Relation Between Sex Hormones and Serum Lipoprotein and Lipoprotein(a) Concentrations in Premenopausal Obese Women

Giovanni De Pergola, Francesco Giorgino, Maria Rosaria Cospite, Vito Angelo Giagulli, Mauro Cignarelli, Giovanni Ferri, and Riccardo Giorgino

Lipoprotein(a) (Lp[a]) is generally considered to be a risk factor for the development of cardiovascular disease, but little is known about the possible influence of obesity on the circulating levels of this lipoprotein. The present study was undertaken to examine this aspect in 136 menstrually active women by comparing the serum concentrations of Lp(a) between 72 obese and 64 age-matched nonobese women.

Since an adverse effect of androgens and a protective effect of estrogens have been described for plasma lipoprotein profiles in obese women, the relation between the circulating levels of Lp(a) and those of several other hormones was also investigated in obese patients. In addition, other lipoproteins, anthropometric parameters (body mass index and waist-to-hip ratio), and insulin were evaluated. The levels of Lp(a) were not significantly different (Mann-Whitney U test, \( \chi^2 \), 3.55; \( p=0.0582 \) [NS]) between obese (rank sum, 5,367) and control (rank sum, 3,949) women; in addition, the percentage of patients with high Lp(a) levels (cutoff defined at 30 mg/dL) did not differ between the two groups (obese women, 30%; control, 21.8%; \( \chi^2 \), 0.96; two-sided \( p=0.341 \) [NS]). Moreover, no correlation was found between Lp(a) and body mass index. Lastly, when the Lp(a) prevalence odds ratio for obesity was examined by adjusting the levels of this lipoprotein for age, triglycerides, total cholesterol, and high density lipoprotein cholesterol, the probability value (0.88) was far from significant. In obese women, no correlation was found between the logarithmically transformed Lp(a) concentrations and all the other variables evaluated in the study. In conclusion, the present study shows that the circulating levels of Lp(a) are not influenced by body weight and cardiovascular risk factors commonly associated with obesity, such as enhanced androgenic activity, hyperinsulinemia, adverse lipoprotein profile, and abdominal fat accumulation. (Arteriosclerosis and Thrombosis 1993;13:675-679)

KEY WORDS • lipoprotein(a) • obesity • body fat distribution • androgens • insulin

ipoprotein(a) (Lp[a]) is a cholesterol-rich plasma lipoprotein that consists of an apoprotein (apo a) attached to the apoprotein B of low density lipoprotein particles by disulfide bonds.\(^1\) It is synthetized by the liver\(^2\) and secreted directly into the systemic circulation.\(^1\) Lp(a) is considered to be a risk factor for the development of cardiovascular diseases. In fact, plasma Lp(a) concentrations >30 mg/dL seem to be strongly associated with an increased risk of developing premature coronary heart disease or cerebral thrombosis.\(^3,4\) and Lp(a) levels in an individual remain remarkably constant.\(^5\) However, although Lp(a) is present in all humans, it can be undetectable in some subjects ("operational null allele").\(^2\)

Lp(a) is generally considered to be an independent risk factor because it is apparently not affected by sex,\(^6\) diet,\(^7\) anthropometric variables (e.g., body mass index [BMI], waist-to-hip ratio [WHR], and skinfold thickness),\(^8\) glycemia,\(^8,9\) exercise,\(^10\) estrogens,\(^10\) or other well-known risk factors for atherosclerosis.\(^8,10\) On the other hand, Lp(a) concentrations seem to be influenced by other variables such as race,\(^1,11\) age,\(^6,12\) fish oil intake,\(^13\) certain drugs (e.g., stanozolol,\(^14\) niacin and neomycin,\(^15\) nicotinic acid,\(^16\) and androgenic progestogens\(^17\)), pregnancy,\(^18\) proteinuria,\(^9,19\), impaired glucose tolerance,\(^20\) and type I and type II diabetes.\(^21,22\)

In women, an adverse plasma lipoprotein profile associated with hyperandrogenism has been found.\(^23-28\) It is noteworthy that in abdominal adipocytes, testosterone promotes cell enlargement and enhances the lipolytic response to catecholamines.\(^29-31\) Since most of the perivisceral abdominal fat is drained by the portal vein,\(^32\) an increase of circulating free testosterone, as has been described in obese women with abdominal fat accumulation,\(^26,33\) may result in elevated portal free fatty acid concentrations that in turn may alter the metabolism of lipoproteins in the liver.\(^24\) Interestingly, no information is available about the prevalence of high Lp(a) levels in obese women as well as about the possible adverse effects of androgens on Lp(a) levels in women.

Therefore, the purpose of the present study was to verify the presence of an association between Lp(a) and...
TABLE 1. Anthropometric and Hormonal Data for Nonobese Control and Obese Premenopausal Women

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Obese</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.82±8.01</td>
<td>28.33±8.89</td>
<td>NS</td>
</tr>
<tr>
<td>(n=64)</td>
<td>(n=72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.71±2.25</td>
<td>37.58±8.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=64)</td>
<td>(n=72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHR</td>
<td>0.75±0.05</td>
<td>0.90±0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=22)</td>
<td>(n=72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>8.73±2.05</td>
<td>17.91±7.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=22)</td>
<td>(n=67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total testosterone (ng/mL)</td>
<td>0.52±0.11</td>
<td>0.73±0.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(n=67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHBG (ng/mL)</td>
<td>3.80±0.54</td>
<td>1.92±0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(n=67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free testosterone (pg/mL)</td>
<td>1.10±0.37</td>
<td>2.44±1.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(n=67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHEAS (ng/mL)</td>
<td>2.229±634</td>
<td>2.358±1.270</td>
<td>NS</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(n=67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androstenedione (ng/mL)</td>
<td>1.43±0.53</td>
<td>2.4±1.36</td>
<td>&lt;0.020</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(n=67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH (ng/mL)</td>
<td>2.82±0.63</td>
<td>3.69±1.83</td>
<td>NS</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(n=67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH (ng/mL)</td>
<td>5.15±0.77</td>
<td>5.02±1.42</td>
<td>NS</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(n=67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>50.80±10.5</td>
<td>42.35±34.9</td>
<td>NS</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(n=67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrone (pg/mL)</td>
<td>42.50±9.60</td>
<td>77.30±39.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(n=46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRL (ng/mL)</td>
<td>13.54±3.12</td>
<td>11.42±4.58</td>
<td>NS</td>
</tr>
<tr>
<td>(n=16)</td>
<td>(n=67)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD. BMI, body mass index; WHR, waist-to-hip ratio; SHBG, sex hormone binding globulin; DHEAS, dehydroepiandrosterone sulfate; PRL, prolactin; LH, luteinizing hormone; FSH, follicle stimulating hormone.

obesity and to investigate the relation between Lp(a) and the androgenic status in premenopausal obese women. Moreover, to study the possible relations of Lp(a) with other metabolic and hormonal variables in obese women, lipoproteins and anthropometric (BMI and WHR) and hormonal (insulin and estrogens) parameters were measured.

Methods

The current study included 72 menstrually active obese women (BMI >28 kg/m²) and 64 age-matched nonobese women. All subjects gave informed consent to the study. Fat distribution was evaluated by WHR, as previously described.33 All patients had normal glucose tolerance according to World Health Organization criteria35 and normal thyroid, liver, and kidney function. None of the patients was pregnant or receiving oral contraceptives or other drug therapies. The subjects under study did not smoke or perform any competitive sport activity. Subjects with other signs or a positive history for cardiovascular disease and subjects with hypertension or electrocardiographic abnormalities were excluded. The presence of acanthosis nigricans, polycystic ovary syndrome,36 or congenital adrenal hyperplasia (21-hydroxylase deficiency)37 was excluded in the subjects because they had normal serum levels of prolactin (PRL), gonadotropins (follicle stimulating hormone [FSH] and luteinizing hormone [LH]), and 17-hydroxyprogesterone. All patients maintained their usual diets. Blood samples for hormonal and metabolic determinations were drawn after an overnight fast on days 5–7 of the menstrual cycle between 8 and 9 AM. Blood pressure was measured on three separate occasions using a mercury sphygmomanometer with an appropriately sized cuff. Blood glucose was determined by the glucose oxidase method (Sclavo, Siena, Italy). Total cholesterol (TC), triglycerides (TGs), and high density lipoprotein cholesterol (HDL-C) were measured using enzymatic assays (Boehringer Mannheim GmbH Diagnostica, Mannheim, FRG). Apoprotein(a) levels were determined by radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden) as previously reported byWiklund et al.38 The sensitivity of this assay was 3 mg/dL; values below that limit were recorded as 2.9 mg/dL.

Most of the hormones (FSH, LH, PRL, total testosterone, free testosterone, androstenedione, dehydroepiandrosterone sulfate [DHEAS], estradiol, estrone, 17-hydroxyprogesterone, and sex hormone binding globulin [SHBG]) were measured in the serum by
TABLE 2. Lipoprotein Profile for Nonobese Control and Obese Premenopausal Women

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Obese</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a) (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>21.87±24.53</td>
<td>28.37±30.97</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>12.02</td>
<td>16.73</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>2.9–112.6</td>
<td>2.9–182.4</td>
<td></td>
</tr>
<tr>
<td>n=64</td>
<td>(n=72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \chi^2 )</td>
<td>3.59</td>
<td>0.058</td>
<td></td>
</tr>
<tr>
<td>TGs (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>72.74±25.29</td>
<td>104.25±52.9</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>68.5</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>38–144</td>
<td>40–280</td>
<td></td>
</tr>
<tr>
<td>n=64</td>
<td>(n=64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \chi^2 )</td>
<td>16.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>1.41±0.35</td>
<td>1.03±0.20</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.44</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.88–2.03</td>
<td>0.71–1.66</td>
<td></td>
</tr>
<tr>
<td>n=64</td>
<td>(n=64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>7.25±1.72</td>
<td>11.5±0.20</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7.25</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>7.1–12.2</td>
<td>11.0–12.0</td>
<td></td>
</tr>
<tr>
<td>n=64</td>
<td>(n=64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \chi^2 )</td>
<td>20.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Lp(a), lipoprotein(a); TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; TC, total cholesterol.

radioimmunological methods using commercially available kits. Both intra-assay and interassay coefficients of variation in all of the above methods were <7.5%.

TABLE 3. Correlation Coefficients Between Log Lp(a) and the Various Parameters in the Obese Group

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>72</td>
<td>0.184</td>
</tr>
<tr>
<td>Log HDL-C</td>
<td>72</td>
<td>0.080</td>
</tr>
<tr>
<td>Log TGs</td>
<td>72</td>
<td>-0.161</td>
</tr>
<tr>
<td>Age</td>
<td>72</td>
<td>0.230</td>
</tr>
<tr>
<td>BMI</td>
<td>72</td>
<td>0.084</td>
</tr>
<tr>
<td>WHR</td>
<td>72</td>
<td>0.072</td>
</tr>
<tr>
<td>Insulin</td>
<td>67</td>
<td>0.059</td>
</tr>
<tr>
<td>DHEAS</td>
<td>67</td>
<td>0.131</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>67</td>
<td>-0.060</td>
</tr>
<tr>
<td>Total testosterone</td>
<td>67</td>
<td>-0.209</td>
</tr>
<tr>
<td>Free testosterone</td>
<td>67</td>
<td>0.003</td>
</tr>
<tr>
<td>Log estradiol</td>
<td>67</td>
<td>-0.157</td>
</tr>
<tr>
<td>Log estrone</td>
<td>46</td>
<td>-0.138</td>
</tr>
<tr>
<td>SHBG</td>
<td>67</td>
<td>0.079</td>
</tr>
<tr>
<td>LH</td>
<td>67</td>
<td>-0.088</td>
</tr>
<tr>
<td>FSH</td>
<td>67</td>
<td>-0.100</td>
</tr>
<tr>
<td>PRL</td>
<td>67</td>
<td>0.006</td>
</tr>
</tbody>
</table>

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TABLE 4. Prevalence Odds Ratio for Obesity After Correction for Lipoproteins and Age

<table>
<thead>
<tr>
<th>B</th>
<th>POR</th>
<th>Lower 95% CL</th>
<th>Upper 95% CL</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a)</td>
<td>0.0780</td>
<td>1.081</td>
<td>0.390</td>
<td>2.998</td>
</tr>
<tr>
<td>TGs</td>
<td>0.4912</td>
<td>1.634</td>
<td>0.678</td>
<td>3.941</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-2.2919</td>
<td>0.101</td>
<td>0.041</td>
<td>0.247</td>
</tr>
<tr>
<td>TC</td>
<td>1.1024</td>
<td>3.011</td>
<td>1.226</td>
<td>7.398</td>
</tr>
<tr>
<td>Age</td>
<td>0.1399</td>
<td>1.150</td>
<td>0.457</td>
<td>2.896</td>
</tr>
</tbody>
</table>

Log likelihood, -65.94; \( \chi^2 \) 51.89; \( p<0.00000 \).
B, regression coefficient; POR, prevalence odds ratio; CL, confidence level; Lp(a), lipoprotein(a); TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; TC, total cholesterol.

General data for both obese and nonobese women (control group) are summarized in Tables 1 and 2.

Statistics

Univariate analysis was carried out to verify the shape of the frequency distribution, and a logarithmic transformation was performed for variables that were not normally distributed. A recode cutoff of all variables was also performed to obtain a transformation of the continuous distribution on a discrete scale. All data are presented as mean±SD except for Lp(a), TGs, and HDL-C (variables not normally distributed), which are shown as the median and range (Table 2). Significance of differences between the groups was determined by a two-tailed t test for normally distributed variables and by a nonparametric Mann-Whitney U test for variables that were not normally distributed (i.e., estradiol, estrone, Lp[a], TGs, and HDL-C). A correlation matrix was used to study the preliminary associations between variables. To assess the influence of each variable on the resulting associations, a logistic unconditioned regression model was built and tested. The prevalence odds ratio was used to evaluate the association of Lp(a) and other lipoproteins to obesity (Table 4). Values of \( p<0.05 \) were considered significant.

Results

Differences Between Groups

Lp(a). Lp(a) values showed a wide distribution in both groups (Table 2); five of 136 women had Lp(a)

TABLE 5. Significant Correlation Coefficients Between Lipoproteins and the Various Parameters in the Obese Group

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>HDL-C</th>
<th>Log TG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>0.331t</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.458t</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.279*</td>
<td>0.263*</td>
<td></td>
</tr>
<tr>
<td>WHR</td>
<td>0.304*</td>
<td>-0.259*</td>
<td>0.310t</td>
</tr>
<tr>
<td>Insulin</td>
<td>-0.401t</td>
<td>0.401t</td>
<td></td>
</tr>
<tr>
<td>Free testosterone</td>
<td>-0.312*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log estradiol</td>
<td>0.267*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log estrone</td>
<td>0.267*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHBG</td>
<td>0.275*</td>
<td>-0.341t</td>
<td></td>
</tr>
</tbody>
</table>

TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TGS, triglycerides; BMI, body mass index; WHR, waist-to-hip ratio; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone binding globulin; LH, luteinizing hormone; FSH, follicle stimulating hormone; PRL, prolactin.

\( p<0.05 \), \( t p<0.01 \), \( tp<0.001 \).
values <3 mg/dL and only two (obese) women showed values >100 mg/dL. Lp(a) did not show a significant relation with any of the tested metabolic lipoprotein, hormonal (androgens, insulin, and estrogens), or anthropometric (BMI and WHR) parameters in either the control (data not shown) or obese women (Table 3). By using the nonparametric Mann-Whitney U test, the levels of Lp(a) were not significantly different ($\chi^2; 3.59, p=0.0582$) between obese (rank sum, 5,367) and control (rank sum, 3,949) women. The percentage of patients with high Lp(a) levels (cutoff defined at 30 mg/dL) did not differ between the two groups (obese women, 22 of 72 [30%]; control nonobese women, 14 of 64 [21.8%]; $\chi^2, 0.90, p=0.341$ [NS]). When the Lp(a) prevalence odds ratio for obesity was examined by correcting the levels of this lipoprotein for age, TGs, TC, and HDL-C, the probability value was far from significant (Table 4).

**Pearson’s correlations of lipids and lipoproteins.** A significant positive correlation was found between TGs and insulin ($r=0.429, p<0.05$) in control women. Significant correlations in obese patients are shown in Table 5. When the prevalence odds ratio for obesity of lipids and lipoproteins was examined by correcting their levels for each other and for age, TC (positively) and HDL-C (negatively) were strongly associated with obesity (Table 4).

**Discussion**

In the present study serum Lp(a) levels were similar in obese and control women, and the percentage of patients with high levels of this lipoprotein (>30 mg/dL) was comparable between the two groups. Moreover, no correlation between Lp(a) and BMI was present, not even after correction of these two parameters for all of the variables associated with obesity (age and lipoproteins), and it is noteworthy that the association between Lp(a) and obesity in the multivariate analysis was far from significant (1.081; range, 0.390–2.998). These results suggest a lack of influence of obesity per se on Lp(a) gene expression. However, since TC (positively) and HDL-C (negatively) were shown to be strongly associated with obesity, the presence of high levels of Lp(a) in obese patients increases the cardiovascular risk to a higher extent than in normal-weight subjects.

We have also investigated a potential relation between abnormalities in lipoprotein metabolism and serum concentrations of androgens in obese patients. Lp(a) did not show any significant correlation with androgens as well as with estrogens, insulin, or WHR. Free testosterone showed a negative correlation with HDL-C levels, whereas SHBG was found to be directly related to HDL-C levels and inversely related to TGs. Similar findings have been reported by Longcope et al. in a group of premenopausal and perimenopausal women. A positive correlation between estradiol and HDL-C was observed in obese women. This finding is in line with the data of Tikkanen and Nikkila, who suggested a suppressive effect of this hormone on hepatic TG lipase.

Taken together, these data suggest that in premenopausal obese women, the increase of free testosterone alters the lipoprotein profile in an unfavorable way, whereas estrogens may play a protective role. In conclusion, in the current study the possible influence of obesity and related risk factors for cardiovascular diseases (increased androgenic activity, hyperinsulinemia, and abdominal fat accumulation) on the circulating levels of Lp(a) has been simultaneously examined in premenopausal women. Our data do not support a direct effect of these factors on Lp(a) concentrations but strongly suggest that the presence of high levels of Lp(a) is genetically independent of the presence of obesity and associated risk factors.

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