Gender Differences in Plasma Levels of Lipoprotein (a) in Patients with Angiographically Proven Coronary Artery Disease

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Summary
The objective of the study was to assess the association between plasma levels of lipoprotein(a) \([\text{Lp(a)}]\) and the presence of angiographically defined coronary artery disease (aCAD). Patients (346 men and 184 women) undergoing selective coronary angiography (SCA) were classified into groups with positive [aCAD(\(+\))] and negative [aCAD(\(–\))] findings and their age, body mass index (BMI), waist circumference, blood pressure, smoking, plasma total, LDL-, HDL-cholesterol (TC, LDL-C, HDL-C), triglycerides (TG), apolipoprotein B (apoB), \(\log(\text{TG/HDL-C})\) and \(\text{TC/HDL-C}\) were determined. Concentration of plasma \text{Lp(a)} was estimated using the commercial solid phase two-side immunoradiometric assay of apolipoprotein apo(a). The plasma \text{Lp(a)} was significantly higher in both women and men with aCAD(\(+\)) compared to those with aCAD(\(–\)). While there was no significant difference in the \text{Lp(a)} level between men and women with aCAD(\(–\)) (median 138 vs. 145 units/l), the women with aCAD(\(+\)) had almost twice as high \text{Lp(a)} levels as men (median 442 vs. 274 units/l, \(p<0.001\)). Women with aCAD(\(+\)) had also significantly lower HDL cholesterol levels (1.09 vs. 1.20 mmol/l, \(p<0.05\)), higher triglycerides (1.82 vs. 1.46 mmol/l, \(p<0.05\)) and \(\log(\text{TG/HDL-C})\) than women with aCAD(\(–\)). The differences in \text{Lp(a)} between positive and negative findings remained highly significant (\(p<0.001\) in women, \(p<0.05\) in men) after the adjustment for age, plasma HDL- and LDL-cholesterol and triglycerides in logistic regression analyses. In logistic regression model the \text{Lp(a)} and \(\log(\text{TG/HDL-C})\) and smoking in women but smoking and age in men were the most powerful predictors of positive aCAD findings. Our findings suggest that \text{Lp(a)} is more strongly associated with aCAD\(+\) in women than in men.

Key words
Lipoprotein(a) • Gender • Coronary artery disease • Coronary angiography • Immunoradiometric assay

Introduction
Lp(a) atherogenicity appears to be related to the mechanism of LDL entrapment in the atheroma (Lundstam et al. 1999), possibly to the initiation of the proteolytic process responsible for extracellular matrix degradation (Bdeir et al. 1999, Ganne et al. 1999) and to its competitive inhibition of plasminogen that impairs the thrombolytic processes (Soulat et al. 1999).

There is a significant correlation between the plasma concentration of Lp(a) and the extent of coronary artery disease (Dangas et al. 1999). In the Prevention Conference V Lp(a) was classified as a “conditional” risk factor for atherosclerosis (Smith et al. 2000) because of the fact that its significance as a risk factor increases in patients with LDL-C levels over 3 mmol/l (Brown et al. 1990, Cremer et al. 1994). Most of the Lp(a) studies have been carried out in men and the data in women are limited. However, the Framingham Heart Study found Lp(a), measured as sinking pre-beta lipoprotein on electrophoresis, to be a strong predictor of myocardial infarction, intermittent claudication, and cerebral vascular disease in women (Bostom et al. 1994). Another study has shown that Lp(a) was a significant risk factor for CAD in both pre- and postmenopausal women (Orth-Gomer et al. 1997).

In the present study, we investigated plasma Lp(a) levels in men and women (patients of Vancouver teaching hospitals) undergoing to selective coronary angiography to assess the associations between Lp(a) concentration and actual angiography findings in men and women.

Methods

Patients

Patients were recruited amongst individuals undergoing selective coronary angiography at two teaching hospitals in Vancouver (St. Paul’s and Vancouver General). Participants of the study were mostly of European background (there were no Afro-Americans). The indications for angiography included exercise-induced chest pain, previously diagnosed myocardial infarction, atypical chest pain, aortic stenosis/regurgitation and mitral regurgitation. Patients with unstable angina and myocardial infarction within the preceding two months were excluded from the study. More than 85 % of women in this study were in menopause. Among patients of both gender with positive SCA 20 % had diabetes.

All participants signed a consent form approved by the Ethics Committees of both hospitals and University of British Columbia. All patients were asked to fill in a questionnaire under a nurse’s or physician’s supervision. This included demographic data, history of vascular disease, family history and presence of major risk factors for CAD. Height, weight and abdominal circumference were measured at the same time.

 Coronary angiograms were obtained by the standard techniques with multiple aspects recorded and evaluated by the cardiologists. The angiograms were defined as to the number of vessels involved (0, 1, 2 or 3) and as to the severity of lesions, namely greater or smaller than 50% lumen obstruction. For the purpose of this study any angiograms without any positive findings were defined as “negative”.

Laboratory assays

Plasma lipids were measured after an overnight fasting in a venous blood sample collected into EDTA-containing vacutainers on the day of the angiogram. The blood was kept at 4 °C, spun within 12 h and aliquots of plasma were frozen at –70 °C until analyses carried out 3 years later. Plasma total cholesterol (TC), triglycerides (TG) and HDL-cholesterol (HDL-C) were measured enzymatically. LDL cholesterol (LDL-C) was calculated according to the Friedewald equation, apolipoprotein B (apoB) was measured nephelometrically (Beckman Array System). Lp(a) concentration was measured using a solid phase two-sided immunoradiometric assay (Mercordia apo(a) RIA, Mercodia AB, Uppsala, Sweden) of apolipoprotein apo(a). Lp(a) assay quality control was monitored by Canadian Reference Laboratory, the coefficient of variations was 12% and 12.5% at 130 and 350 IU/l, respectively.

Statistical analysis

Statistical package (SPSS Base11.0) was used to analyze the data. Multiple logistic regression analysis was used to discriminate between dependent and independent variables. Lp(a) data, because of their extreme skewness, were evaluated by the Mann-Whitney U test.

Results

Of the 184 women and 346 men in whom Lp(a) was measured, 136 women (mean age 64 years) and 297 men (61 years) had angiographic evidence of CAD (aCAD(+)), while 48 women (62 years) and 49 men (57 years) had no angiographic evidence of CAD.
[aCAD(−)]. As shown in Table 1, there were no significant differences between women with or without angiographic evidence of CAD in age, body mass index, concentration of total plasma cholesterol and apoB. Women with aCAD(+) had slightly higher triglycerides, LDL-cholesterol and lower HDL-cholesterol levels compared to aCAD(−), while the two groups of men differed in age only. There were several significant differences between men and women (Table 1). Women were older than men in both aCAD groups; plasma cholesterol, HDL- and LDL-cholesterol and apoB were higher in women compared to men with aCAD(+), while in those with aCAD(−) the only difference was in higher concentration of HDL-C in women.

Table 1. Characteristics of women and men with positive (aCAD+) and negative (aCAD−) angiography findings, lipid concentrations in mmol/l.

<table>
<thead>
<tr>
<th></th>
<th>WOMEN aCAD(+)</th>
<th>aCAD(−)</th>
<th>MEN aCAD(+)</th>
<th>aCAD(−)</th>
<th>WOMEN vs. MEN aCAD(+)</th>
<th>aCAD(−)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=136</td>
<td>n=48</td>
<td>n=297</td>
<td>n=49</td>
<td>P=</td>
<td>P=</td>
</tr>
<tr>
<td>Age</td>
<td>64.2±10.1</td>
<td>62.3±7.3</td>
<td>60.9±9.5</td>
<td>56.8±10.2</td>
<td>0.02</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>27.7±5.5</td>
<td>26.8±4.4</td>
<td>28.3±4.3</td>
<td>28.3±5.6</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>TC</td>
<td>5.52±1.11</td>
<td>5.28±1.09</td>
<td>5.06±0.99</td>
<td>5.08±1.07</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>TG</td>
<td>1.82±1.00</td>
<td>1.46±0.75</td>
<td>1.88±1.37</td>
<td>1.87±1.23</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>LDL-C</td>
<td>3.84±1.07</td>
<td>3.46±1.10</td>
<td>3.30±0.83</td>
<td>3.58±0.99</td>
<td>N.S.</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.09±0.29</td>
<td>1.20±0.35</td>
<td>0.92±0.22</td>
<td>0.92±0.25</td>
<td>N.S.</td>
<td>0.001</td>
</tr>
<tr>
<td>APOB</td>
<td>1.02±0.27</td>
<td>0.94±0.26</td>
<td>0.94±0.22</td>
<td>0.89±0.22</td>
<td>N.S.</td>
<td>0.001</td>
</tr>
<tr>
<td>Log(TG/HDL-C)</td>
<td>0.19±0.27</td>
<td>0.06±0.25</td>
<td>0.25±0.29</td>
<td>0.24±0.28</td>
<td>N.S.</td>
<td>0.036</td>
</tr>
<tr>
<td>TC/HDL/C</td>
<td>5.5±1.9</td>
<td>4.8±1.7</td>
<td>5.8±2.2</td>
<td>5.8±1.8</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

Fig. 1. Lipoprotein(a) (median values) of women and men with positive (aCAD+) and negative (aCAD−) angiography findings.

Most pronounced differences between aCAD(+) and aCAD(−) patients were found in plasma concentration of Lp(a). There was significantly higher plasma Lp(a) level (Fig. 1) in both women (median 442 units/l) and men (274 units/l) with aCAD(+) compared to those with aCAD(−) (141 and 148 units/l, respectively). However, median Lp(a) levels were significantly higher in women compared to men with aCAD(+) (p<0.001, Mann-Whitney U test). There was no significant difference in Lp(a) levels between men and women without angiographic evidence of CAD. The differences in Lp(a) between aCAD(+) and aCAD(−) remained significant (p<0.001 in women, p<0.05 in men) after the adjustment for age, plasma HDL- and LDL-cholesterol and triglycerides.

No associations between plasma Lp(a) and age, BMI, TC, TG, HDL-C and apoB (Table 2) were found in men. However, significant correlations were found between Lp(a) and plasma cholesterol, LDL cholesterol and apoB in women (Table 2). The correlation between Lp(a) and aCAD remained highly significant even after the adjustment for cholesterol in partial correlation analysis. There was no correlation between plasma Lp(a) level and diabetes or positive family history for CAD.

Table 3 shows the results of logistic regression analysis of the differences between aCAD(+) and aCAD(−) groups. In the multivariate logistic regression model, which included parameters such as age, BMI,
smoking, TC, TG, LDL-C, apoB, HDL-C, Lp(a), Log(TG/HDL-C) and TC/HDL-C, the most powerful predictors of aCAD(+) in women were Lp(a), Log(TG/HDL-C) and smoking, while in men the predictors were smoking and age.

Table 2. Pearson correlation analysis between Lp(a) and other parameters

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.141</td>
<td>0.060</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.016</td>
<td>-0.058</td>
</tr>
<tr>
<td>TC</td>
<td>0.211**</td>
<td>0.038</td>
</tr>
<tr>
<td>TG</td>
<td>-0.047</td>
<td>-0.042</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.267**</td>
<td>0.043</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.050</td>
<td>-0.097</td>
</tr>
<tr>
<td>APOB</td>
<td>0.242**</td>
<td>0.091</td>
</tr>
</tbody>
</table>

**Correlation is significant at the p<0.01 level (2-tailed).

Discussion

There is a prevailing consensus that Lp(a) is predictive of both the severity and extent of CAD (Budde et al. 1994, Weber et al. 1997, Wilson et al. 1999) in a number of different populations including Blacks and Whites (Guyton et al. 1985, Marcovina and Koschinski 2000, Paultre et al. 2000). On the other hand, several studies including the Quebec Cardiovascular Study in men (Cantin et al. 1998), other studies from U.S. (Nguyen et al. 1997) and Finland (Salomaa et al. 1994) failed to show any relation between Lp(a) and CAD. While some reports show higher predictive value for CAD of low molecular weight apolipoprotein(a) isoforms (Gazzaruso et al. 1998), others report indicate that the apo(a) phenotypes are distributed similarly in subjects with and without atherosclerosis and are related to other risk factors in both men and women (Bowden et al. 1994).

Table 3. Multivariate regression model for women and men.

<table>
<thead>
<tr>
<th>Independent predictor of aCAD(+)</th>
<th>Exp(B)</th>
<th>95 % C.I. for Exp(B) (lower – upper)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMEN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lp(a)</td>
<td>1.002</td>
<td>(1.001 – 1.003)</td>
<td>0.000</td>
</tr>
<tr>
<td>Log(TG/HDL-C)</td>
<td>6.785</td>
<td>(1.618 – 23.741)</td>
<td>0.009</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.191</td>
<td>(1.016 – 4.723)</td>
<td>0.046</td>
</tr>
<tr>
<td>MEN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>3.752</td>
<td>(1.920 – 7.334)</td>
<td>0.000</td>
</tr>
<tr>
<td>Age</td>
<td>1.041</td>
<td>(1.005 – 1.078)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Model variables: Age, BMI, smoking, TC, TG, LDL-C, ApoB, HDL-C, Lp(a), Log(TG/HDL-C), TC/HDL-C. Exp(B) – estimated odds ratio, C.I. – confidence interval for Exp(B)

The purpose of this study was to determine whether a routine assessment of Lp(a) in patients at risk of CHD further adds to their risk assessment. The objective correlate of disease in our study were the findings on coronary angiography. These were correlated with the plasma concentration of Lp(a) and routine lipids. All our patients were of European descent and therefore more comparable with regard to Lp(a) isoforms than, for instance, Caucasian and African American populations. In our medium sized cohort of patients the routine lipid profile had fairly low predictive value for positive angiographic findings. In men, the differences in lipid parameters between those with aCAD(+) and aCAD(–) were not statistically significant, while women with aCAD(+) had higher LDL-C, TG and lower HDL-C values. The Log(TG/HDL) index which well correlates with other risk factors for CAD as recently reported (Dobíšová and Frohlich 2001), was also significantly increased in women with aCAD(+). There were no significant differences in the Lp(a) plasma level between men and women with negative angiography, while the women with positive findings had Lp(a) levels almost twice as high as men. The multivariate analysis has confirmed that in women plasma Lp(a) besides of Log(TG/HDL) and smoking was a significant independent predictor of positive findings on angiography.

Our findings suggest that Lp(a) measurement is of value in investigation of patients at risk for CAD and that it is a particularly useful predictor of risk in women.
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References


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