Tamoxifen and Estrogen Lower Circulating Lipoprotein(a) Concentrations in Healthy Postmenopausal Women


Abstract Data in the literature suggest that circulating levels of lipoprotein(a) [Lp(a)] and insulinlike growth factor I (IGF-I) respond similarly to therapy with growth hormone, estrogen, or tamoxifen. To more clearly document these relations, we designed a randomized, double-blind, placebo-controlled study of the effects of tamoxifen and continuous estrogen on circulating levels of Lp(a), IGF-I, and IGF binding protein 3 (IGFBP-3) in healthy postmenopausal women. Both estrogen and tamoxifen decreased serum levels of IGF-I to 30% below baseline during the 3 months of treatment, while IGFBP-3 levels were unchanged. Plasma Lp(a) levels decreased to 24% below baseline after 1 month of treatment with either estrogen or tamoxifen (P<.05 for estrogen only); after 3 months Lp(a) decreased to 34% below baseline with tamoxifen therapy (P<.05) but returned to only 16% below baseline with estrogen. The correlation between Lp(a) and IGF-I was highly significant (P<.0001). We conclude that (1) tamoxifen lowers plasma Lp(a) levels in healthy postmenopausal women, (2) the suppressive effects of tamoxifen and estrogen on circulating Lp(a) concentration diverge after the first month of therapy, and (3) circulating levels of Lp(a) and IGF-I are strongly correlated with each other, an indication that they may share regulatory influences. (Arterioscler Thromb. 1994;14:1586-1593.)

Key Words: lipoprotein(a) • insulinlike growth factor I • estrogen replacement therapy • tamoxifen • menopause

Circulating concentration of lipoprotein(a) [Lp(a)] has been positively correlated with the incidence of coronary artery disease,1 restenosis of coronary angioplasty,2 vein graft stenosis after coronary artery bypass surgery,3 and stroke.4 The structure of Lp(a) consists of a low-density lipoprotein (LDL)-like particle, with a novel protein [apolipoprotein(a), or apo(a)] that is disulfide-linked to the apo B-100 moiety of the lipoprotein. The structure of the apo(a) gene is strikingly homologous to that of plasminogen, although there is a deletion of kringles 1 to 3 and a large number of tandem repeats of the kringle 4-like domain.5 However, unlike plasmin, the derivative of plasminogen, Lp(a) does not appear to demonstrate proteolytic activity that could influence fibrinolysis.6 Details of the metabolic regulation of plasma Lp(a) level are only partially understood. A major part of the variability in circulating Lp(a) level is determined by the size of the apo(a) isoform, with serum concentration being inversely correlated with apo(a) molecular weight.7 In general, plasma levels seem to be determined by the rate of secretion and not by the catabolic rate.8

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The lack of knowledge about the metabolic regulation of Lp(a) has hampered efforts to develop adequate therapy for lowering serum levels of the lipoprotein. Niacin and neomycin have been used to lower Lp(a) level,9 and they are the only lipid-lowering drugs that have significant effects on Lp(a) in humans. Data from a number of small trials suggest that several steroid hormones decrease Lp(a) level; among these are estrogen,10-11 estrogen plus progestagen,12 the anabolic steroids stanozolol13 and danazol,14 and progestagen alone.15 We recently found that the competitive partial estrogen receptor antagonist tamoxifen also lowers Lp(a) levels in women with breast cancer16 and in men with heart disease and high Lp(a) levels.17

In contrast to administration of these steroid hormone derivatives, therapy with growth hormone has been noted by two groups to dramatically increase plasma Lp(a) concentration.18,19 Growth hormone also raises the plasma level of insulinlike growth factor I (IGF-I), one mediator of its action.20 Conversely, estrogen and tamoxifen both lower circulating IGF-I concentration.21-25 Therefore, studying the effect of tamoxifen and estrogen on both Lp(a) and IGF-I might help elucidate the regulatory mechanisms involved in hepatic secretion of the latter two.

We report here the results of a randomized, double-blind, placebo-controlled trial comparing the effects of unopposed estrogen and tamoxifen on levels of plasma lipids, Lp(a), IGF-I, and IGF binding protein 3 (IGFBP-3), the largest, most abundant, and most growth hormone-dependent circulating IGFBP.

Methods

Subjects
Thirty-one healthy postmenopausal women were recruited from the community using newspaper advertisements and lists of women who had shown interest in past research studies.
Menopause was defined as either no menses for more than 1 year or a shorter duration of amenorrhea with levels of luteinizing hormone and follicle-stimulating hormone in the postmenopausal range. Exclusion criteria included therapy in the last 3 months with estrogen or with any medications that could affect lipid levels; malignancy; diabetes; renal or hepatic disease; untreated hyperthyroidism or hypothyroidism; or a fasting triglyceride level greater than 300 mg/dL. If a subject was taking thyroid replacement therapy, a normal thyroid stimulating hormone level was documented before she began the study. If a treatment needed to be altered, any changes were made at least 6 weeks before the subject’s entry into the study. All subjects were Caucasian.

**Experimental Protocol**

Informed consent was obtained during the first visit. At the second baseline visit, eligible subjects were randomly assigned to three double-blind treatment arms: a single daily dose of 0.625 mg estrogen (Premarin, from Ayerst); 20 mg tamoxifen (Nolvadex, from ICI Pharma); or placebo. Treatment was continued for 3 months and was followed by 3 months off treatment and then 2 weeks of treatment with 10 mg/d medroxyprogesterone (Provera, from Upjohn) for all three groups. Medroxyprogesterone was administered to eliminate any risk of uterine cancer in those receiving estrogen or tamoxifen but was given to all subjects to maintain the double-blind design. Blood was drawn with the subjects in the fasting state at both baseline time points, at intervals of 1 month during the treatment period, and after 3 months of recovery. At each visit, the subject’s weight, blood pressure, and pulse were recorded, the unused pills were counted, a new 1-month supply of pills was provided, and the subject was asked about any side effects or concurrent illnesses. The subjects were asked to fill out a 3-day dietary questionnaire at baseline, at the end of the treatment phase, and after the recovery phase.

The following were measured at each visit: plasma Lp(a) concentration and serum concentrations of apo B and A-I, cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, IGF-I, and IGFBP-3. In addition, serum chemistry panels were done and thyroid stimulating hormone was assayed at baseline, at the end of the experimental treatment, and after 3 months of recovery.

**Assays**

Samples for Lp(a), IGF-I, and IGFBP-3 were stored at −70°C. All other laboratory measurements were performed on fresh samples.

Lp(a) was measured using an enzyme-linked immunosorbent assay that used a trapping antibody specific for apo(a) and a detection antibody specific for apo B (from Organon Teknika, Biotechnology Research Institute). All samples from a given patient were assessed in triplicate during a single assay run. The median of these values was used for data analysis. The interassay coefficient of variation for Lp(a) was 7.3% and the intra-assay coefficient of variation was 10.6%. Lp(a) was assayed by radioimmunoassay (RIA) after a two-step extraction method to remove the majority of serum IGFBPs. Conventional acid-ethanol extraction of serum IGF-I was followed by cryoprecipitation. With this method, almost all IGFBP-3 is precipitated and more than 90% of the other IGFBPs are also removed. RIA is then performed on the resulting supernatant using a polyclonal antibody to IGF-I. The interassay and intra-assay coefficients of variation were 9.7% and 2.6%, respectively.

IGFBP-3 was assayed by RIA using materials provided by Diagnostic Systems Laboratory. The interassay and intra-assay coefficients of variation were 8.1% and 4.6%, respectively.

All samples for IGF-I and IGFBP-3 from a given time point were run within a single assay. To compare values between time points for each subject, correction factors were used to eliminate differences between assay runs as a source of bias. Five IGFBP-3 samples and 8 to 12 IGF-I samples from each previous assay group were run on a single assay (one for IGFBP-3, one for IGF-I) to generate the correction factors used in the final analysis of the data.

Apo A-I and apo B were assayed using an immunonephelometric assay (Behring Diagnostics, Inc). Cholesterol, triglyceride, and HDL cholesterol levels were measured and 20-test chemistry panels were done using an automated chemistry analyzer (Kodak), and thyroid stimulating hormone was measured using an RIA (Hycor Biomedical Inc). LDL cholesterol values were calculated using the formula of Friedewald et al.

The 3-day dietary histories were assessed by a registered dietician using computer analysis (Nutritionist III, version 6.2, N-Squared Inc), and the daily intakes of calories and protein were tabulated.

**Statistics**

For each laboratory measurement, the two baseline values were averaged after paired Student’s t test failed to detect any significant difference between them. A group-by-time effect was evaluated using an ANOVA for repeated measures. If there was a significant group-by-time effect, pairwise comparisons were made using paired t tests (with Bonferroni corrections for multiple comparisons) to detect a difference between baseline and individual time points. Differences between treatment groups at baseline were assessed using one-way ANOVA with Tukey’s honestly significant difference test. Because Lp(a) values are not normally distributed in this population, these values were transformed with logarithms before analysis. A P<.05 was accepted as an indication of statistical significance.

Pearson’s product moment (r) for the relation between Lp(a) and IGF-I was calculated for each subject. To do a statistical analysis of these individual correlation coefficients as a group, we used a special function, Fisher’s inverse arctan transformation, that would cause the r values to become normally distributed. A one-sample t test was used to evaluate the hypothesis that this r was equal to zero and to construct a 95% confidence interval for the transformed correlation. One-way ANOVA was used to test the hypothesis of no difference in r values between groups, and then 95% confidence intervals were calculated for the transformed r for each group. These confidence intervals were then back-transformed to obtain 95% confidence interval estimates for the r values for each group.

**Results**

Three subjects dropped out of the study; one was from the placebo group and two were from the tamoxifen group. One subject in the tamoxifen group withdrew after 6 days of treatment, complaining of flushing, nausea, and headache. The other subject in the tamoxifen group withdrew because of a scheduling problem and did not return for her visit after 4 weeks of treatment. The subject from the placebo group withdrew after 25 days of treatment, complaining of headache, nausea, malaise, sweats, and hirsutism.

Differences in baseline weight between the three treatment groups were significant (P<.05). There was a trend toward lighter weight for the estrogen group compared with those randomly assigned to receive tamoxifen or placebo (mean±SEM, 60.6±2.6, 75.6±5.4, and 72.5±4.0 kg, respectively), but no significant differences were found using pairwise comparisons. Differences in age between the three treatment groups were also significant (P<.02); the tamoxifen group as a whole was significantly younger than either the estrogen or placebo group (P<.05; mean±SEM, 55.6±3.3, 64.6±1.6, and 64.6±1.8 years, respectively).
respectively). There were no statistically significant differences at baseline for plasma concentrations of Lp(a), apo A-I, or apo B or serum concentrations of cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, IGF-I, or IGFBP-3.

There were significant group-by-time effects for plasma concentrations of Lp(a) \((P=.005)\) and apo A-I \((P<.0002)\) and for serum concentrations of IGF-I \((P<.0001)\), cholesterol \((P=.015)\), LDL cholesterol \((P=.01)\), and HDL cholesterol \((P<.0001)\), whereas there were none for plasma levels of apo B; serum levels of triglyceride, IGFBP-3, or TSH; weight; and dietary intake of total kJ/kg or protein/kg (expressed on the basis of ideal body weight). No subject had abnormal values for serum liver enzymes, kidney function, or electrolytes.

Estrogen and tamoxifen therapies were both associated with a significant decrease in plasma Lp(a) concentration (Fig 1 and Table 1), although these effects had different time courses. Both therapies were associated with an initial decrease of 24% in plasma concentration of Lp(a) (this trend was only significant in the estrogen group; \(P=.016\)), but while the suppressive effect of estrogen on Lp(a) diminished over the subsequent 8 weeks of treatment, the suppressive effect of tamoxifen upon Lp(a) intensified. Thus, after 12 weeks of therapy, there was a significant 34% decrease in plasma concentration of Lp(a) in the tamoxifen group \((P=.032)\), while in the estrogen group plasma Lp(a) was no longer statistically different from baseline, with a 16% decrease.

Serum levels of IGF-I decreased significantly in both the estrogen and tamoxifen groups, while there was no effect in the placebo group (Fig 2 and Table 1). The circulating levels of IGF-I fell similarly in the two treatment groups by 4 weeks of treatment, remained at the same level over the next 8 weeks of treatment, and then returned to baseline after 12 weeks of treatment. In contrast, there was no significant change in serum levels of IGFBP-3 from baseline (Table 1).

Changes in serum concentration of IGF-I over time appeared to parallel those of Lp(a) in many subjects, primarily in members of the two treatment groups. Examples of this phenomenon in two subjects are shown in Fig 3. There was a significant correlation between

![Image of graph]

**Fig 1.** Line graph of mean percent change from baseline of plasma lipoprotein(a) [Lp(a)] concentration versus time in healthy postmenopausal women taking continuous estrogen (open circles), tamoxifen (open triangles), or placebo (solid circles) for 12 weeks, followed by 12 weeks of recovery. Error bars represent SEM, and shaded box represents period of treatment.

![Image of graph]

**Fig 2.** Line graph of mean percent change from baseline of serum insulinlike growth factor I (IGF-I) concentration versus time in healthy postmenopausal women taking continuous estrogen (open circles), tamoxifen (open triangles), or placebo (solid circles) for 12 weeks, followed by 12 weeks of recovery. Error bars represent SEM, and shaded box represents period of treatment.

### TABLE 1. Mean (±SEM) Concentrations of Plasma Lp(a), Serum IGF-I, and IGFBP-3 at Baseline; During 12 Weeks of Treatment With Estrogen, Tamoxifen, or Placebo; and After 12 Weeks of Recovery In Healthy, Postmenopausal Women

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>4 Weeks</th>
<th>8 Weeks</th>
<th>12 Weeks</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a)* mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>19.4 (1.3)</td>
<td>14.4 (1.4)†</td>
<td>15.4 (1.4)†</td>
<td>15.7 (1.4)</td>
<td>18.4 (1.4)</td>
</tr>
<tr>
<td>T</td>
<td>8.9 (1.4)</td>
<td>6.4 (1.8)</td>
<td>5.8 (1.8)</td>
<td>5.5 (1.8)†</td>
<td>7.5 (1.8)</td>
</tr>
<tr>
<td>PL</td>
<td>11.2 (1.4)</td>
<td>10.3 (1.6)</td>
<td>10.9 (1.6)</td>
<td>10.5 (1.6)</td>
<td>10.2 (1.6)</td>
</tr>
<tr>
<td>IGF-I, nmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>18.89 (1.10)</td>
<td>13.97 (1.54)†</td>
<td>13.25 (1.47)†</td>
<td>14.20 (1.21)†</td>
<td>19.05 (1.74)</td>
</tr>
<tr>
<td>T</td>
<td>19.19 (1.70)</td>
<td>13.50 (2.30)†</td>
<td>13.75 (2.19)†</td>
<td>14.19 (2.24)†</td>
<td>19.67 (2.86)</td>
</tr>
<tr>
<td>PL</td>
<td>20.95 (1.62)</td>
<td>19.95 (2.53)</td>
<td>19.85 (2.24)</td>
<td>20.28 (2.52)</td>
<td>19.96 (1.70)</td>
</tr>
<tr>
<td>IGFBP-3, mg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>3.64 (0.13)</td>
<td>3.70 (0.26)</td>
<td>3.51 (0.26)</td>
<td>3.29 (0.19)</td>
<td>3.85 (0.20)</td>
</tr>
<tr>
<td>T</td>
<td>3.62 (0.16)</td>
<td>3.86 (0.28)</td>
<td>3.72 (0.23)</td>
<td>3.50 (0.16)</td>
<td>3.88 (0.21)</td>
</tr>
<tr>
<td>PL</td>
<td>3.90 (0.16)</td>
<td>4.06 (0.24)</td>
<td>3.88 (0.19)</td>
<td>3.53 (0.18)</td>
<td>3.94 (0.19)</td>
</tr>
</tbody>
</table>

Lp(a) indicates lipoprotein(a); IGF-I, insulinlike growth factor I; IGFBP-3, IGF binding protein 3; E, estrogen; T, tamoxifen; and PL, placebo.

* Geometric means and SEM shown.
† \(P<.05\) compared with baseline.
There were no significant differences from baseline in the serum LDL levels of the placebo group during the treatment phase for both the estrogen and tamoxifen groups. However, in the placebo group there was a markedly, albeit nonsignificantly, lower correlation between Lp(a) and IGF-I than was observed in the other two groups (see Table 2 for correlation coefficients and 95% confidence intervals).

Serum levels of both apo A-I and HDL cholesterol were significantly higher in the estrogen group during the treatment phase but were not significantly different from baseline in either the tamoxifen or the placebo group (Fig 4 and Table 3). Estrogen and tamoxifen therapies were associated with a suppression of serum cholesterol concentration throughout the treatment phases, and this effect was still present in the estrogen group after 12 weeks of recovery. The serum concentration of cholesterol was also significantly below baseline in the tamoxifen group (Fig 4 and Table 3). Estrogen and tamoxifen therapies were associated with a suppression of serum cholesterol concentration throughout the treatment phases, and this effect was still present in the estrogen group after 12 weeks of recovery. The serum concentration of cholesterol was also significantly below baseline in the tamoxifen group (Fig 4 and Table 3).

Levels of Lp(a) over time differed in the estrogen and tamoxifen groups: the Lp(a)-lowering effect of estrogen waned after the initial drop at 1 month, while that of tamoxifen intensified throughout the study until the therapy was discontinued. The mechanism underlying this new observation is unknown, but its possible relation to changes in circulating IGF-I is discussed below.

We found the effects of estrogen and tamoxifen on levels of circulating lipid to be similar to those seen in previous studies. Thus, in the estrogen group there was a significant rise in the serum concentrations of HDL cholesterol and apo A-I, along with a tendency toward elevated serum triglyceride levels, while in the tamoxifen group there were no changes in either. Although both serum LDL cholesterol and plasma Lp(a) concentrations dropped significantly during treatment with estrogen and tamoxifen, the repeated-measures ANOVA did not indicate a significant group-by-time effect for concentrations of plasma apo B. This stands in contrast to findings in other studies of decreases in apo B levels during tamoxifen and estrogen therapy. There was, however, a trend toward a decrease in apo B levels during tamoxifen and estrogen therapy.
TABLE 3. Mean (±SEM) Serum Levels of Lipids and Apoproteins at Baseline; During 12 Weeks of Treatment With Estrogen, Tamoxifen, or Placebo; and After 12 Weeks of Recovery In Healthy, Postmenopausal Women

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cholesterol, mmol/L</th>
<th>Triglyceride, mmol/L</th>
<th>HDL cholesterol, mmol/L</th>
<th>LDL cholesterol, mmol/L</th>
<th>Apo A-I, μmol/L</th>
<th>Apo B, μmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E</td>
<td>6.12 (0.22)</td>
<td>1.48 (0.31)</td>
<td>1.47 (0.10)</td>
<td>55.2 (2.0)</td>
<td>2.79 (0.16)</td>
</tr>
<tr>
<td></td>
<td>6.20 (0.15)*</td>
<td>5.27 (0.32)*</td>
<td>1.39 (0.28)</td>
<td>1.71 (0.10)*</td>
<td>64.5 (2.3)*</td>
<td>2.54 (0.13)</td>
</tr>
<tr>
<td></td>
<td>6.33 (0.22)*</td>
<td>5.37 (0.33)*</td>
<td>1.64 (0.47)</td>
<td>1.65 (0.09)*</td>
<td>63.8 (2.9)*</td>
<td>2.63 (0.15)</td>
</tr>
<tr>
<td></td>
<td>6.36 (0.13)*</td>
<td>5.09 (0.24)*</td>
<td>1.32 (0.16)</td>
<td>1.76 (0.09)*</td>
<td>64.9 (2.9)*</td>
<td>2.61 (0.11)</td>
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<tr>
<td></td>
<td>6.41 (0.19)*</td>
<td>5.94 (0.36)</td>
<td>1.38 (0.18)</td>
<td>1.57 (0.09)*</td>
<td>52.4 (2.6)*</td>
<td>2.71 (0.13)</td>
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<tr>
<td></td>
<td>T</td>
<td>6.38 (0.28)</td>
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<td>1.52 (0.10)</td>
<td>4.81 (0.23)</td>
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<td>3.80 (0.19)*</td>
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<td>6.28 (0.33)</td>
<td>1.32 (0.16)</td>
<td>1.55 (0.15)</td>
<td>1.65 (0.09)*</td>
<td>3.85 (0.26)*</td>
<td>4.31 (0.26)*</td>
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<tr>
<td></td>
<td>6.20 (0.25)</td>
<td>1.41 (0.18)</td>
<td>1.47 (0.11)</td>
<td>1.76 (0.09)*</td>
<td>4.13 (0.18)</td>
<td>4.11 (0.21)</td>
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<td>2.61 (0.11)</td>
<td>1.47 (0.10)</td>
<td>1.76 (0.09)*</td>
<td>3.98 (0.18)*</td>
<td>4.34 (0.22)*</td>
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<tr>
<td></td>
<td>PL</td>
<td>52.4 (2.6)*</td>
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<td>59.0 (2.5)</td>
<td>52.4 (2.6)*</td>
<td>61.1 (3.0)</td>
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<td>1.65 (0.09)</td>
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<td>1.65 (0.09)</td>
<td>2.57 (0.21)</td>
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<tr>
<td></td>
<td></td>
<td>1.45 (0.08)</td>
<td>1.64 (0.47)</td>
<td>1.64 (0.47)</td>
<td>1.45 (0.08)</td>
<td>2.44 (0.08)</td>
</tr>
</tbody>
</table>

E indicates estrogen; T, tamoxifen; PL, placebo; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and apo, apolipoprotein. *P < .05 compared with baseline.

for both treatments in this study. Failure to detect a significant difference could have been due to small sample size.

Our data, showing significant decreases in serum IGF-I levels with both estrogen and tamoxifen therapies, are consistent with those of previous studies. Many systemic and local factors influence circulating levels of IGF-I; these include growth hormone status, age, sex, body composition, nutrition, thyroid hormone status, and insulin production. There were small differences in weight and age between the three treatment groups, but the magnitude of these differences would not be expected to cause significant differences in IGF-I concentrations. Indeed, the baseline concentrations of IGF-I for the three groups were very similar (Table 1). There was no effect of treatment on thyroid hormone status, and there were no significant differences in energy or protein intakes between the groups.

In addition to the systemic and local factors mentioned above, IGFBPs may affect assay values for IGF-I; they interfere with the RIA by binding to the radioligand, leading to considerably higher results for IGF-I. Because of the possibility that estrogen and tamoxifen might affect hepatic IGFBP synthesis, we chose an extraction method that removes nearly all of the IGFBPs from the serum and leads to >90% recovery of IGF-I. Therefore, induction of IGFBPs would not affect this assay for circulating IGF-I.

In this study, circulating levels of IGFBP-3 did not change with either estrogen or tamoxifen therapy. However, the RIA for IGFBP-3 probably detects both the native binding protein and its proteolytic fragments. Because pregnancy induces an IGFBP-3-specific serine protease that in turn induces breakdown of binding protein (thereby also freeing IGF-I), it is logical to assume that estrogen, tamoxifen, or both could induce a similar phenomenon—an effect that would not be detectable with the methods used in this study. Given that various IGFBPs regulate IGF-I action in vivo, data on intact IGFBPs will be necessary for interpretation of the biological implications of changes in circulating IGF-I levels.

Several findings from our study can be put in the context of the known physiology of the somatotroph axis. IGF-I is secreted by the liver in response to growth hormone. The resultant rise in IGF-I exerts a negative feedback on growth hormone release, in part through its stimulation of hypothalamic somatostatin release. Estrogen therapy suppresses hepatic IGF-I secretion and increases spontaneous and exercise-induced growth hormone levels. Although loss of negative feedback by IGF-I could be one of the mechanisms of this increase in circulating growth hormone, a pituitary stimulus by estrogen may also be involved. Tamoxifen therapy also suppresses IGF-I secretion, but Pollak and coworkers (Tannenbaum et al) have demonstrated in rats that, in contrast to estrogen, tamoxifen attenuates pituitary growth hormone secretion by stimulating endogenous release of somatostatin.

The differing effects of tamoxifen and estrogen on growth hormone secretion could explain the difference in plasma Lp(a) concentrations with these two therapies. Lp(a) is also secreted by the liver, and circulating levels of Lp(a) increase markedly with growth hormone administration. There is, to date, no known feedback exerted by Lp(a) on pituitary growth hormone secretion. We found that continuous estrogen therapy lowered plasma Lp(a) levels after 1 month of therapy.
but was associated with a subsequent rise during the second and third months of therapy. With tamoxifen therapy $\text{Lp}(a)$ fell progressively throughout the 3 months. We hypothesize that a secondary rise in growth hormone secretion caused by estrogen therapy could cause the late increase in plasma $\text{Lp}(a)$ concentration. A lack of growth hormone elevation with tamoxifen therapy could account for the continued suppression of circulating $\text{Lp}(a)$ levels during treatment. Assessing growth hormone serum concentration was beyond the scope of this study, as it would have required frequent sampling over a 24-hour period to compensate for the great variability in concentration.

It is notable that there was a significant correlation between circulating concentrations of $\text{Lp}(a)$ and IGF-I. This is, to our knowledge, the first documentation of such a relationship. One would expect that the relation of IGF-I to $\text{Lp}(a)$ would be seen with other drugs that lower $\text{Lp}(a)$, and we have preliminary evidence that IGF-I and $\text{Lp}(a)$ concentrations mirror each other during niacin therapy. However, although tamoxifen and estrogen had different effects on plasma $\text{Lp}(a)$ concentration after the initial month of treatment in this study, it must be pointed out that their effects on serum IGF-I concentration were nearly identical, inducing stable suppression throughout the treatment phase. Also, the correlation between $\text{Lp}(a)$ and IGF-I was markedly stronger in the subjects receiving either estrogen or tamoxifen than in those receiving placebo, although the differences between the groups were of only borderline significance ($P=.062$). Thus, while $\text{Lp}(a)$ and IGF-I clearly have similar responses to several agents, there are differences suggesting that the relation between the regulatory mechanisms that ultimately govern their circulating concentrations is complex. In particular, it is not possible to tell from our data whether IGF-I secretion and $\text{Lp}(a)$ secretion are both regulated by growth hormone and estrogen, whether IGF-I and $\text{Lp}(a)$ might also affect each other's secretion, or whether they may only be correlated at all when there are major changes in growth hormone or estrogen levels. Further study is needed in this area.

$\text{Lp}(a)$ has recently been shown to be related to the metabolism of another growth factor, tumor growth factor-$\beta$ (TGF-$\beta$), which is a major inhibitor of proliferation for many types of cells, including vascular smooth muscle cells. Lawn and colleagues have recently shown that $\text{Lp}(a)$ competitively inhibits the action of plasmin to activate TGF-$\beta$. Thus, we speculate that in, for example, the arterial wall, estrogen and tamoxifen could have a major effect on the stimulation of cell proliferation through two mechanisms: (1) the suppression of circulating IGF-I levels and (2) the suppression of $\text{Lp}(a)$, which acts as a competitive inhibitor of TGF-$\beta$. Such effects of estrogen and tamoxifen on cell proliferation would have important implications for these agents' effects on atherosclerosis.

IGF-I is thought to be passed through endothelial cells and into the subendothelial space, in much the same manner as insulin. There are preliminary data to suggest that IGFBP-3 binds to heparin as well as to cultured endothelial cells (the surface of which have proteoglycans dominated by heparan sulfate and heparinlike glycosaminoglycans). The extracellular matrix of the atherosclerotic arterial intima has long been known to contain a complex mixture of glycosaminoglycans, including heparan sulfate. Thus, IGFBP-3 could potentially localize IGF-I in and around atherosclerotic lesions. IGF-I expression is increased in vascular smooth muscle after balloon denudation in the rat. The full expression of the mitogenic effects of platelet-derived growth factor (PDGF) in vitro is dependent on the presence of IGF-I. PDGF is produced by macrophages in all phases of atherosclerosis and is thought to be one of the principal growth-regulatory molecules supporting this disease process. We are unaware of any evidence that estrogen or tamoxifen alters the expression of IGF-I in the cells of the arterial wall, but tamoxifen has been observed to lower IGF-I mRNA in liver and lung metastases of breast cancer in a rat model. Thus, IGF-I has multiple mechanisms by which it could gain access to, and modify the physiology of, atherosclerotic lesions.

A comparison of the effects of estrogen and tamoxifen on the plasma and serum components measured in this study illustrates that tamoxifen is not a pure estrogen receptor antagonist but rather a partial competitive antagonist. It is perhaps all the more notable that not only does tamoxifen parallel estrogen in its ability to diminish the risk of osteoporosis, but it also appears to do so in its ability to reduce the risk of sudden death from myocardial infarction. Inasmuch as lipid effects explain only a fraction of the cardioprotective effects of estrogen, we propose that a coordinated decrease in stimuli for cell proliferation might function as an additional mechanism shared by estrogen and tamoxifen by which they could inhibit the atherosclerotic process.

In summary, we found that both tamoxifen and unopposed estrogen therapies lower circulating levels of $\text{Lp}(a)$ in healthy postmenopausal women. However, the effects of these two drugs diverge after the first 4 weeks, as plasma $\text{Lp}(a)$ concentrations return toward baseline with estrogen therapy but continue to drop throughout the 12-week treatment period in the group given tamoxifen. Furthermore, we demonstrated that circulating levels of IGF-I and $\text{Lp}(a)$ are highly correlated with each other, particularly during treatment with estrogen or tamoxifen. These observations complement the recently published findings that growth hormone administration causes plasma $\text{Lp}(a)$ concentrations to increase along with circulating IGF-I levels.

We speculate that the regulation of plasma $\text{Lp}(a)$ concentration is linked to that of IGF-I, in both its response to stimuli such as growth hormone and its suppression by estrogen and tamoxifen. Given the reported role of $\text{Lp}(a)$ in suppressing TGF-$\beta$ activation, we further speculate that $\text{Lp}(a)$ may function as the second messenger for growth hormone: while IGF-I mediates a growth-promoting response to growth hormone, $\text{Lp}(a)$ might mediate a loss of growth inhibition.

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