Lp(a) Concentration and Apo(a) Isoform Size
Relation to the Presence of Coronary Artery Disease in Familial Hypercholesterolemia

J.-F. Bowden, P.H. Pritchard, J.S. Hill, J.J. Frohlich

Abstract We studied the relation between the concentration of lipoprotein(a) [Lp(a)] in plasma, apolipoprotein (a) [apo(a)] phenotype, and the clinical expression of coronary artery disease (CAD) in a previously described cohort of patients with familial hypercholesterolemia (FH) and an appropriate population of control subjects. The plasma concentration of Lp(a) was markedly skewed in both the FH and control populations; however, the distribution was less skewed in FH (50% greater than 300 mg/L) compared with control subjects (27% greater than 300 mg/L). Patients with FH had significantly higher median and mean log Lp(a) levels compared with control subjects. There was no difference in the level of Lp(a) between men and women in both the control and FH groups. Frequency distribution analysis of the major apo(a) isoform size for each subject showed that, in contrast to the near-normal distribution seen in control subjects, two major subpopulations were apparent in the FH cohort, based on apo(a) isoform size >700 kD or ≤700 kD. There was no correlation between Lp(a) plasma concentration and apo(a) isoform size in either population. FH subjects with smaller apo(a) isoforms were more likely to have a history of, signs of, or symptoms of CAD than those with larger isoforms. These data illustrate that on the basis of Lp(a) plasma concentration alone, there is no significant difference between FH patients with and without signs or symptoms of CAD. In the control population the smaller apo(a) isoforms were associated with higher Lp(a) levels, whereas in the FH population both small and large apo(a) isoforms were associated with higher Lp(a) levels. The combination of high serum Lp(a) levels and small apo(a) isoform size portends the greatest risk for FH patients developing CAD. We speculate that specific differences in Lp(a) metabolism in patients with FH lead to differences in both apo(a) isoform size distribution and Lp(a) plasma concentration compared with control subjects. (Arterioscler Thromb. 1994;14:1561-1568.)

Key Words • lipoprotein(a) • apoprotein (a) • apo(a) • isoform size • familial hypercholesterolemia • coronary artery disease

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein (LDL)-like lipoprotein particle whose level in plasma is strongly correlated with coronary artery disease (CAD), acute myocardial infarction, and cerebrovascular disease. Consequently, Lp(a) is considered to be an independent risk factor for CAD in the general population. The level of Lp(a) in plasma is genetically determined and appears to be unaffected by sex or diet. Until recently, the level of Lp(a) was thought to be unaffected by age, but in one study postmenopausal women were observed to have increased levels of Lp(a). Recent studies have shown that smaller apo(a) isoforms are more likely to have a history of, signs of, or symptoms of CAD than those with larger isoforms. These data illustrate that on the basis of Lp(a) plasma concentration alone, there is no significant difference between FH patients with and without signs or symptoms of CAD. In the control population the smaller apo(a) isoforms were associated with higher Lp(a) levels, whereas in the FH population both small and large apo(a) isoforms were associated with higher Lp(a) levels. The combination of high serum Lp(a) levels and small apo(a) isoform size portends the greatest risk for FH patients developing CAD. We speculate that specific differences in Lp(a) metabolism in patients with FH lead to differences in both apo(a) isoform size distribution and Lp(a) plasma concentration compared with control subjects. (Arterioscler Thromb. 1994;14:1561-1568.)

Key Words • lipoprotein(a) • apoprotein (a) • apo(a) • isoform size • familial hypercholesterolemia • coronary artery disease

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein (LDL)-like lipoprotein particle whose level in plasma is strongly correlated with coronary artery disease (CAD), acute myocardial infarction, and cerebrovascular disease. Consequently, Lp(a) is considered to be an independent risk factor for CAD in the general population. The level of Lp(a) in plasma is genetically determined and appears to be unaffected by sex or diet. Until recently, the level of Lp(a) was thought to be unaffected by age, but in one study postmenopausal women were observed to have increased levels of Lp(a). Recent studies have shown that smaller apo(a) isoforms are more likely to have a history of, signs of, or symptoms of CAD than those with larger isoforms. These data illustrate that on the basis of Lp(a) plasma concentration alone, there is no significant difference between FH patients with and without signs or symptoms of CAD. In the control population the smaller apo(a) isoforms were associated with higher Lp(a) levels, whereas in the FH population both small and large apo(a) isoforms were associated with higher Lp(a) levels. The combination of high serum Lp(a) levels and small apo(a) isoform size portends the greatest risk for FH patients developing CAD. We speculate that specific differences in Lp(a) metabolism in patients with FH lead to differences in both apo(a) isoform size distribution and Lp(a) plasma concentration compared with control subjects. (Arterioscler Thromb. 1994;14:1561-1568.)

Key Words • lipoprotein(a) • apoprotein (a) • apo(a) • isoform size • familial hypercholesterolemia • coronary artery disease

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein (LDL)-like lipoprotein particle whose level in plasma is strongly correlated with coronary artery disease (CAD), acute myocardial infarction, and cerebrovascular disease. Consequently, Lp(a) is considered to be an independent risk factor for CAD in the general population. The level of Lp(a) in plasma is genetically determined and appears to be unaffected by sex or diet. Until recently, the level of Lp(a) was thought to be unaffected by age, but in one study postmenopausal women were observed to have increased levels of Lp(a). Recent studies have shown that smaller apo(a) isoforms are more likely to have a history of, signs of, or symptoms of CAD than those with larger isoforms. These data illustrate that on the basis of Lp(a) plasma concentration alone, there is no significant difference between FH patients with and without signs or symptoms of CAD. In the control population the smaller apo(a) isoforms were associated with higher Lp(a) levels, whereas in the FH population both small and large apo(a) isoforms were associated with higher Lp(a) levels. The combination of high serum Lp(a) levels and small apo(a) isoform size portends the greatest risk for FH patients developing CAD. We speculate that specific differences in Lp(a) metabolism in patients with FH lead to differences in both apo(a) isoform size distribution and Lp(a) plasma concentration compared with control subjects. (Arterioscler Thromb. 1994;14:1561-1568.)

Key Words • lipoprotein(a) • apoprotein (a) • apo(a) • isoform size • familial hypercholesterolemia • coronary artery disease
populations, which suggests that the determinant for risk of CAD is determined by the Lp(a) locus.

Heterozygous familial hypercholesterolemia (FH) is a genetically inherited disorder of the LDL receptor that results in decreased LDL catabolism. This produces hypercholesterolemia, tendon xanthomas, and premature CAD.\(^\text{27}\) Lp(a) levels have been reported to be up to threefold higher in FH patients compared with control subjects.\(^\text{58-30}\) Furthermore, Lp(a) levels have been reported to be higher in those FH patients who had developed CAD than in those who did not.\(^\text{29,30}\) However, in a more recent study of FH patients by Mbewu et al.,\(^\text{31}\) Lp(a) levels were raised, but there was no correlation with CAD. In contrast, Ghiselli et al.\(^\text{32}\) reported that Lp(a) levels are not raised in FH patients.

To provide additional data on the relation between Lp(a) concentration, apo(a) isoform size, and CAD in patients with FH, we studied these parameters in a previously described cohort of FH patients with heterogeneous genetic background residing in the Vancouver area.\(^\text{33}\) We have previously shown that even in the presence of overt hypercholesterolemia, the development of signs or symptoms of CAD is markedly influenced by a number of risk factors, including lipid profile, smoking, and hypertension. In addition, the relative contribution of these factors to the risk of developing CAD varied considerably between men and women. In the present study we posed the following question: Is there a relation between the concentration of Lp(a) in plasma, apo(a) isoform size, and the incidence of CAD in patients with FH?

**Methods**

**Patients and Control Subjects**

The study cohort consisted of 155 normolipemic volunteer subjects and 115 subjects with heterozygous FH selected from among patients attending the Lipid Clinic at University Hospital in Vancouver. FH was diagnosed on the basis of the following criteria: (1) a level of LDL cholesterol (LDL-C) greater than the 95th percentile corrected for both age and sex and (2) tendon xanthomas in the patient or first-degree relative. With the varied ethnic base of the Vancouver population (largely European and Asian [Chinese and Indian]), there was considerable heterogeneity in the genetic background of both the study and control populations. The presence of CAD in the FH cohort was determined by a retrospective chart review, in which CAD was defined as the presence of angina (history of typical exercise-related chest pain), myocardial infarction (demonstrated by electrocardiogram and/or serum enzyme changes), angiographically demonstrated disease, angioplasty, or a history of coronary bypass surgery.

**Plasma Lipid, Lipoprotein, and Apolipoprotein Determinations**

Venous blood was collected from all subjects after an overnight fast of at least 12 hours. The EDTA plasma was separated from cells by low-speed centrifugation (1200g for 20 minutes) and was analyzed immediately or frozen at −70°C. Total cholesterol (TC) and triglycerides (TG) were measured by established enzymatic methods.\(^\text{35}\) High-density lipoprotein (HDL-C) was determined as the amount of cholesterol remaining after precipitation of apoB-containing lipoproteins with heparin/MnCl\(_2\).\(^\text{36}\) LDL-C was calculated from the formula $\text{TC} - \text{(HDL-C)} - \text{TG/2.2}$, where all values were expressed in millimoles per liter. ApoA-I and apoB were determined by immunonephelometry by means of the Beckman Array System.

**Lp(a) Assay**

Plasma Lp(a) concentration was determined with an established commercially available radioimmunoassay kit that uses a monoclonal antibody against purified apo(a) (Pharmacia). Results are reported as units per liter, with a detection limit of 3 U/L. The manufacturer reports that 1 U of apo(a) is approximately equal to 0.7 mg Lp(a).

**Apo(a) Phenotyping**

Apo(a) phenotyping was performed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) by a modification of the method of Guo et al.,\(^\text{37}\) followed by immunoblotting. Briefly, thawed plasma samples containing 20 ng Lp(a) were mixed in SDS-PAGE sample buffer (25 mmol/L tris[hydroxymethyl]aminomethane [Tris], 200 mmol/L glycine, and 5% SDS, pH 8.3). Dithiothreitol was added to a final concentration of 20 mmol/L, and the samples were heated at 95°C for 10 minutes before loading buffer (1.5 g sucrose per milliliter of sample buffer) was added. Reference plasma samples of known apo(a) size were included with each gel. The size of the apo(a) in these reference samples was determined previously by comparison to a series of phosphorylase b (M\(_r\), 97.4 kD) oligomers (Sigma). SDS-PAGE was carried out with Bio-Rad mini PROTEAN II dual-slab gels of 1.5-mm thickness containing 2.7% acrylamide and 0.8% bisacrylamide, stabilized with 1% agarose (low melting point). Electrophoresis was carried out at 20°C for 1.5 hours at a constant voltage of 100 V. Electrophoretic protein of nitrocellulose was performed as described previously.\(^\text{38}\) The nitrocellulose blots were incubated in 20 mmol/L Tris (pH 7.5), 150 mmol/L NaCl, and 5% nonfat dry milk protein at 20°C for 18 hours. Apo(a) bands were detected by the alkaline phosphatase color development method with biotinylated goat anti-rabbit IgG (H+L, Bio-Rad) and biotinylated alkaline phosphatase. Under our experimental conditions, a difference in molecular weight of 50 000 D can be differentiated from the Western blot, and at least one apo(a) isoform (and a maximum of two) was detected in all plasma samples analyzed. In approximately 60% of the samples analyzed two differently sized isoforms were detectable. These were termed major and minor, with the major band being the more heavily stained. For the purposes of this study, we confined our analysis to the major isoform band.

**Statistical Methods**

Comparative significance of serum lipids, sex, and age between control subjects and FH patients and between those FH patients with CAD and those without CAD was tested with Student's t test. Due to the highly skewed distribution of plasma Lp(a) concentrations, the Kruskal-Wallis nonparametric test was used to test the significance of Lp(a) levels between control subjects versus FH patients and between those FH patients with CAD versus those without CAD. Logarithmic transformation of Lp(a) plasma levels allowed the data to be expressed in a log-normal distribution, which permitted calculation of a mean and SD for each group. For all statistical calculations, the SYSTAT computer program was used.

**Results**

We previously reported the lipid and lipoprotein levels observed in a cohort of patients with FH and a control population.\(^\text{39}\) Table 1 summarizes the lipid and lipoprotein levels observed in a subset of our original study cohort, in whom we measured Lp(a) plasma concentration and apo(a) isoform size. As expected, patients with FH had significantly higher TC, LDL-C, and apoB levels compared with control subjects. They also had significantly lower levels of HDL-C and apoA-I. The control population contained approximately equal numbers of men and women, whereas the FH population contained...
slightly more women than men (58% versus 42%). On average, there was no age difference between the two populations.

### Lp(a) Concentration in Plasma

Fig 1 shows the Lp(a) plasma concentration in the FH and control populations described in Table 1. Fig 1A shows the expected skewed frequency distribution of Lp(a) levels; median values are indicated in the inset table. Both control and FH populations showed the expected skewed distribution, but the distribution in the FH population was less skewed than that in the control population. This is indicated in Fig 1B, which shows the cumulative frequency of Lp(a) concentrations for both populations. There were proportionally more control subjects than FH patients for any given concentration of Lp(a) (for instance, 73% of control subjects had an Lp(a) concentration <300 U/L, compared with only 50% of FH patients). This indicates that patients with FH generally had higher Lp(a) levels than did subjects in the control population. Comparison of the median values of Lp(a) shows that there was a significantly higher (P<.001) level of Lp(a) in the plasma of FH patients (median, 306 U/L) compared with control subjects (median, 130 U/L). Fig 1C shows the logarithmic transformation of the distribution (shown in Fig 1A) to produce a log-normal distribution. Calculation of a mean and SD from these data permits comparison of population means by Student's t-test. The data shown in the panel inset indicate that the concentration of Lp(a) is significantly higher (P<.05) in the FH population compared with the control population.

Since the FH and control populations had different although not statistically significant average ages and sex ratios, it is possible that these differences affected the Lp(a) distribution. Segregation of the data on the basis of age and sex indicated that there was no significant effect of either of these two variables on plasma Lp(a) concentration. This confirms the observations of others.

Table 2 summarizes observed differences between FH patients with and without symptoms of CAD. Proportionally, twice as many men as women had CAD (64% versus 36%). FH patients with CAD were significantly older and had lower HDL-C and higher TG compared with FH patients without CAD. Although the levels of LDL-C were not significantly different, apoB levels were significantly higher in those patients with CAD.

Fig 3 shows the Lp(a) plasma concentration in the FH population with and without CAD. Fig 3A shows the frequency distribution of Lp(a) levels; median values are indicated in the inset table. Comparison of the median and mean values of Lp(a) indicated that there was no difference in the level of Lp(a) in the plasma of FH patients with CAD (median, 287 U/L) compared with those patients without CAD (median, 307 U/L). Fig 3B shows the cumulative frequency of Lp(a) concentrations for both populations. For any given concentration of Lp(a), there were proportionally equal numbers of FH patients with and without CAD. These data

---

**Table 1. Lipid, Lipoprotein, and Apolipoprotein Levels in Control and Familial Hypercholesterolemic Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=155)</th>
<th>FH (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>79 (51%)</td>
<td>67 (58%)</td>
</tr>
<tr>
<td>Men</td>
<td>76 (49%)</td>
<td>48 (42%)</td>
</tr>
<tr>
<td>Age, y</td>
<td>43.9±17.94</td>
<td>47.5±15.1</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>3.35±0.93</td>
<td>7.01±1.8*</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.33±0.28</td>
<td>1.16±0.29*</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.2±1.05</td>
<td>9.03±1.98*</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.14±0.55</td>
<td>1.63±0.88*</td>
</tr>
<tr>
<td>Apolipoprotein A-I, g/L</td>
<td>1.49±0.28</td>
<td>1.29±0.28*</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>0.83±0.37</td>
<td>1.52±0.42*</td>
</tr>
</tbody>
</table>

FH indicates familial hypercholesterolemic subjects; LDL, low-density lipoprotein; and HDL, high-density lipoprotein. Values are mean±SD.

*P<.005.

---

**Figure 1.** Graphs show relative distribution of plasma lipoprotein(a) [Lp(a)] in control subjects (c) and in patients with familial hypercholesterolemia (FH) (•). A, Frequency distribution; B, cumulative frequency; and C, log transformation of data in panel A.
Apo(a) Isoform Size

Apo(a) isoform size in each plasma sample was determined by SDS-PAGE. Rather than classify the observed molecular weights against the six-isoform model of Utermann et al.20 or even the 23-allele model of Kamboh et al.39 or the 34-allele model of Marcovina et al.,13,15 we chose to report the size of each apo(a) isoform as a molecular weight. All persons enrolled in this study had detectable apo(a) protein bands, which agreed with the studies of others.11,39 This indicates that no null alleles were present in our study cohort.

Fig 4 shows the major apo(a) isoform size distribution in the control and FH populations. Fig 4A shows the frequency distribution of isoform size; median values are shown in the inset table. Comparison of median apo(a) values shows that there was no significant difference between control subjects (median, 746 kD) and FH patients (median, 751 kD). When means were calculated, there was also no significant difference between the two groups (means, 735 ± 110 kD and 714 ± 115 kD, respectively). However, qualitative analysis of the frequency distribution indicated that there was a distinct difference in the distribution pattern of apo(a) isoforms; specifically, there was a noticeable lack of the intermediate apo(a) isoforms in the FH population, with an approximate molecular weight of 750 kD. This difference was better distinguished by the cumulative frequency shown in Fig 4B. For any given apo(a) isoform size ≤700 kD, there were proportionally more FH patients than control subjects. This indicates that FH patients were more likely to have a smaller apo(a) isoform.

Fig 5 shows the distribution of the major apo(a) isoform sizes in FH patients with and without CAD. Fig 5A shows the frequency distribution of the major apo(a) isoform sizes; medians are shown in the inset table. Qualitatively, there was a distinct shift to a smaller apo(a) isoform size in those patients with CAD. Comparison of medians shows a significantly smaller apo(a) isoform size (P < .05) in those patients with CAD (median, 657 kD) than in those with no CAD (median, 766 kD). Fig 5B shows the cumulative frequency for the two groups. The data illustrate that proportionally more patients with CAD had a smaller apo(a) isoform.

Relation Between Lp(a) Plasma Concentration and Apo(a) Isoform Size and the Presence of CAD

The scattergrams shown in Fig 6 show the relation between the concentration of Lp(a) in plasma and the
molecular size of apo(a). Fig 6A shows the relation in the control population, and Fig 6B shows the relation in the FH population. It is apparent that there is considerable variation in the plasma concentration of Lp(a) for any given apo(a) isoform size. This is true for both control and FH populations, particularly for the smaller apo(a) isoform sizes. A greater proportion of FH patients compared with control subjects had a higher plasma concentration of Lp(a) associated with larger apo(a) isoforms. However, when the relation was compared between those patients with CAD and those without CAD, there was no obvious dissimilarity. There was an apparent inverse relation between the two variables in the control population (r = -0.228) and to a lesser degree in the FH population (r = -0.048). In general, in the control population the smaller apo(a) isoforms were associated with higher Lp(a) levels, whereas in the FH population both small and large apo(a) isoforms were associated with higher Lp(a) levels.

The isoform size data were analyzed by segregating the study populations into two groups: ≤700 kD and >700 kD (Fig 7). The proportion of subjects in the control population with a major isoform size >700 kD (63%) was similar to the proportion of patients in the FH population without CAD (60%). In contrast, the proportion of FH patients with a major isoform size >700 kD with CAD (37%) was significantly decreased. This decrease was associated with a concomitant increase in the proportion of patients with the smaller apo(a) isoforms. Thus, although Lp(a) levels in the plasma were not significantly different between those patients with and without CAD, it seems that the smaller apo(a) isoform size is associated with coronary heart disease.

Discussion

The present study was undertaken to determine the relation between plasma levels of Lp(a), apo(a) isoform...
size, and the occurrence of signs or symptoms of CAD in subjects with heterozygous FH. The data from this study extend the findings of our previous study, in which we described the genetic and environmental factors affecting the incidence of CAD in these subjects. 38

In agreement with previous reports, 29-31,40 our results show that patients with FH had significantly higher levels of Lp(a) compared with healthy control subjects. There has been much debate over the metabolic basis for the widely variable elevated plasma Lp(a) levels, yet the explanation is still elusive. It is known that the concentration of Lp(a) is independent of LDL levels. 2-9 In FH patients, it is unlikely that the increased plasma concentration of Lp(a) is due merely to high plasma LDL concentrations, since in one study the level of Lp(a) was twofold higher than in hypercholesterolemic control subjects with similar LDL levels. 31 Also, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, which lower the concentration of LDL, have no effect on the plasma concentration of Lp(a). 41 Lp(a) is catabolized by a pathway independent of the LDL receptor. Knight et al 42 showed that a defect in the LDL receptor does not result in a change in the catabolic rate of Lp(a) or Lp(a) plasma concentration. Rather than a decreased clearance rate, experimental evidence suggests that elevated levels of Lp(a) are due to an increased synthetic rate, as originally reported by Kremppler et al. 43 However, the effect of apo(a) isoform size could not be discounted. In a more recent, highly detailed study, Rader et al 44 showed that Lp(a) levels are determined by the production rate and, more importantly, are independent of apo(a) isoform size. The cellular mechanism, however, is still elusive. There are no data indicating a factor (transcriptional or otherwise) linked to the apo(a) gene locus that either regulates the apo(a) gene or the apo(a) protein.

Numerous studies have shown an association between the concentration of Lp(a) in plasma and the incidence of CAD in the general population, 2-5 wherein the risk threshold for developing myocardial infarction has been set at between 200 and 300 mg/L. 7,8 We asked whether the same holds true for our FH population. Although the FH patients in our study had levels of Lp(a) twofold higher than those in healthy control subjects, there was no apparent correlation between heart disease and plasma Lp(a) concentration. Mbewu et al 31 reported results similar to ours in an age- and sex-matched English heterozygous FH population of 134 subjects. Although the control and FH populations examined in our study were not age and sex matched, our results
indicate that the level of Lp(a) was not significantly affected by either age or sex. However, in contrast to these data, two studies have reported an association of elevated Lp(a) plasma levels of FH patients with heart disease. It is difficult to reconcile this discrepancy. Sandholzer et al. in their multipopulation study noted that for ethnically homogeneous study populations, apo(a) isoform size correlated with the incidence of CAD, but for an ethnically diverse population, the differences were not significant. It is known that the Chinese have lower Lp(a) levels than do white populations, whereas Indians have higher concentrations of Lp(a). Also, Africans and African Americans have levels of Lp(a) that are several-fold higher than those of whites. Our FH population exhibited a varied ethnic base (largely European and Asian [Chinese and Indian], with African American and Asian origin); there were no individuals of African descent, and this genetic heterogeneity may therefore confound trends between Lp(a) levels and disease that would otherwise be apparent in a genetically homogeneous population. We believe that the genetic heterogeneity in our group of patients is an advantage.

Our results imply, therefore, that in the FH population, an elevated plasma concentration of Lp(a) does not indicate a higher risk for developing CAD, ie, elevated levels of Lp(a) are characteristic of the FH condition but do not constitute an independent risk factor for the development of CAD. Consequently, measurement of Lp(a) plasma concentration alone will not provide a useful prognostic indicator of risk. In the wider context, these results also imply that it is important to consider the genetic background of each individual patient before evaluating the risk for developing CAD. In contrast, it is important to remember that our study has considered only signs or symptoms of CAD. A more detailed angiographic analysis of both cohorts would be required before we could definitively describe the relation between Lp(a) levels in plasma and risk of CAD. Such a study, however, is beyond the scope of the present investigation.

In addition to measuring the concentration of Lp(a) in plasma, we also determined the apo(a) phenotype for each plasma sample. It is known that those persons with smaller apo(a) isoforms have higher Lp(a) plasma levels. We wished to investigate whether a specific apo(a) isoform associated with elevated levels of Lp(a) in FH patients is associated with an increased incidence of CAD. Apo(a) phenotyping showed that there was a difference in the distribution in the size of the apo(a) isoforms between the control and FH populations. However, correlation between apo(a) isoform size and Lp(a) plasma concentration indicated that it would be difficult to distinguish even a subset of these two populations on the basis of either of these two variables. The correlation between apo(a) isoform size and Lp(a) plasma concentration was weaker in the FH population; there were a number of patients with large apo(a) isoform size and high plasma concentration of Lp(a). Our principal interest was to see if those FH patients with CAD could be selectively distinguished from the general FH population. The data indicate that whereas proportionally the same number of FH patients free of heart disease (40%) and normolipemic control subjects (37%) had small apo(a) isoforms, the proportion of those FH patients with CAD and an isoform size ≤700 kDa was greater (64%). These findings are in keeping with those of Secc et al., who also showed a higher prevalence of smaller apo(a) isoforms combined with elevated levels of Lp(a) in FH patients with CAD. Thus, FH patients with CAD tended to have a smaller apo(a) isoform size compared with those patients with no clinical signs of CAD. There are not enough data to explain why this is the case, but this might provide the basis for future investigation. The implication of these results is that in FH, apo(a) isoform size is a greater risk factor for developing CAD than is the level of Lp(a) in plasma. Thus, the small apo(a) isoforms are potentially the most atherogenic.

In conclusion, this study demonstrates that the level of Lp(a) in our cohort of patients with FH is significantly higher than in control subjects. This elevated level of Lp(a) appears to be associated with the FH condition rather than the presence of clinically significant CAD. In contrast, despite the same apo(a) isoform distribution, a greater proportion of patients with CAD had a smaller apo(a) isoform size. Thus, we propose that the combination of high serum Lp(a) levels and small apo(a) isoform size portends the greatest risk for FH patients developing CAD. Since the level of Lp(a) was not different between patients with and without CAD, measurement of apo(a) isoform size rather than Lp(a) concentration may prove to be a better prognostic indicator of development of heart disease in FH.

Acknowledgments

This study was supported by grants from the University Hospital Foundation and Merck Frosst. We are indebted to Drs M. Hayden, S. Langlois, and D. Seccome for providing clinical data and plasma from their patients with FH. We would also like to thank H. Vannetta and D. Sidpra for their technical assistance.

References


Lp(a) concentration and apo(a) isoform size. Relation to the presence of coronary artery disease in familial hypercholesterolemia.
J F Bowden, P H Pritchard, J S Hill and J J Frohlich

Arterioscler Thromb Vasc Biol. 1994;14:1561-1568
doi: 10.1161/01.ATV.14.10.1561
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/14/10/1561

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/