Aging Metabolism

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Effects of Age, Sex, and Menopausal Status on Plasma Lipoprotein(a) Levels

The Framingham Offspring Study

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Background. Lipoprotein(a) (Lp(a)) is an atherogenic particle that structurally resembles a low density lipoprotein (LDL) particle but contains a molecule of apolipoprotein(a) attached to apolipoprotein B-100 by a disulfide bond. Because elevated plasma levels of Lp(a) have been shown to be an independent risk factor for coronary artery disease, it is important to define normal ranges for this lipoprotein.

Methods and Results. We have measured Lp(a) in 1,284 men (mean age, 48±10 years) and 1,394 women (mean age, 48±10 years) free of cardiovascular and cerebrovascular disease and not on medications known to affect lipids who were seen at the third examination cycle of the Framingham Offspring Study. Plasma Lp(a) levels were measured by an enzyme-linked immunosorbent assay, which uses a "capture" monoclonal anti-apo(a) antibody that does not cross-react with plasminogen, and a polyclonal anti-apo(a) antibody conjugated to horseradish peroxidase. The assay was calibrated to total Lp(a) mass. The Lp(a) frequency distribution was highly skewed to the right, with 56% of the values in the 0–10-mg/dL range. Mean plasma Lp(a) concentrations were 14±17 mg/dL in men and 15±17 mg/dL in women. Values of more than 35 mg/dL were above the 90th percentile and values of more than 22 mg/dL were above the 75th percentile in both men and women.

Conclusions. We have determined mean Lp(a) levels for men and women participating in the Framingham Offspring Study. In this population, there was an inverse association between plasma levels of Lp(a) and triglycerides for both sexes (p<0.006), but triglycerides accounted for only approximately 0.5% of the variation in Lp(a) levels. Associations of Lp(a) levels with total and LDL cholesterol levels were not significant after correction for the estimated contribution of Lp(a) cholesterol to total and LDL cholesterol. After controlling for age, Lp(a) values were 8% greater in postmenopausal women than in premenopausal women, but this difference was not statistically significant. Body mass index, alcohol consumption, cigarette smoking, use of β-blockers or cholesterol-lowering medications, and use of drugs for the treatment of diabetes and hypertension were not correlated with Lp(a) levels. (Circulation 1993;87:1135–1141)

KEY WORDS • Framingham Offspring Study • coronary artery disease • triglycerides • cholesterol

Both retrospective and prospective population studies have shown a positive association between plasma levels of lipoprotein(a) [Lp(a)] and risk of coronary artery disease (CAD)1–3 and stroke.4,5 Lp(a), as described by Berg in 1963,6 is a highly heterogeneous plasma lipoprotein that shows pre-β migration on plasma lipoprotein electrophoresis and has a flotation density in the 1.04–1.13-g/mL range.7

Protein structure accounts for most of Lp(a) heterogeneity. The protein moiety of Lp(a) is composed of one molecule of apolipoprotein (apo) B-100, the major protein constituent of low density lipoproteins (LDL), and one molecule of apo(a), a large glycoprotein attached to apo B-100 by a disulfide bond.8,9 cDNA nucleotide sequence analyses have shown that apo(a) has a high degree of homology with plasminogen, a plasma protein involved in the fibrinolytic process.10 Because of this homology, Lp(a) may compete with plasminogen and, hence, interfere with the thrombolytic process.11,12 The apo(a) gene contains a DNA sequence that is 91% homologous to that of kringle 5 of plasminogen and multiple copies of a sequence with 75–85% homology to that of kringle 4 of plasminogen.13 Kringles are protein domains that resemble a Danish pastry and are characterized by a tertiary structure containing three internal disulfide bonds. The number of kringle 4 repeats in apo(a) is highly variable and genetically determined.14 This variability results in the existence of different-size isoforms of apo(a) with apparent molec-
ular weights ranging between 280 and 800 kg.10 The gene coding for apo(a) is located on the long arm of chromosome 6, in close proximity to the gene for plasminogen.17,18 The location of the apo(a) gene and its high degree of homology with the plasminogen gene have prompted the hypothesis that the former derives from duplication of the plasminogen gene.13 In addition, it has been suggested that the polymorphism in kringle 4 repeats in the apo(a) gene arises from internal recombination. This is due to the presence, in an intervening sequence of the kringle 4, of repetitive sequences involved in recombination and gene conversion in the eukaryotic genome.19 No agreement on the definite number of apo(a) alleles in the general population has been reached. Gaubatz et al20 have reported a total of 11 apo(a) isoforms in a mixed population, whereas we have identified 12 polymorphic-size apo(a) molecules.21 Recently, 19 apo(a) gene alleles, differing in size, have been identified by pulsed-field gel electrophoresis,19 and Kamboh et al22 have reported 24 apo(a) alleles, including a null allele.

It has been shown that Lp(a) levels are significantly higher in subjects with CAD and in subjects with stroke than in subjects free of atherosclerosis.1-7,23 The increased risk of CAD attributed to elevated plasma levels of Lp(a) appears to be independent of other lipoprotein parameters. However, Lp(a) may act synergistically with high levels of LDL, other risk factors, or both to increase the risk of CAD.5,24 Elevated plasma levels of Lp(a) can be detected using electrophoretic methods,25 but immunoassay techniques have much greater precision and sensitivity.

In the present study, we have defined normal ranges for plasma levels of Lp(a) in a large caucasian population in North America that is free of symptoms of atherosclerotic disease. Our data show that plasma Lp(a) levels are independent of all other plasma lipid or lipoprotein levels, except for a very modest inverse association with triglycerides. In this population, Lp(a) levels in men were not significantly different than those in women. Our data also indicate that factors such as body mass index (BMI), cigarette smoking, use of \( \beta \)-blockers, and other antihypertensive drug use, which are known to affect other plasma lipoproteins, do not influence plasma levels of Lp(a) in this population.

**Methods**

**Study Population**

A total of 1,284 men (mean age, 48±10 years) and 1,394 women (mean age, 48±10 years) participating in the Framingham Offspring Study (third examination cycle) were studied. All participants were caucasian. The design and methodology of the Framingham Offspring Study have been described elsewhere.26 Exclusion criteria included presence of CAD and stroke. Occurrence of myocardial infarction, angina pectoris, and stroke was assessed as previously described.27

**Lipid and Apolipoprotein Analyses**

After an overnight fast, blood was drawn from each subject into tubes containing EDTA at a final concentration of 1 mg/mL. Plasma was separated by centrifugation at 2,500 rpm for 30 minutes at 4°C. Plasma aliquots were quickly frozen and stored at −80°C for the measurement of apo A-I, apo B, and Lp(a). High density lipoprotein (HDL) cholesterol was measured after precipitation of LDL and very low density lipoprotein (VLDL) cholesterol with dextran sulfate-Mg2+.5 Plasma levels of total cholesterol, HDL cholesterol, and triglycerides were measured by automated enzymatic methods with an Abbott Diagnostics ABA-200 bichromatic analyzer and Abbott A-Gent enzymatic reagents.29 VLDL and LDL cholesterol were calculated after ultracentrifugation of the plasma at a density of 1.006 g/mL as follows: VLDL cholesterol=total cholesterol−1.006 g/mL infranate cholesterol, and LDL cholesterol=1.006 g/mL infranate cholesterol−HDL cholesterol. Plasma levels of apo A-I and apo B were measured by double-sandwich enzyme-linked immunoassay (ELISAs) using affinity-purified anti–apo A-I and anti–apo B polyclonal antibodies, respectively, as previously described.30 Our laboratory participates in the Centers for Disease Control (CDC) (Atlanta, Ga.) lipid standardization program, is certified by this organization, and serves as one of the CDC network laboratories that standardize other laboratories.

**Lipoprotein(a) Assay**

Lp(a) was measured in plasma using a commercially available ELISA (Terumo Medical Corporation, Elkton, Md.).31-33 Plasma samples, diluted 1:201, were incubated for 1 hour at room temperature in microtiter strip wells coated with a specific monoclonal anti-Lp(a) antibody that recognizes all apo(a) isoforms and does not cross-react with plasminogen. Unbound antigen was then removed by extensive washing. After a 20-minute incubation at room temperature with a polyclonal anti-Lp(a) antibody conjugated with the enzyme horseradish peroxidase, plates were washed and incubated with hydrogen peroxide (substrate) and O-phenylenediamine (chromogen) for an additional 20 minutes. The enzymatic reaction was then stopped by the addition of sulfuric acid. The absorbance was read at 492 nm using a Dynatech MR 600 microtiter plate reader (Dynatech Inc., Vienna, Va.). Lp(a) values were calculated from the standard curve constructed for each plate. The Lp(a) standards and controls provided by Terumo Med. Co. were calibrated to a reference preparation of human plasma obtained from Dr. John Albers (Northwest Lipid Research Clinic). The value of the reference preparation was derived from a double-antibody radioimmunoassay calibrated with purified Lp(a).34 Mean intra-assay and interassay coefficients of variation for this ELISA were 2.8% and 4.3%, respectively. Lp(a) plasma concentrations are reported as total Lp(a) mass (mg/dL).

**Calculations**

Total and LDL cholesterol and total apo B values were corrected for the contribution of Lp(a) cholesterol and Lp(a) apo B, respectively. According to compositional data,35,36 cholesterol accounts for approximately 30% and apo B for approximately 16% of total Lp(a) mass. To calculate corrected total and LDL cholesterol, total Lp(a) mass was multiplied by 0.3, and this value was subtracted from total cholesterol and LDL cholesterol values. Similarly, the corrected apo B value was obtained by subtracting \( [Lp(a) \text{ mass} \times 0.16] \) from total apo B concentration.
TABLE 1. Plasma Biochemical Parameters in Men and Women Free of Cardiovascular and Cerebrovascular Disease Participating in the Framingham Offspring Study

<table>
<thead>
<tr>
<th></th>
<th>Men (n=1,284)</th>
<th>Women (n=1,394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48±10</td>
<td>48±10</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>140±106</td>
<td>105±123*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>211±39</td>
<td>211±43</td>
</tr>
<tr>
<td>VLDL cholesterol (mg/dL)</td>
<td>31±21</td>
<td>23±20*</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>136±34</td>
<td>131±37*</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>45±12</td>
<td>57±15*</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>96±23</td>
<td>92±20*</td>
</tr>
<tr>
<td>Lipoprotein(a) (mg/dL)</td>
<td>14±17</td>
<td>15±17</td>
</tr>
</tbody>
</table>

VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein. Values are mean±SD.

*Significant difference between men and women, p<0.01.

Statistical Analysis

Analyses of the data were performed with the SAS statistical package (SAS Institute, Cary, N.C.). Mean plasma levels of lipids, lipoproteins, and Lp(a) were determined for each sex, and differences were tested by t test. Because the distribution of Lp(a) values was highly skewed, a logarithmic (log) transformation was performed. Triglyceride and VLDL cholesterol values also were log transformed. The Pearson correlation method was used to test the association between Lp(a) and BMI. The Spearman test was used to assess the relation between Lp(a) and smoking; alcohol consumption (subjects were reported as either drinking or non-drinking); and use of medications for diabetes, hypertension, or hypercholesterolemia. The contribution of plasma triglyceride levels to Lp(a) variability was determined by multivariate analysis. All data in the text are presented as mean±SD.

Results

Plasma levels (mean±SD) of triglycerides, total cholesterol, VLDL cholesterol, LDL cholesterol, HDL cholesterol, glucose, and Lp(a) in 1,284 men and 1,394 women participating in the third cycle of the Framingham Offspring Study are reported in Table 1. Lp(a) concentrations were not statistically different for men and women. Triglyceride, VLDL cholesterol, LDL cholesterol, and glucose levels were significantly lower in women than in men, whereas HDL cholesterol levels were significantly higher in women. Figure 1A shows the frequency distribution of Lp(a) levels in 2,678 subjects. Although the observed range is from 0.09 to 109.2 mg/dL, the distribution is highly skewed, with 56% of the population having Lp(a) concentrations between 0 and 10 mg/dL. The frequency distribution of plasma Lp(a) levels in subjects in this range (0–10 mg/dL) is illustrated in Figure 1B. Mean plasma concentrations of Lp(a) in men and women, according to age, are reported in Table 2. There was no significant difference between Lp(a) concentrations in men and women for any age group, although there was a trend toward an increase in plasma levels in each sex between the ages of 20 and 59 years. The concentration of Lp(a) in plasma appeared to decrease slightly in subjects more than 60 years old, with the exception of men more than 69 years old; however, the number of subjects in the latter group was very small (n=11).

Selected percentiles for plasma Lp(a) levels in men and women are shown in Table 3. Lp(a) concentrations of more than 22 mg/dL were above the 75th percentile and values of more than 38 mg/dL were above the 90th percentile for the Framingham Offspring population, in both men and women.

When subjects of all ages (20–70+ years) were included in the analysis, there was a significant association between age and Lp(a) levels only in women (Table 4). Total plasma cholesterol and Lp(a) levels were positively correlated in men and women (p<0.0007 and p<0.0003, respectively). Similarly, an association between LDL cholesterol and Lp(a) concentrations was observed in both sexes (p<0.0001). However, the Lp(a) cholesterol contribution to total and LDL cholesterol levels was taken into account, these correlations were no longer statistically significant (Table 4). A weak inverse association was also observed between triglyc-

![FIGURE 1. Panel A: Frequency distribution of plasma lipoprotein(a) in participants of the Framingham Offspring Study, who were free of cardiovascular and cerebrovascular disease. Panel B: Frequency distribution of lipoprotein(a) levels in the 0–10-mg/dL range.](http://circ.ahajournals.org/)

Table 2. Lipoprotein(a) Plasma Levels, According to Age and Sex, in Subjects Free of Coronary Artery Disease and Stroke Participating in the Framingham Offspring Study

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Lipoprotein(a) (mean±SD mg/dL)</td>
<td>Lipoprotein(a) (mean±SD mg/dL)</td>
<td>p*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>34</td>
<td>11.3±12.4</td>
<td>23</td>
<td>10.6±11.7</td>
<td>NS</td>
</tr>
<tr>
<td>30–39</td>
<td>245</td>
<td>13.5±14.3</td>
<td>279</td>
<td>12.8±14.6</td>
<td>NS</td>
</tr>
<tr>
<td>40–49</td>
<td>432</td>
<td>14.4±17.2</td>
<td>475</td>
<td>15.1±16.0</td>
<td>NS</td>
</tr>
<tr>
<td>50–59</td>
<td>360</td>
<td>15.3±17.7</td>
<td>396</td>
<td>17.0±19.3</td>
<td>NS</td>
</tr>
<tr>
<td>60–69</td>
<td>189</td>
<td>13.2±17.1</td>
<td>191</td>
<td>16.2±18.6</td>
<td>NS</td>
</tr>
<tr>
<td>70+</td>
<td>11</td>
<td>17.6±18.8</td>
<td>17</td>
<td>16.6±23.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Significance for difference between men and women.
eride and Lp(a) plasma levels in men (p<0.004) and in women (p<0.006). Alterations in triglyceride levels accounted for only 0.7% and 0.5% of the variation in Lp(a) levels in men and women, respectively. Total plasma apo B levels were not associated with Lp(a), but when the apo B content of Lp(a) was subtracted from total plasma apo B (corrected apo B), a weak negative correlation was observed in men (p<0.05).

The effect of menopausal status on Lp(a) was assessed by comparing Lp(a) concentrations in premenopausal and postmenopausal women. The mean plasma concentration of Lp(a) in postmenopausal subjects was 19% higher than the mean found in premenopausal subjects (p<0.004) (Table 5). After controlling for age, Lp(a) levels in postmenopausal women were still higher (8%), but this difference was no longer statistically significant (Table 5). In addition, the mean plasma Lp(a) level in 30 postmenopausal women, who were taking estrogen at the time of sampling, was not different from the mean of 58 age-matched postmenopausal women not taking estrogen (19.9 versus 18.0 mg/dL, respectively).

When an additional 956 subjects who were on medications known to affect plasma lipids were included in the statistical analysis, treatments with oral hypoglycemic agents, insulin, thyroid medication, cholesterol-lowering drugs, potassium-sparing and other diuretics, peripheral vasodilators, \( \beta \)-blockers, and other antihypertensive drugs did not have a significant effect on Lp(a) plasma levels. Furthermore, BMI, cigarette smoking, and alcohol consumption did not correlate with plasma Lp(a) levels.

**Discussion**

In our study, we report normal ranges of plasma Lp(a) concentrations for an adult caucasian population free of CAD and stroke. The highly skewed distribution and the wide range of Lp(a) values were not surprising because similar ranges and distributions have been previously reported in smaller caucasian populations.\(^{11,20,37,38}\) Both the mean levels of Lp(a) and its distribution appear to be different in various ethnic groups.\(^{11,39}\) For example, in black populations, a gaussian distribution is observed with mean Lp(a) levels twofold to threefold higher than those found in caucasian populations.\(^{39}\) These ethnic differences may be significantly determined by genetic factor(s). It is known that plasma Lp(a) levels, which are inversely related to the number of kringle 4 repeats in the apo(a) gene, are very heritable, as shown by studies conducted in monozygotic and dizygotic twins\(^{40,41}\) and in families.\(^{3,16,42}\) In Sudanese blacks, however, the contribution of isofrom size to the variability in plasma Lp(a) levels is only about 19%.\(^{39}\) In caucasians, the number of kringle 4 repeats in the apo(a) gene accounts for 69% of the interindividual differences in Lp(a) concentrations, and other sequences at the apo(a) locus account for an additional 22%. The apo(a) gene, therefore, may account for more than 90% of the variance in plasma Lp(a) levels.\(^{43}\) This conclusion is consistent with the fact that we saw relatively little or no effect of environmental or other factors on Lp(a) concentrations in our population.

Lp(a) plasma levels were positively correlated with total cholesterol and LDL cholesterol levels in this population. The method used to calculate LDL cholesterol included Lp(a) cholesterol as well as LDL cholesterol. The positive associations between Lp(a) and total cholesterol and LDL cholesterol levels found in this

**Table 3. Percentiles for Plasma Levels of Lipoprotein(a) (mg/dL) in Subjects Free of Coronary Artery Disease and Stroke Participating in the Framingham Offspring Study**

<table>
<thead>
<tr>
<th>Percentiles</th>
<th>5</th>
<th>10</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>90</th>
<th>95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.6</td>
<td>1.0</td>
<td>2.6</td>
<td>7.6</td>
<td>21.2</td>
<td>38.0</td>
<td>49.6</td>
</tr>
<tr>
<td>Women</td>
<td>0.7</td>
<td>1.1</td>
<td>3.0</td>
<td>8.2</td>
<td>22.7</td>
<td>37.5</td>
<td>52.9</td>
</tr>
</tbody>
</table>

**Table 4. Correlations of Plasma Levels of Lipoprotein(a) With Age and Plasma Levels of Lipids, Lipoproteins, Apolipoproteins, and Glucose**

<table>
<thead>
<tr>
<th></th>
<th>Men (n=1,284)</th>
<th>Women (n=1,394)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( r^* )</td>
<td>( p )</td>
</tr>
<tr>
<td>Age</td>
<td>0.011</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.094</td>
<td>0.0007</td>
</tr>
<tr>
<td>Total cholesterol (corrected)†</td>
<td>-0.023</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.081</td>
<td>0.004</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>-0.022</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.153</td>
<td>0.0001</td>
</tr>
<tr>
<td>LDL cholesterol (corrected)†</td>
<td>0.036</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.009</td>
<td>NS</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>-0.006</td>
<td>NS</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Apolipoprotein B (corrected)‡</td>
<td>-0.066</td>
<td>0.05</td>
</tr>
<tr>
<td>Glucose</td>
<td>-0.050</td>
<td>NS</td>
</tr>
</tbody>
</table>

VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; Lp(a), lipoprotein(a).

*Pearson correlation coefficient.
†Corrected for contribution of Lp(a) cholesterol.
‡Corrected for contribution of Lp(a) apolipoprotein B.
study were entirely due to the contribution of Lp(a) cholesterol to the LDL fraction, as shown by the lack of significant correlations after total cholesterol and LDL cholesterol levels were corrected for Lp(a) cholesterol.

The reason for the slight but significant inverse association between Lp(a) and plasma triglyceride levels in the Framingham Offspring Study is not known. Accumulating evidence shows that plasma triglycerides may play an important role in Lp(a) metabolism. It has been reported that in the postprandial state, a higher proportion of Lp(a) is found in the triglyceride-rich lipoprotein fraction, and more large triglyceride-rich apo(a)-containing particles may be synthesized in the fed state than in the fasting state. As indicated by McConathy et al, the antigenic determinants of apo(a) in the triglyceride-rich Lp(a) particles in hypertriglyceridemic subjects may be partially masked, resulting in lower measurable Lp(a) values. However, triglyceride concentrations up to 500 mg/dL do not interfere with the Lp(a) measurement in this assay. To rule out any triglyceride effect, we excluded subjects with triglyceride values of more than 500 mg/dL from the analyses, and the inverse correlation between Lp(a) and triglycerides remained statistically significant. A recent study reported that only about 4% of the total plasma apo(a) was found in the VLDL fraction of normal subjects in the fasted state. The modest inverse correlation between Lp(a) and triglyceride levels could be due to the fact that apo(a) can be found in a variety of apo B-100-containing lipoproteins and that when it is present on triglyceride-rich lipoproteins, it can be catabolized more rapidly than when it is on regular Lp(a).

Lp(a) levels are relatively unaffected by changes in diet and by most of the medications currently used to treat hypercholesterolemia, with the exception of niacin. Medications routinely used to treat metabolic disorders such as diabetes, hypertension, and thyroid dysfunction are known to have an effect on lipid metabolism. There was no association in our population between use of these agents and plasma levels of Lp(a). There also was no correlation of Lp(a) with BMI, although the latter is a strong determinant of other plasma lipoproteins. These results support the concept that Lp(a) metabolism is largely independent of that of other lipoproteins.

At present, the data on the effects of alcohol on Lp(a) are limited and inconclusive. For example, the authors of one study proposed that moderate ethanol intake may lead to an increase in Lp(a), whereas other investigators reported a significant increase in plasma Lp(a) concentrations in alcoholic men during a 4-day period of abstinence. In contrast to both of these reports, we saw no association between alcohol consumption and plasma concentrations of Lp(a).

Several studies have suggested that Lp(a) may be subject to hormonal control. Lp(a) levels have been shown to fluctuate in pregnant women and return to basal values post partum. Studies in postmenopausal women on estrogen, progesterone, or estrogen-progesterone treatment report 16–50% decreases in Lp(a) levels. Albers et al reported a 65% reduction in plasma Lp(a) concentrations in postmenopausal women after treatment with stanazolol, an anabolic steroid structurally related to testosterone, and postmenopausal women treated with danazol showed a 78% decrease in Lp(a) levels. Furthermore, estrogen therapy in a man with familial hypercholesterolemia and in men with prostatic cancer resulted in significant decreases (80% and 50%, respectively) in Lp(a) concentrations. Men who were orchiectomized experienced a 20% reduction in Lp(a), and the authors suggest that testosterone, in addition to estrogen, may have a lowering effect on Lp(a). The effect of menopausal status on Lp(a) levels remains unclear. The fact that we saw no difference between age-adjusted premenopausal and postmenopausal women or between age-matched women off and on estrogen appears to contradict those of several studies. This discrepancy may be partially explained by the fact that only a cross-sectional examination of Lp(a) levels was possible in our population, whereas most of the observations in other studies were based on before-and-after-treatment measurements of Lp(a) in the same individuals.

It is not known whether hormones affect plasma Lp(a) levels through modification in synthesis or catabolism of Lp(a) particles. A fraction of Lp(a) may be catabolized via the LDL fraction through recognition of the apo B-100 present in the particle by the receptor. It has been shown that estrogen administration increases the expression of the LDL receptors on hepatic cell membranes in mice and that overexpression of the LDL receptor in transgenic mice results in an accelerated catabolism of Lp(a). However, data showing that this process significantly contributes to Lp(a) catabolism in humans have not been reported.

Vascular injury and thrombus formation are important mechanisms in the pathogenesis of the initiation and progression of atherosclerotic lesions as well as in the manifestation of acute coronary syndromes. It has been shown that Lp(a), by virtue of its homology to plasminogen, may compete with plasminogen in many steps of the fibrinolytic cascade. In fact, Lp(a) may compete with plasminogen for the binding to plasminogen receptors on the endothelium surface and consequently inhibit the activation of plasminogen. Lp(a) can also compete with plasminogen for the binding to fibrin. It is very likely that increased plasma levels of Lp(a) interfere with the process of fibrinolytic degradation of blood clots, promoting progression of atherosclerotic lesions. Thus, it is important to set ranges for normal and elevated levels of this lipoprotein. In this study, we used an ELISA to define normal ranges in participants in the Framingham Offspring Study. According to our data, Lp(a) levels of more than 38 mg/dL are above the 90th percentile in men and women.
have previously shown that approximately 19% of subjects with CAD have Lp(a) levels above this level. Moderately elevated Lp(a) levels (22–38 mg/dL) are between the 75th and 90th percentiles. Further research is needed to evaluate the risk attributable to Lp(a) levels in this range.

Acknowledgment

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