Relationship of Endogenous Sex Steroid Hormones to Lipids and Apoproteins in Postmenopausal Women

Lewis H. Kuller, James P. Gutai, Elaine Meilahn, Karen A. Matthews, and Pam Plantinga

The relationships between blood levels of estrogen and lipoprotein lipids and apoproteins were evaluated in 120 women early in the climacteric. Among women who were 1-year amenorrheic, not taking hormone replacement therapy, and with follicle-stimulating hormone levels >720 ng/ml, serum estradiol levels were positively related to concentrations of the high density lipoprotein 2 cholesterol (HDL2c) subfraction. There was a substantial decrease in HDLc and apoprotein (apo) A-I in women whose estradiol levels decreased to ≤2.5 pg/ml from the first to the second postmenopausal examination. In a sample of women evaluated during the perimenopause (3-months' amenorrheic), those with the highest concentrations of estradiol or estrone showed a (nonsignificantly) higher level of HDLc and a lower level of low density lipoprotein cholesterol (LDLc) than did those with the lowest concentration of estradiol or estrone. Estradiol levels declined dramatically between the perimenopausal and the postmenopausal examinations, and this was accompanied by a decrease in HDLc and a nonsignificant increase in LDLc. HDLc levels fell substantially in those women whose estradiol decreased below the sensitivity of the assay. The change, however, was not statistically significant. Estrone is the primary postmenopausal estrogen, and levels are directly related to obesity, as are levels of insulin. The interrelationship among obesity, conversion of estrone to estradiol at the tissue level, and insulin (or insulin sensitivity) is probably the primary determinant of HDLc concentration among postmenopausal women.

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women living in Pittsburgh, Pennsylvania, randomly selected from driver's license lists who were premenopausal and ages 42 to 50 at baseline. The study was approved by the Biomedical Institutional Review Board of the University of Pittsburgh. The women were not taking hormone therapy at entry into the study and had not undergone hysterectomy or bilateral oophorectomy. Other exclusion criteria included treated hypertension, thyroid disease, and diabetes mellitus. Baseline examinations were conducted between November 1983 and May 1985 and included measures of age, alcohol intake, cigarette smoking, physical activity, height, weight, and (in a subsample) waist-to-hip ratio. The detailed laboratory methods have previously been described.

The women fasted for 12 hours before a venipuncture for measurement of lipoprotein lipids, apoproteins, and triglycerides. Using sera, high density lipoprotein cholesterol (HDLc) was measured by a heparin-manganese precipitation procedure. The HDLc subfraction, HDLc, forms a precipitate after addition of dextran sulfate to the supernatant obtained with heparin-manganese chloride. The cholesterol content of the supernatant was measured, and the concentration of HDLc was found by subtracting HDLc from the concentration of total HDLc. Triglycerides were determined enzymatically, and low density lipoprotein cholesterol (LDLc) was calculated by using the Friedewald formula.

Sample serum (5 ml) for apoprotein determinations were frozen at −70°C for up to 3 months before overnight shipment on dry ice to the laboratory. Apo A-I and B were assayed by electrophromunoperoxidase assay. The intra-assay coefficient of variation for apo A-I was 6.7% at a mean concentration of 139 mg/dl, and for apo B it was 9.9% (mean=106 mg/dl). An enzyme-linked immunosorbent assay was used to determine the apo A-II levels. The intra-assay coefficient of variation for apo A-II was 7.1% (mean=31 mg/dl).

After the baseline examination, women completed and returned monthly postcards with information about their menstrual status. After 12 months' amenorrhea, the women were scheduled for postmenopausal examinations identical to their baseline evaluations. FSH and LH, as well as the total serum estradiol and estrone, were measured. An FSH level above 720 ng/ml was considered to be characteristic of postmenopausal status in the women who had been amenorrheic for at least 12 months.

The estrogen concentrations, estrone and estradiol, were measured by highly specific methods involving extraction, column chromatography, and radioimmununoperoxidase assay by use of a specific antibody from sheep. During the extraction step, a small amount of radioactive (3H) steroid was added to each sample to correct for procedural losses during extraction and subsequent chromatography. The purpose of the extraction step is to transfer the steroid hormone from an aqueous phase in the plasma to an organic phase (carbon tetrachloride) in which it is very soluble. The chromatography step separates the hormone from other similar hormones and increases the specificity of the assay system. A "specific antibody" radioimmunoassay is only specific for those compounds that have been checked for cross-reactivity. The within-assay variation was 10%, while the between-assay variation was 15% for estrone. For estradiol, the within-assay variation was 8% and the between-assay variation was 10%. For individuals whose hormone levels were found to be below the sensitivity level of the assay (2.5 pg/ml), the sensitivity level was used in the analyses.

We had previously evaluated the short- and long-term variability of sex steroid hormone measurements in the same laboratory. Short-term variability was evaluated by having blood drawn from nine postmenopausal women at half-hour intervals. The results showed the intra-individual correlation for estrone to be 0.89 and for estradiol to be 0.86. Blood samples were drawn again 4 weeks later, with a resulting intra-individual correlation over 1 month of 0.72 for estrone and 0.45 for estrogen. The variability over 3 years was evaluated among 178 older postmenopausal women; the intra-individual correlation for this group was 0.56 for estrone and 0.36 for estradiol. The variability of estrone was similar to that for HDLc, HDLc, and systolic or diastolic blood pressure over 3 years. A frozen, stored aliquot was analyzed in the laboratory along with each batch of hormones measured to serve as a control for evaluation of the effects of long-term freezing and laboratory drift. There was no evidence of laboratory drift nor any effect of long-term freezing at −70°C.

Some baseline and follow-up results from this study have been published. At baseline, the mean age of the women was 47 years, 75% had some college education, and 9% (n=48) were black. The mean values (mg/dl) were total cholesterol=184, HDLc=59.3, HDLc=20.8, HDLc=38.5, LDLc=108, fasting triglycerides=83.7, apo A-I=143, apo A-I=52.3, and apo B=93.6. The mean body mass index (BMI) (weight over height squared) was 24.8. Approximately 70% of the women were nonsmokers at entry, and 34% reported at least one drink of alcohol per week. The women reported expending an average of 1453 kilocalories of physical activity per week, and they reported consuming 30% of their calories from fat. The primary determinants of HDLc and subfraction levels were alcohol intake, physical activity, cigarette smoking, and BMI.

**Sample Description**

As of March 11, 1989, 210 women had become menopausal; 72 of these women were taking hormone replacement therapy and were excluded from further analysis. There were no significant differences in the levels of baseline lipoproteins or apoproteins between women who were prescribed therapy and those who were not. Of the remaining 138 menopausal women, blood samples were available for measurement of estrone in 120 and for estradiol in 99. Estradiol was not measured in 21 women because of an inadequate amount of serum for doing the analysis. Women who did not have blood specimens for any hormone measurements either did not come in for an examination or refused the venipuncture. Six women came in for their examination and had measurements of hormones after the cutoff point for data analyses.

The 120 women for whom blood samples were available became menopausal between February 1985 and March 1989. Three women had levels of estradiol >100 pg/ml or estrone >200 pg/ml and were eliminated.
from the analyses of hormones and risk factors. The initial blood samples were obtained after about 12 months of amenorrhea. FSH levels were available for 114 of the 120 women who had estrogen measurements at the first postmenopausal examination (Table 1). There were no significant differences for any of the lipoproteins or apoproteins between the quintiles of estradiol. The mean HDLc was 55.7 mg/dl for women in the lowest four quintiles and 65.0 mg/dl for women in the highest quintile (p=0.02, nonparametric one-way analysis of variance). The mean LDLc was 15.7 mg/dl for women in the four lowest quintiles and 25.1 mg/dl for those in the highest quintile (p=0.002). The mean LDLc was 128.6 mg/dl for those in the four lowest quintiles and 114.5 mg/dl for women in the highest quintile (p=0.14). The mean BMI was 26.8 for those in the four lowest quintiles and 23.7 among women in the highest quintile, and the waist-to-hip ratio was 0.77 for those in the four lowest quintiles and 0.72 for women in the highest quintile. Overall, women in the highest quintile of estradiol had higher HDLc and HDL2c, and lower LDLc, total cholesterol, triglycerides, and apo B than women in the lower four quintiles. The lack of a linear relationship between estradiol and lipoprotein levels could be due to within-individual variability of estradiol or possibly to a threshold effect of level of estradiol.

We have attempted to further evaluate the relationship between relatively high estradiol and estrone levels and lipoproteins and apoproteins. We measured free estradiol levels by using equilibrium dialysis methods. The correlation between total and free estradiol was extremely high.
Table 2. Mean Values (mg/dl) for Lipoproteins and Apoproteins according to Level of Estradiol in Women at 1-Year Postmenopause. The Healthy Women Study

<table>
<thead>
<tr>
<th>Estradiol (pg/ml)</th>
<th>N</th>
<th>Total chol</th>
<th>LDLc</th>
<th>HDLc</th>
<th>HDL&lt;sub&gt;2c&lt;/sub&gt;</th>
<th>HDL&lt;sub&gt;c&lt;/sub&gt;</th>
<th>Fasting TG</th>
<th>Apo A-I</th>
<th>Apo A-II</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.5*</td>
<td>27</td>
<td>204.6</td>
<td>125.6</td>
<td>60.5</td>
<td>17.5</td>
<td>43.0</td>
<td>92.2</td>
<td>138.2</td>
<td>54.2</td>
<td>103.3</td>
</tr>
<tr>
<td>2.6–6.3</td>
<td>12</td>
<td>203.6</td>
<td>126.6</td>
<td>55.6</td>
<td>18.2</td>
<td>37.4</td>
<td>106.7</td>
<td>143.6</td>
<td>48.8</td>
<td>98.9</td>
</tr>
<tr>
<td>6.4–11.0</td>
<td>20</td>
<td>192.8</td>
<td>119.0</td>
<td>49.6</td>
<td>13.6</td>
<td>36.0</td>
<td>120.7</td>
<td>146.3</td>
<td>48.9</td>
<td>96.7</td>
</tr>
<tr>
<td>11.1–30.0</td>
<td>20</td>
<td>220.4</td>
<td>145.3</td>
<td>55.5</td>
<td>14.7</td>
<td>40.8</td>
<td>98.1</td>
<td>148.0</td>
<td>52.8</td>
<td>111.1</td>
</tr>
<tr>
<td>≥30.1</td>
<td>17</td>
<td>193.8</td>
<td>114.5</td>
<td>65.0</td>
<td>25.1</td>
<td>39.9</td>
<td>71.2</td>
<td>148.4</td>
<td>49.8</td>
<td>93.5</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>203.4</td>
<td>126.5</td>
<td>57.4</td>
<td>17.5</td>
<td>39.8</td>
<td>97.5</td>
<td>144.5</td>
<td>51.3</td>
<td>101.2</td>
</tr>
</tbody>
</table>

P value, Kruskal-Wallis ANOVA (nonparametric) 0.13 0.14 0.02 0.02 0.23 0.02 0.21 0.55 0.12

*Includes all measures below the sensitivity of the assay.

Chol=cholesterol, LDLc=low density lipoprotein, HDLc=high density lipoprotein, TG=triglyceride, Apo=apolipoprotein, TG=triglyceride

Table 3. Mean Values (mg/dl) for Lipoproteins and Apoproteins according to Level of Estrone in Women at 1-Year Postmenopause. The Healthy Women Study

<table>
<thead>
<tr>
<th>Estrone (pg/ml)</th>
<th>N</th>
<th>Total chol</th>
<th>LDLc</th>
<th>HDLc</th>
<th>HDL&lt;sub&gt;2c&lt;/sub&gt;</th>
<th>HDL&lt;sub&gt;c&lt;/sub&gt;</th>
<th>Fasting TG</th>
<th>Apo A-I</th>
<th>Apo A-II</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;31.9</td>
<td>25</td>
<td>203.6</td>
<td>128.6</td>
<td>54.0</td>
<td>16.7</td>
<td>37.2</td>
<td>104.8</td>
<td>145.1</td>
<td>50.8</td>
<td>107.3</td>
</tr>
<tr>
<td>31.9–40.7</td>
<td>23</td>
<td>203.7</td>
<td>128.2</td>
<td>61.0</td>
<td>19.3</td>
<td>41.8</td>
<td>93.3</td>
<td>145.1</td>
<td>52.2</td>
<td>98.8</td>
</tr>
<tr>
<td>40.8–49.9</td>
<td>23</td>
<td>208.3</td>
<td>128.2</td>
<td>58.7</td>
<td>17.4</td>
<td>41.3</td>
<td>107.0</td>
<td>147.0</td>
<td>53.9</td>
<td>107.3</td>
</tr>
<tr>
<td>50.0–61.5</td>
<td>23</td>
<td>198.4</td>
<td>122.9</td>
<td>54.8</td>
<td>13.8</td>
<td>41.1</td>
<td>103.2</td>
<td>145.5</td>
<td>50.5</td>
<td>104.2</td>
</tr>
<tr>
<td>&gt;61.5</td>
<td>25</td>
<td>201.4</td>
<td>126.2</td>
<td>59.3</td>
<td>20.8</td>
<td>38.6</td>
<td>79.4</td>
<td>146.3</td>
<td>48.3</td>
<td>100.9</td>
</tr>
<tr>
<td>Total</td>
<td>119</td>
<td>203.1</td>
<td>126.0</td>
<td>57.5</td>
<td>17.6</td>
<td>39.9</td>
<td>97.4</td>
<td>145.8</td>
<td>51.1</td>
<td>103.7</td>
</tr>
</tbody>
</table>

P value, Kruskal-Wallis ANOVA (nonparametric) 0.85 0.84 0.25 0.17 0.31 0.12 0.97 0.77 0.68

See the legend to Table 2 for an explanation of the abbreviations.

(0.85), and only 2% of the total estradiol was free. There were no consistent differences in the results with free estradiol values as compared with those with total estradiol.

The multiple regression analysis included other determinants of HDLc, HDL<sub>2c</sub>, and LDLc. Our results showed both BMI and waist-to-hip ratio to be inversely related to HDLc and HDL<sub>2c</sub> (Table 4), and the waist-to-hip ratio to be directly related to LDLc. Age was significantly and negatively related to HDL<sub>2c</sub>. The regression coefficient for estradiol in the equation predicting HDL<sub>2c</sub> was not significant but was in the same direction (positive) as the univariate comparison in Table 2. The univariate and multivariate relationships of estrone with HDL<sub>2c</sub> levels were similar.
Table 4. Determinants of HDLc, HDL2c, and LDLc. Results of Multiple Linear Regression Analysis, Beta Coefficients

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>HDLc</th>
<th>HDL2c</th>
<th>LDLc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrone (top quintile vs. lower four) (pg/ml)</td>
<td>3.42 (3.1)</td>
<td>3.79 (2.4)</td>
<td>4.60 (8.2)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.20 (0.7)</td>
<td>-1.11 (0.5)*</td>
<td>4.34 (1.7)*</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>-51.81 (18.6)*</td>
<td>-25.04 (14.1)‡</td>
<td>97.90 (48.6)†</td>
</tr>
<tr>
<td>Body mass index [weight (kg)/height² (m)]</td>
<td>-0.99 (0.3)*</td>
<td>-0.85 (0.2)*</td>
<td>0.56 (0.7)</td>
</tr>
<tr>
<td>Adjusted R²</td>
<td>0.20</td>
<td>0.21</td>
<td>0.07</td>
</tr>
<tr>
<td>SE</td>
<td>13.0</td>
<td>9.86</td>
<td>34.11</td>
</tr>
<tr>
<td>Estradiol (top quintile vs. lower four) (pg/ml)</td>
<td>4.55 (4.2)</td>
<td>4.85 (3.1)</td>
<td>-3.73 (10.9)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.43 (0.8)</td>
<td>-1.21 (0.6)*</td>
<td>3.58 (2.0)‡</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>-49.89 (21.2)†</td>
<td>-21.90 (15.7)</td>
<td>125.27 (55.6)†</td>
</tr>
<tr>
<td>Body mass index [weight (kg)/height² (m)]</td>
<td>-0.99 (0.3)*</td>
<td>-0.93 (0.2)*</td>
<td>0.10 (0.9)</td>
</tr>
<tr>
<td>Adjusted R²</td>
<td>0.20</td>
<td>0.26</td>
<td>0.07</td>
</tr>
<tr>
<td>SE</td>
<td>13.25</td>
<td>9.80</td>
<td>34.79</td>
</tr>
</tbody>
</table>

Values in parentheses are SE.

*p<0.001, †p<0.05, ‡p<0.01.*

HDLc=high density lipoprotein cholesterol, LDLc=low density lipoprotein cholesterol, SE=standard error.

Table 5. Comparison of Changes in Lipoprotein and Apoprotein Levels for Women in Highest Quintile of Estradiol at First Postmenopausal Examination with Women in Remaining Four Quintiles

<table>
<thead>
<tr>
<th>Estradiol group</th>
<th>N</th>
<th>Estradiol</th>
<th>HDLc</th>
<th>HDL2c</th>
<th>HDL2c</th>
<th>LDLc</th>
<th>Apo A-I</th>
<th>Apo A-II</th>
<th>Apo B</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest four quintiles</td>
<td>29</td>
<td>1.6</td>
<td>-0.3</td>
<td>-1.2</td>
<td>0.9</td>
<td>3.5</td>
<td>-1.1</td>
<td>-0.6</td>
<td>6.4</td>
<td>4.0</td>
</tr>
<tr>
<td>Highest quintile</td>
<td>10</td>
<td>43.5</td>
<td>0.5</td>
<td>-3.8</td>
<td>4.3</td>
<td>-4.0</td>
<td>0.4</td>
<td>-0.2</td>
<td>4.6</td>
<td>-2.5</td>
</tr>
<tr>
<td>Decreased below sensitivity of assay</td>
<td>4</td>
<td>-</td>
<td>-2.6</td>
<td>-6.2</td>
<td>3.6</td>
<td>-3.2</td>
<td>-12.5</td>
<td>-1.0</td>
<td>-0.8</td>
<td>10.5</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>12.3</td>
<td>-0.07</td>
<td>-1.9</td>
<td>1.8</td>
<td>1.6</td>
<td>-0.7</td>
<td>-0.5</td>
<td>6.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Values of estradiol are pg/ml. Other values are mg/dl.

See the legend to Table 2 for an explanation of the abbreviations.

Changes in hormones and lipoproteins over time were also evaluated. To date, 39 women have had repeat estradiol measures and 52 women have had repeat estradiol measures at the second annual postmenopausal visit, approximately 1 year after the initial postmenopausal exam. Estradiol levels decreased an average of 12.3 pg/ml (SD=22.8, SE=3.7), and estrone decreased 9.8 pg/ml (SD=23.3, SE=3.2). The correlation between estradiol measures 1 year apart was ρ=0.10 (p=0.27); for estrone measures, it was ρ=0.32 (p=0.009). There were no consistent relationships between changes in estradiol or estrone and changes in lipoprotein levels 1 year later. In the 52 women with repeat estrone measures, their HDLc levels decreased 0.26 mg/dl, HDL2c levels decreased 2.5 mg/dl, LDLc increased 2.1 mg/dl, and triglycerides increased 2.7 mg/dl (not shown). The average changes for the 39 women who had repeat estradiol measurements were similar to the total group of 52 women.

In the 10 women whose levels were in the highest quintile at their first postmenopausal examination, estradiol decreased an average of 43.5 pg/ml (Table 5). In four of these women, estradiol declined below the level of the sensitivity of the assay (2.5 pg/ml), and for these four women, HDLc decreased 2.6 mg/dl and HDL2c declined 6.2 mg/dl. For the remaining six women whose levels remained above the third quintile of estradiol levels, the changes in HDL2c were much less (not shown). For the entire sample of 39 women with repeat estradiol measurements, nine (23%) had a decrease in estradiol to below the sensitivity of the assay (Table 6). In these nine women, HDLc decreased 4.5 mg/dl, while for the remaining 30 women, HDLc decreased only 1.1 mg/dl. These changes were consistent with an effect of estradiol on HDLc and subtraction levels. The differences in lipoprotein changes between individuals who did or did not have a decrease of estradiol to below the sensitivity of assay were not significant because of the relatively small sample size.

There were 56 postmenopausal women who had undergone a perimenopausal (defined as 3-months' amenorrhea) examination and for whom blood samples had been stored at -70°C. All these women had been followed up carefully after the perimenopausal visit. Some had gone on to become menopausal, and others had remained premenopausal during the study. None were taking hormone replacement therapy or had had an oophorectomy at the time of the perimenopausal visit. Their median estradiol at the perimenopausal exam was...
correlated with BMI (rho=0.28, p=0.021).

The differences in the mean LDLc was 131.2 for women in the lowest tertile of estradiol, 118.7 for those in the highest. The differences in the mean LDLc were 16.5 mg/dl and estradiol, 37.0 pg/ml. The HDLc declined an average of 7.5 mg/dl among these women as compared to 4.4 mg/dl for the 13 women for whom estradiol levels remained above the level of the sensitivity of the assay (<2.5 pg/ml).

Because of the small sample size, we divided the estradiol and estrone levels into tertiles rather than quintiles (Table 7). Estradiol was ≤17 pg/ml in the lowest grouping, >17.0 to 64.0 for the middle group, and >64.0 pg/ml in the highest tertile. HDLc varied from 21.6 mg/dl for those in the lowest tertile to 25.5 mg/dl for those in the highest. The mean LDLc was 131.2 for women in the lowest tertile of estradiol and 118.7 for those in the highest. The differences in HDLc and LDLc between the tertile HDLc and LDLc were smaller than those for the estradiol tertiles.

Among the 56 perimenopausal women studied, seven have not become menopausal, four have gone on to become postmenopausal but did not have a follow-up visit, three had insufficient blood samples at their postmenopausal examination, three became menopausal after the analysis had been completed, 11 started taking hormone replacement therapy, and 28 became postmenopausal and had repeat hormone studies at both the perimenopausal and first postmenopausal exams. There were no significant differences in the perimenopausal lipoprotein, apoprotein, and hormone levels between the women who did and those who did not have repeat hormone measurements at the first postmenopausal visit.

We evaluated the changes in hormones and lipoproteins between perimenopause and postmenopause for the 28 women who became menopausal and did not take hormone replacement therapy (Table 8). Estrone levels decreased 16.5 pg/ml and estradiol, 37.0 pg/ml. The HDLc declined an average of 7.5 mg/dl among these seven women as compared to 4.4 mg/dl for the 13 women for whom estradiol levels remained above the level of sensitivity of the assay. There was, however, substantial variability in the change in lipoprotein levels in both groups.

Estrone is the primary postmenopausal hormone. The estrone differences were significantly and inversely correlated with changes in LDLc (rho=−0.39, p=0.02) and changes in total cholesterol (rho=−0.41, p=0.02). Women who maintained relatively high estrone levels from peri- to postmenopause experienced a smaller increase in LDLc. There was no relationship of change in estrone to change in HDLc or subfractions. The levels of
Table 8. Changes in Hormone and Lipoprotein Levels in 28 Peri- to Postmenopausal Women

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean change</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>3.8</td>
<td>4.2</td>
</tr>
<tr>
<td>HDLc (mg/dl)</td>
<td>-0.1</td>
<td>2.3</td>
</tr>
<tr>
<td>HDLc (mg/dl)</td>
<td>-5.8</td>
<td>2.1</td>
</tr>
<tr>
<td>HDLc (mg/dl)</td>
<td>5.8</td>
<td>1.4</td>
</tr>
<tr>
<td>HDLc (mg/dl)</td>
<td>5.4</td>
<td>9.1</td>
</tr>
<tr>
<td>HDLc (mg/dl)</td>
<td>2.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Estradiol (pg/ml)*</td>
<td>-37.0</td>
<td>10.7</td>
</tr>
<tr>
<td>Estrone (pg/ml)</td>
<td>-16.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.6</td>
<td>0.15</td>
</tr>
<tr>
<td>BMI [weight (kg)/height² (m)]</td>
<td>0.66</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*n=20 with estradiol measures.
See the legend to Table 2 for an explanation of the abbreviations.

the lipoproteins were all highly and significantly correlated between the perimenopausal and the postmenopausal exams (total HDLc, rho=-0.70; HDLc, rho=0.53; LDLc, rho=0.80). The peri- and postmenopausal hormone levels were not significantly correlated (estradiol rho=-0.22, p=0.18, estrone rho=0.28, p=0.08). Perimenopausal hormone levels are primarily determined by ovarian function, while postmenopausal hormone levels are derived from the aromatization of androstenedione to estrone and from estrone to estradiol.

Discussion

Changes in lipoproteins during peri- and postmenopause are due to a combination of aging, hormonal changes, and behavioral factors such as weight gain, exercise, smoking, and alcohol consumption. One of the most interesting and puzzling aspects of the menopause is the relatively small change in HDLc concentration in spite of a marked decline in estradiol levels. The results of analyses of the peri- and postmenopausal women in this study show that the estradiol levels decreased from a median of 30.4 pg/ml at the first perimenopausal visit (3-months amenorrhea), to 8.9 pg/ml at the first postmenopausal visit (12-months amenorrhea) to 5.1 pg/ml at the second postmenopausal visit (24-months amenorrhea). The serum samples were all assayed at the same time; thus, laboratory drift is an unlikely explanation for an overall decline in estradiol level. The estradiol and estrone measurements were assayed without knowledge of the prior hormone levels and, as noted, with careful quality control in the laboratory, including re-analysis of the same control aliquots with each batch of hormone measurements.

Compared to the large decrease in estradiol levels, estrone levels decreased only modestly from a median of 49.9 pg/ml at the perimenopausal visit to a median of 46.8 pg/ml at the initial postmenopausal visit and a median of 38.3 pg/ml at the second postmenopausal visit. We previously reported that women who had become menopausal and were not taking hormone replacement therapy had an average 3 mg/dl decrease in HDLc and a 1.5 mg decrease in HDLc as compared with no decrease in total HDLc and a 0.4 mg/dl increase in HDLc for women who remained premenopausal. LDLc increased 12 mg/dl in the menopausal women and 5.4 mg/dl in those who remained premenopausal. Changes in smoking, alcohol intake, and weight did not account for the decrease in HDLc in the first 3.5 years of follow-up. The only consistent finding from the examination of the relationship of the hormones and lipoprotein levels was a higher HDLc and HDLc and a lower LDLc level among women who were in the highest quintile of estradiol level. A similar, but smaller, association with estrone levels was observed.

We have evaluated the association between hormones and lipoproteins by measuring changes in hormones and lipoprotein levels from the peri- to the initial postmenopausal exam and then to the second postmenopausal exam. The decline in estradiol among women in the highest quintile was accompanied by a substantial fall in HDLc. Both estradiol and HDLc declined substantially from the perimenopausal to the postmenopausal examination, but there was no consistent relationship between change in the estrogen levels and change in any of the other lipoprotein concentrations.

It is difficult to characterize the levels of these hormones during the perimenopausal period because of the rapid decrease in ovarian function. Any attempt, therefore, to correlate change in hormones and lipoproteins may be particularly difficult during the perimenopause except by multiple measurements over relatively short time intervals. Even then, the within-individual variability in hormone levels may be greater than the between-individual variability and may mask a relationship between the hormone and lipoprotein changes.

The postmenopausal women in this study had FSH levels consistent with postmenopausal status. The most likely reason that some of these women had higher estradiol levels was that they continued to have anovulatory cycles early in the climacteric with high estradiol levels unopposed by progesterone. This may have resulted in higher HDLc, LDLc, and apo A-I and lower apo B and LDLc levels relative to women with lower estradiol concentrations. Using the same laboratory, Cauley et al.14 recently reported that for 176 postmenopausal women (mean age of 58 and 9 years postmenopausal) the mean estrone level was 29.8 pg/ml and that 73% of the women had estradiol levels below the sensitivity of the assay. There was no relationship in those women between hormone and lipoprotein levels.

The results of this study do not explain why HDLc declines very little around the time of the menopause and why cross-sectional studies do not show any substantial change in HDLc with increasing age among women. It is possible that total HDLc does not change substantially, but that the relative proportion of HDLc to HDLc or to other subfractions changes during the menopause. We have previously reported that the primary determinant of postmenopausal estrone is obesity,14 and the important role of obesity as a major determinant of postmenopausal estrogen level is generally accepted.15 We have also shown obesity to be associated with increased insulin levels which are, in turn, correlated with lower HDLc and subfractions.23 The balance, therefore, between levels of sex...
steroid hormones and insulin and perhaps insulin sensitivity may in part determine the concentration of HDLc and subfractions among postmenopausal women.24

It is also possible that conversion of estrone to estradiol at the tissue level or the interaction between estradiol and specific receptors and subsequent protein synthesis may be primary factors in determining the levels of HDLc and its subfractions. Measurement of hormone levels in the serum may, therefore, not correlate with lipoproteins, especially in older women. Cauley et al.,25 however, have shown endogenous estrogen blood levels to be related to bone mineral density, suggesting some biological effect of the serum concentrations. Estrogen replacement therapy when given orally raises HDLc and subfractions and lowers LDLc levels. Many liver enzymes and proteins are also increased, probably due to the initial passage of the hormone through the liver. When hormones are given by injection, implantation, or transdermally, the change in HDLc level is much smaller and inconsistent in spite of a substantial increase in blood estradiol level.26–30

Clearly, there is not a simple relationship between the estrogen and lipoprotein and apoprotein levels at the time of menopause. The most likely hypothesis based on current data is that high estradiol levels early after menopause are a measure of anovulatory cycles resulting in higher HDLc and, especially, HDLc levels. Estrone derived from the aromatization of androstenedione (an adrenal hormone) is the primary postmenopausal estrogen and maintains the higher HDLc level among postmenopausal women as compared to men. Both estrone and insulin levels are directly related to obesity. Women gain both in weight and percentage of body fat as they get older.23

The interrelationship between insulin and estrone and possibly the extent of conversion of estrone to estradiol at the tissue level and subsequent activation of protein synthesis may partially determine HDLc level among postmenopausal women and, consequently, the progression of atherosclerosis. It would be of great interest, therefore, to evaluate the relationships between estrogen levels during the peri- and postmenopausal periods, insulin levels and the extent of atherosclerosis, as well as the development of symptomatic atherosclerotic disease.31,32,33 Finally, if the relationships among sex steroid hormones, insulin, and atherosclerosis can be clarified, then it might be possible to more carefully identify the individual women who are most likely to benefit from postmenopausal hormone replacement therapy for the prevention of cardiovascular disease.

References


Index Terms: estrogen • lipoproteins • apoproteins • menopause • obesity
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