Effects of Hormone Replacement Therapy on Lipoprotein(a) and Lipids in Postmenopausal Women

Chee Jeong Kim, Hak Chul Jang, Dong Hee Cho, Yong Ki Min

Abstract High concentrations of lipoprotein(a) [Lp(a)], an independent risk factor for atherosclerosis, cannot be managed by the usual lipid-lowering agents. It has been suggested that Lp(a) levels are related to female sex hormones. Estrogen replacement therapy makes the lipid profiles favorable for delaying atherosclerosis in postmenopausal women. The effects of the combination therapy of estrogen and progesterone on lipids are controversial. This study was designed to evaluate the effect of female sex hormones on the concentration of Lp(a) and to clarify the influence of progesterone on the effect of estrogen in postmenopausal women. Postmenopausal women were divided into four groups: control; 0.625 mg conjugated equine estrogen (CEE) plus 10 mg medroxyprogesterone acetate (MPA); 0.625 mg CEE plus 5 mg MPA; and 0.625 mg CEE only. Medication for 2 months lowered the concentrations of Lp(a) by 20% in all treated groups. The decrease was more pronounced in subjects with a relatively higher basal Lp(a) concentration. Estrogen replacement therapy raised the concentration of high-density lipoprotein cholesterol and decreased low-density lipoprotein cholesterol without changing total cholesterol. The combination therapy of estrogen and progesterone abolished the effect of estrogen on high-density lipoprotein cholesterol. Hormone replacement therapy lowered Lp(a) levels in postmenopausal women. The effect was prominent in subjects with high basal Lp(a) levels. This decrease may be one of the mechanisms of the cardioprotective effects of estrogen. The cardioprotective effect of estrogen cannot be applied to the combination therapy due to the adverse effect of progesterone on high-density lipoprotein cholesterol. (Arterioscler Thromb. 1994;14:275-281.)

Key Words • lipoprotein(a) • lipids • estrogen • progesterone • menopause

Lipoprotein(a) [Lp(a)] consists of low-density lipoprotein (LDL)–like particles and a specific glycoprotein, apolipoprotein(a) [Apo(a)]. A high concentration of Lp(a) is thought to be an independent risk factor for cardiovascular and cerebrovascular diseases. It cannot be lowered by the usual treatments for hyperlipidemia, and only a few drugs reduce Lp(a) concentrations.

Recently, epidemiological investigations have reported that concentrations of Lp(a) are higher in postmenopausal women than in premenopausal women and that postmenopausal women taking female sex hormones have lower Lp(a) levels than those not taking such medication. Small-sized studies also show that hormone replacement therapy (HRT) in postmenopausal women lowers the concentration of Lp(a) markedly.

Premenopausal women have lower cardiovascular morbidity and mortality than men of a similar age. After menopause, the incidence of cardiovascular diseases increases and no difference is noticed during the eighth decade between men and women. Female sex hormones have been used for the alleviation of postmenopausal symptoms and the treatment of osteoporosis. Most but not all reports have shown that estrogen replacement therapy in postmenopausal women reduces cardiovascular mortality. The changes in lipid profiles and the modulation of vasomotor tone have been proposed as the mechanisms of the cardioprotective effect of estrogen.

The effect of estrogen on various kinds of cholesterol has been well described in many studies; it delays atherosclerosis by increasing the concentration of high-density lipoprotein cholesterol (HDL-C) and by decreasing the concentration of low-density lipoprotein cholesterol (LDL-C). Because estrogen replacement therapy increases the risk of endometrial cancer, progesterone has been added, and the risk has become negligible. However, progesterone has an adverse effect on lipids. The effect of the combination therapy of estrogen and progesterone on lipids has been evaluated by many authors, but most studies had relatively small numbers of cases and yielded inconsistent results. Thus, the purposes of this study were to evaluate the effect of estrogen and progesterone on the concentration of Lp(a) and to clarify the influence of progesterone on lipid levels when administered with estrogen to postmenopausal women.

Methods

Subjects

This study was a prospective, controlled trial to evaluate HRT on Lp(a) and lipid levels in postmenopausal women. Between April 1991 and March 1992, 184 women who had been amenorrheic for over 1 year without hysterectomy or had serum follicle-stimulating hormone concentrations over 20 mIU/L were enrolled. Their ages ranged from 33 through 68 years with a mean of 51.1 ± 4.9 years. Patients who had diseases that influence lipid levels, such as diabetes mellitus, chronic...
liver disease, infectious diseases, or other endocrinologic diseases, were excluded. None had received hormonal preparations before the study. The subjects were divided into four groups: group A (n=29), a control group without medication; group B (n=67), treated with 0.625 mg conjugated equine estrogen (CEE) and 10 mg medroxyprogesterone acetate (MPA); group C (n=65), treated with 0.625 mg CEE and 5 mg MPA; and group D (n=23), treated with 0.625 mg CEE alone in subjects with a prior hysterectomy. The medication was prescribed cyclically every 30 days for 2 months. CEE was administered from the 26th through the 25th day, and MPA was added from the 16th through the 25th day. No medication was prescribed from the 26th through the 30th day.

**Determination of Lp(a) and Lipid Concentrations**

After overnight fasting, blood samples were placed in disodium-EDTA tubes and plain tubes before and after the completion of medication for 2 months. Serum was isolated and stored at −70°C for later Lp(a) measurement. The concentration of Apo(a) was determined by two-site immunoradiometric assay using a commercial radioimmunoassay kit (Pharmacia) as described. In brief, the assay is based on the direct sandwich technique, in which two monoclonal antibodies are directed against separate antigenic determinants on the Apo(a) molecule. The concentration of Lp(a) protein was calculated approximately by using a conversion factor of 1 as proposed by Pharmacia Co. Interassay coefficients of variation were 5.8% and 7.2% for high (mean, 45.7 mg/dL) and low (mean, 12.3 mg/dL) control levels, respectively. Intra-assay coefficient of variation was 2.6%. The concentrations of total cholesterol and triglyceride were determined by an enzymatic method using an automatic analyzer (Hitachi 7150). The concentrations of total protein, albumin, fasting blood sugar, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, and creatinine were also measured. The concentrations of HDL-C, LDL-C, and very-low-density lipoprotein cholesterol (VLDL-C) were determined by electrophoretic methods using an HDL-C supply kit (Herelena Laboratory). The lipoproteins were separated according to their electrophoretic mobility on cellulose acetate in a Tris (2-amino-3-[hydroxymethyl]-1,3-propanediol)-barbital buffer, pH 8.8. Fractions were visualized with the production of quinoneimine by an enzymatic method using cholesterol esterase, cholesterol oxidase, 4-aminoantipyrine, phenol, and peroxidase. The relative percent of each fraction was obtained by scanning in a densitometer equipped with a 500- or 505-nm filter (Helena Laboratory). The concentrations of HDL-C, VLDL-C, and LDL-C were calculated by multiplying each ratio with total cholesterol. Follicle-stimulating hormone was measured by immunoradiometric assay using a radioimmunoassay kit (Serono Diagnostic).

**Statistical Analysis**

Data were expressed as mean±SD; Lp(a) data were also expressed as median. The data were stored on an IBM computer using DIABASE III+ (Ashton-Tate). Statistical analysis was performed with the STATISTICAL PACKAGE FOR THE SOCIAL SCIENCES (SPSS Inc.). The concentrations of Lp(a), VLDL-C, and triglyceride were transformed logarithmically if necessary. A Wilcoxon signed-rank test was used to compare the concentrations of Lp(a), VLDL-C, and triglyceride before and after medication. Differences in the other parameters were analyzed by paired t test. ANOVA or a Kruskal-Wallis test was used to evaluate the differences among groups. A Mann-Whitney U test, Student’s unpaired t test, logistic regression analysis, and multiple stepwise regression analysis were used to observe the parameters influencing the effect of medication. The relations between Lp(a) and other parameters were analyzed by simple linear regression and multiple stepwise regression. Significance was inferred when P<.05.

**Results**

**Baseline Data**

The distribution of Lp(a) levels was skewed (Fig 1); concentrations between 10 and 20 mg/dL were the most frequent. The mean and median values of total cases were 35.9±34.7 and 23.9 mg/dL, respectively. Basal clinical characteristics were similar in all groups (Table 1). Age, body mass index, total cholesterol, and LDL-C were higher in groups A and D than in groups B and C. The concentration of Lp(a) was lower in group D than in other groups. None of these differences were significant.

**Changes of Lp(a) With HRT**

After 2 months of medication, the concentrations of Lp(a) were reduced from 36.7±30.9 mg/dL, 36.5±35.2 mg/dL, and 31.2±33.8 mg/dL to 28.5±24.4 mg/dL, 28.1±30.7 mg/dL, and 24.6±30.4 mg/dL in group B (P<.0001), group C (P<.0001), and group D (P<.001), respectively (Table 2). Lp(a) concentrations did not alter in the control group. The decreases of Lp(a) concentrations expressed as percentages were 14.7±44.4%, 22.2±34.8%, and 25.7±33.4% in groups B, C, and D, respectively.

**Table 1. Comparison of Baseline Clinical and Biochemical Parameters Among Four Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Age, y</th>
<th>BMI, kg/m²</th>
<th>TC, mg/dL</th>
<th>Lp(a), mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>51.7±7.3</td>
<td>24.7±3.0</td>
<td>223.8±25.8</td>
<td>36.4±43.3 (18.7)</td>
</tr>
<tr>
<td>B</td>
<td>50.7±4.0</td>
<td>24.2±3.1</td>
<td>215.1±35.9</td>
<td>36.7±30.9 (27.9)</td>
</tr>
<tr>
<td>C</td>
<td>50.8±4.7</td>
<td>24.2±2.5</td>
<td>218.4±41.2</td>
<td>36.5±35.2 (23.9)</td>
</tr>
<tr>
<td>D</td>
<td>52.3±3.8</td>
<td>24.7±2.3</td>
<td>224.7±31.2</td>
<td>31.2±33.8 (19.3)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; TC, total cholesterol; and Lp(a), lipoprotein(a). Values are mean±SD (median). There were no statistically significant comparisons.
**TABLE 2. Changes in Lipoprotein(a) Concentrations 2 Months After HRT**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basal (mg/dL)</th>
<th>2 Months (mg/dL)</th>
<th>Change (mg/dL)</th>
<th>Change, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>36.4±43.34</td>
<td>36.4±37.93</td>
<td>28.7±12.2</td>
<td>23.1</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Group B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>36.7±30.9</td>
<td>28.5±24.4</td>
<td>-8.2±12.2</td>
<td>27.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Group C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>36.5±35.2</td>
<td>28.1±30.7</td>
<td>-8.4±12.5</td>
<td>23.1</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Group D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>31.2±33.8</td>
<td>24.6±30.4</td>
<td>-6.7±9.1</td>
<td>14.7</td>
<td></td>
</tr>
</tbody>
</table>

HRT indicates hormone replacement therapy; NS, not significant. Values are mean±SD (median) and are expressed in milligrams per deciliter.

**Parameters Influencing the Effect of HRT on Lp(a)**

When treated subjects were divided into a response group (n=126), in which the concentration of Lp(a) was decreased with medication, and a nonresponse group (n=29), in which the concentration of Lp(a) was increased or not changed, predictive variables for response were high concentrations of Lp(a), globulin, and total protein (Table 3). Among these, logistic regression analysis showed that high concentrations of Lp(a) and globulin were independent variables.

**TABLE 3. Parameters Influencing the Effect of HRT on Lipoprotein(a) Concentrations**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Response (n=29)</th>
<th>Response (n=126)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>212.1±39.8</td>
<td>219.3±37.0</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C</td>
<td>68.8±16.8</td>
<td>67.8±15.3</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C</td>
<td>127.6±28.7</td>
<td>133.8±28.2</td>
<td>NS</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>20.8±21.7</td>
<td>39.3±34.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>129.6±81.6</td>
<td>130.2±68.2</td>
<td>NS</td>
</tr>
<tr>
<td>Protein</td>
<td>7.4±0.3</td>
<td>7.6±0.4</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.7±0.2</td>
<td>4.7±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Globulin</td>
<td>2.7±0.4</td>
<td>2.9±0.4</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>18.7±3.6</td>
<td>20.0±5.6</td>
<td>NS</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>13.9±6.1</td>
<td>16.8±8.2</td>
<td>NS</td>
</tr>
<tr>
<td>SAP, IU/L</td>
<td>77.2±20.7</td>
<td>83.2±20.8</td>
<td>NS</td>
</tr>
<tr>
<td>FSH, mIU/L</td>
<td>64.3±34.3</td>
<td>70.4±29.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); AST, aspartate aminotransferase; ALT, alanine aminotransferase; SAP, serum alkaline phosphatase; and FSH, follicle-stimulating hormone. Values are mean±SD.

**Changes in Other Lipids**

The concentrations of total cholesterol were decreased with medication in group B (215.1±35.9 mg/dL versus 197.1±33.3 mg/dL, P<.001) and group C (218.4±41.2 mg/dL versus 200.3±37.8 mg/dL, P<.001), but were not changed in group D (224.7±31.2 mg/dL versus 214.9±30.4 mg/dL, not significant [NS]) (Table 4 and Fig 3).

The concentrations of HDL-C were decreased from 69.6±15.8 mg/dL to 65.7±12.8 mg/dL in group B, which took 10 mg MPA, but this did not achieve significance (P=.053). In group C, which took 5 mg MPA, the concentrations of HDL-C were not changed (67.2±15.6 mg/dL versus 65.0±16.5 mg/dL, NS). However, the concentrations of HDL-C were increased from 66.5±15.2 mg/dL to 72.3±17.3 mg/dL (P<.05) in group D, which took estrogen alone.

The concentrations of LDL-C were decreased with medication from 131.1±25.8 mg/dL, 131.3±29.4 mg/dL, and 139.7±27.0 mg/dL to 120.0±24.7 mg/dL, 119.1±28.8 mg/dL, and 127.6±26.9 mg/dL in groups B (P<.001), C (P<.001), and D (P<.05), respectively. No difference was noticed in the control group.

The concentrations of VLDL-C decreased in all groups but were significant only in group B (P<.05). Triglyceride concentrations increased insignificantly in all treated groups.

**Parameters Associated With Lp(a) Concentration**

The relations between the concentration of Lp(a) and biochemical or clinical parameters were observed in all cases. The concentrations of VLDL-C (r=.31, P<.0000), total cholesterol (r=.19, P<.0111), and serum alkaline

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![Image](http://atvb.ahajournals.org/)

**Fig 2.** Scatterplot showing correlation between basal lipoprotein(a) [Lp(a)] levels and difference changes after hormone replacement therapy.
TABLE 4. Changes in Lipid Profiles 2 Months After HRT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A Basal</th>
<th>Group A 2 Month</th>
<th>Group B Basal</th>
<th>Group B 2 Month</th>
<th>Group C Basal</th>
<th>Group C 2 Month</th>
<th>Group D Basal</th>
<th>Group D 2 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>223.8±25.8</td>
<td>212.9±34.8</td>
<td>215.1±35.9</td>
<td>201.3±37.8</td>
<td>218.4±41.2</td>
<td>214.9±30.4</td>
<td>224.7±31.2</td>
<td>214.9±30.4</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C</td>
<td>72.0±17.2</td>
<td>67.8±19.6</td>
<td>69.6±15.8</td>
<td>65.7±12.8</td>
<td>67.2±15.6</td>
<td>65.0±16.5</td>
<td>66.5±15.2</td>
<td>72.3±17.3</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;.001</td>
<td>.053</td>
<td>NS</td>
<td>&lt;.001</td>
<td>NS</td>
<td>&lt;.05</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>134.4±20.9</td>
<td>131.5±27.3</td>
<td>131.1±25.8</td>
<td>120.0±24.7</td>
<td>131.3±29.4</td>
<td>119.1±28.8</td>
<td>139.7±27.0</td>
<td>127.6±28.9</td>
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<tr>
<td>P</td>
<td>NS</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
<td>NS</td>
<td>&lt;.01</td>
<td>NS</td>
<td>&lt;.05</td>
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</tr>
<tr>
<td>VLDL-C</td>
<td>16.4±9.8</td>
<td>15.1±9.8</td>
<td>16.7±14.8</td>
<td>15.4±12.3</td>
<td>17.0±15.9</td>
<td>15.7±12.6</td>
<td>18.6±11.7</td>
<td>15.0±12.3</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
<td>NS</td>
<td>&lt;.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>TG</td>
<td>137.8±71.4</td>
<td>133.2±53.5</td>
<td>120.5±65.2</td>
<td>136.0±76.7</td>
<td>120.3±58.5</td>
<td>140.0±86.1</td>
<td>140.1±70.5</td>
<td>150.9±100</td>
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<td>P</td>
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</tr>
</tbody>
</table>

HRT indicates hormone replacement therapy; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; and TG, triglyceride. Values are mean±SD and are expressed in milligrams per deciliter.

Recent epidemiological studies report that Lp(a) concentrations increase after menopause just like those of total cholesterol and LDL-C and that postmenopausal women taking estrogen have lower concentrations of Lp(a) than those not on estrogen replacement therapy. The authors of the Framingham Offspring Study insist that Lp(a) levels are correlated with age and that the effect of the menopausal state is not statistically significant after controlling for age. However, we do not agree with the Framingham Offspring Study.
studies, including the present study, report a significant effect of female sex hormone on Lp(a); moreover, the association of Lp(a) with age may be a consequence of postmenopausal change. Small-sized studies show that estrogen, norethisterone, or stanozolol therapy in postmenopausal women lowers the concentration of Lp(a) by 41% to 51%,21,22 Our data indicated a lesser degree of decrease than previous studies. The discrepancy can be explained by differences in regimen, dose, and duration of follow-up. In addition, previous studies were done in selected cases with high basal concentrations of Lp(a). We had a far greater number of cases, and the cases were better controlled than in other studies.

The influence of kind or dosage of female sex hormone on the concentration of Lp(a) has not been clarified. In this study, single estrogen replacement therapy and the combination therapy of estrogen and progesterone yielded a similar effect. A higher dose of progesterone (10 mg MPA) did not show any additional effect compared with a lower dose (5 mg MPA).

Basal concentration of Lp(a) was positively related to difference and percent change of the concentration of Lp(a). This finding implies that the Lp(a)-lowering effect is more prominent in subjects with high basal levels and is consistent with a previous report that included nine cases. This is clinically very important, because the individuals who have the highest risk due to high Lp(a) levels will benefit most from HRT. Percent change was positively related to the concentration of globulin, which did not correlate with basal Lp(a) concentration in all subjects. Because none of the subjects had diseases that can raise the concentration of globulin, and because some authors insist that Lp(a) is an acute-phase protein,27 one possible explanation is stress due to postmenopausal symptoms, which can be improved markedly after therapy. Nevertheless, the significance is obscure and further evaluation is needed.

Most previous studies have measured the concentration of Lp(a), but we measured Apo(a) concentration and converted it to Lp(a) concentration. The concentration of Lp(a) has not yet been internationally standardized. The Pharmacia Co has shown that Apo(a) concentration is closely related to Lp(a) concentration, as determined by radial immunodiffusion (r = .94) or enzyme-linked immunosorbent assay of Biopol (r = .90) (personal letter from Gunnel Janssen, July 2, 1992). The conversion ratio between Lp(a) and Apo(a) concentrations recommended by Pharmacia was 1.

The concentrations of Lp(a) measured by the Pharmacia radioimmunoassay kit were higher than those measured by other methods (personal letter), so this study showed higher values compared with previous studies. HDL-C concentrations were also higher than those of most studies because they were measured by the electrophoresis method, which yields values 23.9% higher than precipitation methods.38

Lp(a) concentration has been thought to be unrelated to clinical or biochemical parameters but to be determined mainly by genetic variations.39 However, most studies had relatively small numbers of cases and evaluated the relation in selected cases, such as a narrow range of age or as a part of risk factor analysis for cardiovascular disease. Recent reports with large numbers of cases or that are designed to evaluate specific parameters20-22,36 have shown that sex, age, sex hormones, and some biochemical parameters influence Lp(a) concentration. Because Lp(a) is produced in the liver,40 biochemical parameters related to the liver functions were also analyzed in addition to lipids. Our data indicated that the concentration of Lp(a) was independently related to VLDL-C, serum alkaline phosphatase, albumin, and total cholesterol. If VLDL-C is excluded because VLDL-C determined by electrophoresis contains cholesterol of Lp(a) particle, then serum alkaline phosphatase, albumin, and total cholesterol are related to Lp(a) concentration. These discrepancies among studies are thought to lie in the major influence of genetic variation on the concentration of Lp(a). Neither studies with small
numbers of cases nor uncontrolled studies can overcome a high β error by genetic determination, and the influence of parameters can be masked. Thus, investigations that compare the concentration of Lp(a) between independent groups must have large numbers of cases or large differences that overwhelm the genetic control.

In the 1970s, cohort studies for the effect of estrogen on cardiovascular disease showed different results, with relative risks of 0.3 through 1.6.24-25 But most cohort studies in the 1980s reported that estrogen replacement therapy in postmenopausal women reduces cardiovascular morbidity or mortality with relative risks of 0.3 through 0.75.24,26 Several mechanisms have been proposed for the cardioprotective effect of estrogen. Among them, change of lipid profiles was the most attractive.27,28 Estrogen replacement therapy in postmenopausal women reduced LDL-C and increased HDL-C. Total cholesterol was either decreased or not changed. In the present study, LDL-C and HDL-C changed as in previous studies, and in group D, to whom only estrogen was administered, total cholesterol did not change. The findings might be favorable for thetherosclerosis system and are consistent with recent cohort studies. But the lipid change is not a return to the premenopausal state, but rather the therapeutic effect of estrogen, because the concentrations of total cholesterol and LDL-C are increased and HDL-C is not changed after menopause.36,41,42

Endometrial cancer is one of the serious complications of estrogen replacement therapy. When progesterone is added to prevent endometrial hyperplasia, the risk of endometrial cancer becomes negligible.30,31 It is generally accepted that progesterone decreases HDL-C concentration and increases the risk of cardiovascular disease.27,32 Many studies have evaluated the influence of progesterone on lipid profiles when it is sequentially combined with estrogen in postmenopausal women. However, the results of these small-sized studies are not conclusive.24 Several studies have also suggested that the therapeutic effect of estrogen is better than estrogen alone for the prevention of atherosclerosis because it results in a decrease in triglyceride, factor VII, and protein C levels and that there is no difference in HDL-C levels between these two groups. In our study, estrogen alone increased HDL-C, but the combination of 5 mg MPA with estrogen offset the effect of estrogen on HDL-C, and the HDL-C concentration was not changed. The combination of 10 mg MPA with estrogen decreased HDL-C with borderline significance (P=.053). These findings are consistent with old reports but are at odds with the new argument about the innocuous nature of progesterone.

In summary, estrogen replacement therapy in postmenopausal women lowers the concentration of Lp(a), especially in subjects with high basal concentrations. It might be one of the mechanisms for the cardioprotective effect of estrogen replacement therapy. The combination of estrogen and progesterone did not result in any additional reduction of Lp(a) concentration, nor did the dose of progesterone influence the results. Thus, HRT can be used for lowering the concentration of Lp(a) in selected patients. But because the combination therapy of estrogen and progesterone negated the effect of estrogen on HDL-C, the cardioprotective effect of estrogen replacement therapy cannot be extended to combination therapy.

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