Serum Concentrations of Apolipoprotein A-I, Apolipoprotein B, and Lipoprotein(a) in a Population Sample

Aila Leino, Olli Impivaara, Merja Kaitsaari, and Jorma Järvisalo

Serum concentrations of apolipoprotein (apo) A-I, apo B, and lipoprotein(a) [Lp(a)] were studied with respect to age and sex in a Finnish population sample of 575 subjects (286 men and 289 women), ages 27–67 years. Apo A-I and apo B were measured with an immunoturbidimetric method calibrated against WHO International Reference Materials. Lp(a) was measured by RIA. Apo A-I and apo B concentrations were almost normally distributed (apo A-I: mean 1.38 g/L vs median 1.34 g/L for men, and 1.58 g/L vs 1.55 g/L for women; apo B: mean 1.21 g/L vs median 1.20 g/L for men and 1.09 g/L vs 1.05 g/L for women). The distribution of Lp(a) was markedly skewed (mean 190 mg/L vs median 86 mg/L for men, and 169 mg/L vs 85 mg/L for women). The 95% intervals for apo A-I were 1.09–1.84 g/L for men and 1.06–2.28 g/L for women; for apo B, they were 0.63–1.88 g/L and 0.56–1.82 g/L, respectively. Apo A-I concentrations appeared to be unrelated to age, whereas apo B and Lp(a) concentrations were age-dependent. Cutoff values based on the 90th percentile for apo B and the 10th percentile for apo A-I are proposed for identifying subjects at increased risk of coronary heart disease.

Indexing Terms: cardiovascular risk factors/reference values/sex- and age-related effects/epidemiology

The risk of cardiovascular disease associated with an abnormal plasma lipoprotein status is generally assessed by measuring the concentrations of total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and then calculating the concentrations of low-density lipoprotein cholesterol (LDL-C), even if this method is notoriously inaccurate (1, 2). Severe coronary heart disease has been reported in association with greatly lowered serum apolipoprotein (apo) A-I concentrations, and patients with high concentrations of apo B have shown a high prevalence of atherosclerotic disease (3, 4). High concentrations of serum lipoprotein(a) [Lp(a)] have been observed in patients with increased atherogenesis and thrombogenesis (5). However, the clinical benefits of these measurements have not been fully determined because of methodological problems and inadequate standardization (6). Recently, however, consensus has been achieved on apo A-I and apo B standardization (7, 8). Measurements of serum apo A-I, apo B, and Lp(a) are relatively simple and could be used in clinical practice instead of or in parallel with lipoprotein cholesterol measurements, provided appropriate reference values are available.

Population-based studies are needed to establish consistent cutoff values of apolipoproteins for identifying subjects at high risk of atherosclerotic disease. We report age- and sex-specific percentile values for serum apo A-I, apo B, and Lp(a) derived from a Finnish population sample. Further, we propose preliminary cutoff values for serum apo A-I, apo B, and Lp(a) that may prove useful in assessing high-risk patients.

Materials and Methods

Our purpose was to recruit 600 subjects, 60 of each sex in five age strata (27, 37, 47, 57 and 67 years), over 1 year. These age groups were chosen to prevent the examinations from coinciding with regular health examinations organized by occupational health services (usually at ages ending off with 0 or 5). To allow for refusals, we drew a stratified random sample of 1800 people from the population registers of the city of Turku and some adjacent rural and urban communities in southwestern Finland.

The subjects in each stratum were invited in randomly selected order. If no response was obtained even after repeated invitations, subjects further on the list were contacted. During the year, 575 subjects (286 men and 289 women) were examined. This number was recruited by contacting 871 subjects (452 men and 419 women) by mail. A questionnaire asking about health status and current medication was enclosed with the invitation letter. Among the 575 participants, 22 (7.7%) men and 11 (3.8%) women reported that they had had coronary heart disease diagnosed by a physician. Diabetes had been diagnosed by a physician in seven men (2.5%) and five women (1.7%). The subjects were not requested to change their diets or other habits in any way except to have an overnight fast. The results were derived from all participants, without any exclusions.

Before implementation, the study was reviewed and approved by the ethical committee of the Research Centre.

Standing height and weight were measured, and body mass index [weight (kg)/height (m)^2] was calculated. Blood specimens were collected in the morning (between 0730 and 0930), after an overnight fast. Serum was obtained after allowing the blood to clot at room temperature for 30 min. After centrifugation (920 g, 15 min, 24 °C), the specimens were stored frozen at −20 °C for no longer than 2 weeks. All measurements were carried out in duplicate, and the mean of the two
measurements was considered the final result. Apo A-I and apo B were measured by immunoturbidimetry (9), with Orion kits (Orion Diagnostica, Espoo, Finland) standardized by the manufacturer against WHO International Reference Materials for apo A-I SP1–01 and for apo B SP3–07 and with an Olli CD analyzer (Kone Oy, Helsinki, Finland). Lp(a) was determined by using a solid two-site immunometric assay (10) (Pharmacia, Uppsala, Sweden) standardized by the manufacturer against highly purified, fully validated, commercial Lp(a) preparation. Minimal differences were observed in a separate test series between apolipoprotein analyses from fresh and frozen serum samples; the error of measurement (analysis of variance) for apo A-I was 1.8%, for apo B 1.3%, and for Lp(a) 2.8%. Cholesterol and triglycerides were measured enzymatically (11, 12) with reagents supplied by Merck (Darmstadt, Germany) and with the Olympus AU 510 analyzer (Olympus, Hamburg, Germany). HDL-C concentrations were measured after precipitation with dextran sulfate (13). LDL-C was calculated according to the Friedewald formula (14): LDL-C = cholesterol – HDL-C – (0.45 × triglycerides). The between-assay variations were 4% for both apo A-I (at 1.42 g/L) and apo B (at 1.01 g/L), 4.4% for Lp(a) (at 180 mg/L), 2.0% for cholesterol (at 4.5 mmol/L), 3.3% for triglycerides (at 1.28 mmol/L), and 1.9% for HDL-C (at 1.13 mmol/L).

Student's t-test was used to compare the results between men and women. Whenever the distributions deviated from normal, the calculations were carried out after transformations according to Box and Cox (15, 16). The relationships between serum apolipoprotein concentrations and age were studied by analysis of variance; those between apo A-I and HDL-C and between apo B and LDL-C were assessed by calculating Pearson product moment correlations.

Results

Table 1 shows some clinical characteristics and the average values for body mass index, lipids, and apolipoproteins in the study population by sex. The distribution of Lp(a) was skewed, and a logarithmic transformation was therefore carried out. Table 2 shows the percentile values of serum apo A-I, apo B, and Lp(a) in the study population by age and sex. Apo A-I concentrations were significantly higher in women than in men (P <0.0001), whereas apo B values were higher in men than in women (P <0.0001). No significant difference in Lp(a) concentrations was observed between sexes. Serum apo A-I concentrations appeared to be unrelated to age both in men and in women. In contrast, the distributions of apo B and Lp(a) were age-dependent (P <0.0001 and <0.05, respectively). Among men, average apo B values increased with age up to 47 years and decreased thereafter; the same trend was observed for LDL-C. Women's apo B concentrations also increased with age, especially after menopause. Apo B values in the younger age cohorts were higher among men than among women, whereas the cohorts at 57 years and 67 years showed a reverse relation. A tendency towards higher Lp(a) values was observed in both sexes when older age groups (57 and 67 years) were compared with the younger.

Table 3 summarizes the proposed cutoff values for serum apo A-I, apo B, and Lp(a) values considered to imply an increased risk for coronary disease. In both sexes, apo A-I was positively correlated with HDL-C (r = 0.82), and apo B was positively correlated with total cholesterol (r = 0.84) and LDL-C (r = 0.86). We saw no significant correlations between these lipid fractions and Lp(a).

Discussion

When the new standardized methods were adopted by our laboratory, measured serum apo A-I concentrations showed an average increase of 5.5% and serum apo B increased by 9.6%. Earlier reference values are no longer valid (17, 18). To date, no population-based reference values based on methods calibrated against WHO International Reference Materials have been published. The differences between calibrations and other analytical approaches should be taken into account when our values are compared with those reported previously. Compared with our study, the apolipoprotein and lipid values reported from the ARIC study (19), carried out in a middle-aged American population, gave a slightly more favorable lipid profile. The high frequency of the apoE4 allele in Finns, which has been shown to be linked with an unfavorable lipid profile (20), might be one factor contributing to the observed differences. The ARIC study, however, was based on subjects not taking any medication potentially affecting lipid metabolism and used unstandardized apolipoprotein methods, whereas we used standardized methods and made no exclusions. Jungner et al. (18), who reported serum apo A-I and apo B values from a Swedish study population, used the same meth-
ods and reagents as ours but different means of calibration. Our apo A-I concentrations were higher and our apo B lower than theirs in both sexes. The average serum total cholesterol was somewhat higher in the Swedish series (5.7 mmol/L in both sexes) than in ours (5.6 mmol/L). The slight differences in lipid concentrations hardly explain the observed differences in the apo A-I and apo B concentrations, which can probably be attributed largely to differences in calibration practices between the laboratories. And, in spite of methodological differences, a study from Yugoslavia (21) reported apo A-I and apo B values quite similar to ours.

Our age- and sex-specific patterns of serum apo A-I and apo B concentrations are similar to those reported previously (17, 18, 22). Women tend to have higher apo A-I concentrations than men, and age seems to have little influence on apo A-I. In contrast, apo B values clearly increase with age in both sexes. The marked age-related increase in women’s apo B concentrations probably reflects the metabolic changes occurring during and after menopause. Similar changes have been observed in serum total cholesterol concentrations in women (23–25).

In many countries, including Finland, recommendations have been issued for screening and managing dyslipidemia (26). To date, no limits for clinical intervention have been established for apo A-I, apo B, and Lp(a). Referring to earlier recommendations for serum cholesterol concentrations, Albers and Marcovina (27) proposed that similar cutoff values should be established for apolipoproteins to identify subjects at increased risk of coronary heart disease. They concluded that apo A-I values below the 10th percentile and apo B values above the 90th percentile could be considered to imply an increased risk of coronary heart disease. On the same grounds, they postulated that apo B concentrations below the 75th percentile would be desirable. On the basis of these concepts, we present decision limits for apo A-I, apo B, and Lp(a) from our study population (Table 3).

Our observations on the skewed distribution of serum Lp(a) concentrations and the slight (nonsignificant) differences that they show between men and women are consistent with previous reports (28–30). Dahlen et al. (31) and Armstrong et al. (32) suggested that Lp(a) concentrations >300 mg/L implied an increased risk of coronary heart disease. As much as 15–25% of the population reportedly exceed this limit (28, 33). In our study, 18% of men and 16% of women had Lp(a) concentrations >300 mg/L.

With improving insights into the mechanisms by which lipoproteins abet atherosclerosis or provide protection against it (34, 35), the measurement of serum apoprotein concentrations for clinical purposes is likely to increase in importance—especially for apo A-I and apo B, now that the methods have been standardized—and population-based reference values will become available. Our data on apo A-I and apo B are derived from a relatively small and homogeneous Finnish population and, therefore, may not be entirely applicable to other populations. Further studies utilizing standardized methods should be carried out in larger and more variable populations. As for determination of Lp(a), further evaluations and appropriate standardization of the methods are needed to improve the

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**Table 2. Distribution (percentiles) of serum apo A-I, apo B, and Lp(a) concentrations in men and women by age.**

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Apo A-I, g/L</th>
<th></th>
<th>Apo B, g/L</th>
<th></th>
<th>Lp(a), mg/L</th>
<th></th>
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<tr>
<td></td>
<td>n 10 25 50 75 90</td>
<td></td>
<td>10 25 50 75 90</td>
<td></td>
<td>10 25 50 75 90</td>
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<td></td>
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<td></td>
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<tr>
<td>27</td>
<td>47 1.09 1.19 1.31 1.43 1.58</td>
<td></td>
<td>0.66 0.78 1.01 1.28 1.42</td>
<td></td>
<td>12 29 61 174 788</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>62 1.08 1.19 1.33 1.58 1.70</td>
<td></td>
<td>0.78 0.96 1.12 1.32 1.41</td>
<td></td>
<td>22 35 74 178 344</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>62 1.13 1.22 1.36 1.53 1.77</td>
<td></td>
<td>0.97 1.14 1.31 1.47 1.70</td>
<td></td>
<td>16 86 87 179 324</td>
<td></td>
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<tr>
<td>57</td>
<td>62 1.13 1.21 1.40 1.58 1.67</td>
<td></td>
<td>0.89 1.09 1.23 1.47 1.69</td>
<td></td>
<td>18 50 99 252 578</td>
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<tr>
<td>67</td>
<td>53 1.07 1.16 1.33 1.54 1.69</td>
<td></td>
<td>0.85 1.10 1.26 1.46 1.58</td>
<td></td>
<td>16 62 181 340 659</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>286 1.09 1.19 1.34 1.54 1.69</td>
<td></td>
<td>0.79 1.01 1.20 1.41 1.59</td>
<td></td>
<td>15 41 86 235 518</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>60 1.18 1.37 1.58 1.69 1.90</td>
<td></td>
<td>0.56 0.73 0.81 0.99 1.14</td>
<td></td>
<td>12 18 56 145 424</td>
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</tr>
<tr>
<td>37</td>
<td>59 1.25 1.37 1.51 1.77 1.97</td>
<td></td>
<td>0.64 0.72 0.88 1.12 1.12</td>
<td></td>
<td>12 27 76 189 311</td>
<td></td>
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<tr>
<td>47</td>
<td>63 1.21 1.34 1.57 1.75 1.88</td>
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<td>0.79 0.89 1.00 1.22 1.47</td>
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<td>13 39 80 154 420</td>
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<td>57</td>
<td>60 1.33 1.41 1.59 1.89 2.09</td>
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<td>0.91 1.12 1.24 1.49 1.67</td>
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<td>17 46 134 281 699</td>
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<td>67</td>
<td>59 1.20 1.32 1.55 1.77 1.97</td>
<td></td>
<td>0.98 1.10 1.29 1.53 1.74</td>
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<td>17 43 87 235 528</td>
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<tr>
<td>All</td>
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<td></td>
<td>0.71 0.85 1.05 1.29 1.55</td>
<td></td>
<td>14 33 85 204 446</td>
<td></td>
</tr>
</tbody>
</table>

* After logarithmic transformation.

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**Table 3. Proposed cutoff values for serum apo A-I, apo B, and Lp(a) in identifying subjects at increased risk of atherosclerotic vascular disease.**

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
<th>Designation</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo A-I, g/L</td>
<td>&lt;1.09</td>
<td>Increased risk</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Apo B, g/L</td>
<td>&lt;1.41</td>
<td>Desirable values</td>
<td>&lt;75</td>
</tr>
<tr>
<td>1.41–1.59</td>
<td>1.29–1.55</td>
<td>Increased risk</td>
<td>75–90</td>
</tr>
<tr>
<td>&gt;1.59</td>
<td>&gt;1.55</td>
<td>High risk</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Lp(a), mg/L</td>
<td>&lt;235</td>
<td>Desirable values</td>
<td>&lt;75</td>
</tr>
<tr>
<td>235–518</td>
<td>204–446</td>
<td>Increased risk</td>
<td>75–90</td>
</tr>
<tr>
<td>&gt;518</td>
<td>&gt;446</td>
<td>High risk</td>
<td>&gt;90</td>
</tr>
</tbody>
</table>

* Based on results for 286 men and 289 women, ages 27–67.
comparability of values obtained in different studies. Our preliminary population-based reference values for Lp(a) may be useful in this process.

References
5. Mbewu AD, Durrington PN. Lipoprotein(a); structure, properties and possible involvement in thrombogenesis and atherogenesis. Atherosclerosis 1990;85:1–14.