Relation of Lipoprotein(a) in 11- to 19-Year-Old Adolescents to Parental Cardiovascular Heart Disease

Juan-Carlos Vella¹ and Eugenio Jover²

We studied several risk factors in relation to parental cardiovascular heart disease: total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein (apo) A-I, apo B, and lipoprotein(a) [Lp(a)] were determined in 322 serum samples (43 from subjects with and 279 without parental cardiovascular heart disease). The distribution of Lp(a) concentrations in our young population was similar to that of other white populations, i.e., markedly skewed, with higher frequencies at low values. As compared with children whose parents did not report cardiovascular heart disease, those with affected parents had a higher mean Lp(a) (0.23 vs 0.18 g/L; P <0.05). Moreover, 42% of the children with parental cardiovascular heart disease, but only 19% of those with no parental cardiovascular heart disease, exhibited Lp(a) values >0.30 g/L. These results suggest not only that Lp(a) is an important risk factor for cardiovascular heart disease, but also that Lp(a) is more strongly related to the risk of cardiovascular heart disease than are HDL- and LDL-cholesterol and apo A-I and B.

Indexing Terms: apolipoproteins · arteriosclerosis · cholesterol · possibly heritable disorders

Serum cholesterol has been widely accepted as a risk factor for cardiovascular heart disease (CHD) (1), although high concentrations of cholesterol in the low-density lipoprotein (LDL) fraction and decreased amounts of cholesterol in the high-density lipoprotein (HDL) fraction are more predictive of CHD in adults (2).³ On the other hand, a clear association between increased concentrations of apolipoprotein (apo) B and decreased amounts of apo A-I and various manifestations of CHD has been confirmed (3, 4). Furthermore, individuals with increased concentrations of lipoprotein(a) [Lp(a)] have a greater risk of developing premature CHD (5–7).

Lp(a) is a cholesterol-rich plasma lipoprotein with pre-beta mobility in lipoprotein electrophoresis, primarily included in the HDL density class; for this reason, it was also named "sinking pre-beta" (5). The major protein component of Lp(a) besides apo(a) is apo B, and much of the apo B and apo(a) present in Lp(a) are joined by one or more disulfide bridges (6). Nevertheless, Lp(a) is not a catabolic product of other lipoproteins containing apo B (9). Furthermore, the serum concentration of Lp(a) may be genetically determined (10), and serum concentrations of Lp(a) remain constant even after metabolic perturbations that markedly change the amounts of the other lipoproteins present (11). Although the initial stages of arteriosclerosis are strongly related to childhood concentrations of serum lipids and lipoproteins (12), only very limited information is available concerning Lp(a) lipoprotein in the second decade of life.

The purpose of the present research was to (a) determine the relation of Lp(a) in 11- to 19-year-old adolescents to their parents' CHD; (b) determine the distribution of Lp(a) concentrations in the second decade of life; and (c) assess the relationship of Lp(a) to apolipoproteins and other lipid markers.

Materials and Methods

Subjects

The study consisted of 322 healthy volunteers, ages 11 to 19 years, boys and girls recruited from three different schools in Burgos, Spain. The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983. Serum samples were obtained under standardized conditions (13), after a 12- to 14-h fast. Venous blood was drawn into evacuated tubes without any additives, and the serum was promptly separated by low-speed centrifugation (1500 × g for 15 min) and kept in aliquots at 4 °C (to measure the concentrations of cholesterol, triglycerides, apo A-I and B, and to separate lipoproteins) or −80 °C (to measure Lp(a)). A parental history of CHD was obtained by means of questionnaires completed by both parents; among the children included in this study, 43 (13%) had parents with a maternal or paternal history of CHD; the parents of 279 boys and girls did not have a parental history of CHD. The data on parental history were not verified by examination of case records.

Methods

The HDL fractions were separated by precipitation with polyethylene glycol at a defined pH and concentration (14) by a commercially available method (Immuno, Vienna, Austria). Concentrations of cholesterol were determined by a commercially available (Cromatest, Barcelona, Spain) enzymatic method (15), except that LDL cholesterol was calculated by the formula of Friedewald et al. (16), and very-low-density lipoprotein cholesterol was estimated as triglycerides/2.18. Serum triglycerides were determined by a commercially available (Croma-
test) enzymatic method (17). Apo A-I and apo B in whole serum were quantified by commercially available (Beckman, Brea, CA) rate nephelometry methods (18). Lp(a) was quantified by a commercially available (Terumo, Elkton, MD) enzyme immunoassay (19) between 2 and 6 weeks after the sample collection.

Statistical Analyses

For statistical analyses we used the Statistical Package for the Social Sciences (SPSS) (20). The highly skewed distribution of Lp(a) concentrations and parental CHD, a sample odds ratio was calculated in a 2 × 2 table, with the demarcation lines for Lp(a) as 0.30 and 0.10 g/L for “high” and “low” concentrations, respectively. The sample odds ratio is calculated as (b × c)/(a × d), where a is the number of subjects with parental CHD and with Lp(a) values <0.10 g/L, b is the number of subjects with parental CHD and with Lp(a) values >0.30 g/L, c is the number of subjects without parental CHD and with Lp(a) values <0.10 g/L, and d is the number of subjects without parental CHD and with Lp(a) values >0.30 g/L. Because LDL cholesterol is calculated by the Friedewald formula, this value represents the cholesterol contained in both LDL and Lp(a) lipoproteins. Because the Lp(a) lipoproteins contain 45% cholesterol by mass (21), we used 1.16 × Lp(a) concentration [Lp(a) in g/L] to obtain the Lp(a) cholesterol in mmol/L (1.16 = 0.45 × 100 × 0.0258); after subtracting this term for each subject, we calculated these correlations, too. The correlation between apo B and Lp(a), after subtracting the apo B contained in Lp(a) lipoprotein [Lp(a)−apo B] from total apo B, was also calculated.

Results

The distribution of Lp(a) concentrations for the subjects without parental CHD (n = 279) was markedly skewed, with the highest frequencies at low values (Figure 1, top), as has been observed for other white populations (5, 11, 22–24). The distribution of Lp(a) concentrations for the subjects with parental CHD (n = 43), shown in Figure 1 (bottom), is not a gaussian distribution, but the mean (0.23 g/L) is similar to the median (0.18 g/L), and the distribution is bimodal with clusters at 0.00–0.30 g/L and >0.30 g/L. The sample odds ratio as a measure of the association between serum Lp(a) concentrations and parental CHD was 2.6685 (P <0.001), for Lp(a) values >0.30 g/L vs values <0.10 g/L [(18 × 110)/(14 × 53)]. The prevalence of parental CHD after stratification according to Lp(a) concentration (Table 1) shows a strong association between the parental CHD and increased Lp(a) concentrations in young people. When the limit values were compared according to positive or negative parental CHD, 42% of the adolescents whose parents (mother or father) reported CHD exhibited Lp(a) values >0.30 g/L, but only 19% of those with no parental CHD did.

Characteristics of the subjects and the concentrations of the lipoproteins are shown in Table 2, according to

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<th>Table 1. Prevalence of Parental Cardiovascular Heart Disease after Stratification According to Lp(a)</th>
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CHD in their parents; those whose parents reported CHD had a higher mean concentration of Lp(a) than did those whose parents did not: 0.23 vs 0.18 g/L (P < 0.05).

There was a statistically significant correlation by both Pearson (r) and Spearman (r_s) correlation coefficients between Lp(a) and total cholesterol (r = 0.27, r_s = 0.24), Lp(a) and LDL cholesterol (r = 0.26, r_s = 0.22), and Lp(a) and apo B (r = 0.24, r_s = 0.21). There was no correlation between Lp(a) and age, body mass index, HDL cholesterol, triglycerides, or apo A-I. Subtracting estimated Lp(a) cholesterol from LDL cholesterol abolished the correlation between Lp(a) and LDL cholesterol. On the other hand, if Lp(a) apo B was subtracted from total apo B, the statistically significant correlation between apo B and Lp(a) disappeared; furthermore, if the contribution of Lp(a) cholesterol to LDL cholesterol was subtracted, then the differences in LDL cholesterol between the two groups was reduced.

Discussion

In this study the concentrations of Lp(a) were significantly greater in adolescents whose parents (mother or father) reported CHD; none of the other lipoprotein variables we examined exhibited a significant difference between the two groups of subjects. These results agree with a previous study in middle-aged men (25), and partially disagree with another study of survivors of myocardial infarction and control subjects (26), in which other lipoprotein markers (total cholesterol, HDL cholesterol, LDL cholesterol, apo A-I, and apo B) differed significantly between the patients and the controls.

The distribution of Lp(a) values in our young population without parental history of CHD was similar to that in other white populations. The differences in mean and median Lp(a) are attributable to both the method used and the true differences in different populations. The distribution of Lp(a) values in children whose parents have had CHD is bimodal, and the cluster at 0.00–0.30 g/L might be considered as a less-intense risk factor than the cluster >0.30 g/L. Consequently, results agree with the observation (27) that serum apo(a) can substitute for a knowledge of the parental history of CHD; however, in our study only 41.9% (18 of 43) of the subjects with parental CHD have Lp(a) concentrations >0.30 g/L. When mean values for subjects without parental history of CHD and with Lp(a) values >0.30 or <0.30 g/L are compared, then highly significant differences appear for total cholesterol, LDL cholesterol, and apo B.

The sample odds ratio confirms the association between increased Lp(a) concentrations and CHD, even in the second decade of life. The prevalence of subjects with parental CHD increases with Lp(a) concentrations >0.30 g/L in our study cohort (Table 1), suggesting that 0.30 g/L might be a useful demarcation line in 11- to 19-year-old subjects, too; these results agree with other studies (5, 28). In our study, Lp(a) is more strongly related to the risk of CHD than are total cholesterol, HDL cholesterol, LDL cholesterol, and even apo A-I and B; these results disagree with another study (29), in which the concentrations of apo A-I and B in children were associated with myocardial infarction in their parents.

The statistically significant correlations obtained in our study have been noted previously: between Lp(a) and total cholesterol (11, 24), between Lp(a) and LDL cholesterol (24), and between Lp(a) and apo B (22). The disappearance of the statistically significant correlations between Lp(a) and apo B and between Lp(a) and LDL cholesterol, after subtracting the estimated Lp(a) apo B and Lp(a) cholesterol, respectively, support the concepts that Lp(a) is not a catabolic product of other lipoproteins and that Lp(a) is an independent risk factor for myocardial infarction. The high Lp(a) concentrations in serum and the hypercholesterolemia could be two interacting factors, as Wiklund et al. (30) recently suggested.

In conclusion, our results support the concept that the concentrations of Lp(a) are more strongly related to risk
of CHD than are other lipoproteins, even apo A-I and B, with a cutoff value for Lp(a) at 0.30 g/L. On the other hand, the distribution of Lp(a) values in our young population is similar to that of other white populations (Figure 1, top). Finally, the correlation between Lp(a) and apo B is not strong enough to dispute the independence of Lp(a) and apo B as risk factors.

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References