8) and the potential synergistic effect of regular physical activity and HRT on plasma fibrinogen concentrations are poorly understood. Given the critical role of fibrinogen in the development of a potentially fatal occlusive thrombus, further studies are needed to elucidate the mechanisms responsible for lowering plasma fibrinogen levels.

In conclusion, the results of the present study indicate that physically active postmenopausal women have lower plasma fibrinogen levels compared to their age-matched healthy sedentary counterparts. Furthermore, the lower plasma fibrinogen levels associated with regular physical activity were evident, independent of HRT use. Thus, one of the possible mechanisms by which regular physical activity may favorably affect both the risk of CVD and the thrombotic tendency among postmenopausal women may be through lower plasma fibrinogen levels. The favorable changes in thrombotic tendency among postmenopausal women may be through lower plasma fibrinogen levels.
REFERENCES


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