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ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 1187–1191
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Impact of markedly elevated serum lipoprotein(a) levels (≥100 mg/dL) on the risk of coronary heart disease

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Received 8 August 2006; accepted 7 April 2007

Abstract

The serum lipoprotein(a) [Lp(a)] concentration is under genetic control, and most humans have values lower than 30 mg/dL. Subjects with markedly elevated serum Lp(a) concentrations, that is, ≥100 mg/dL, are rarely encountered, and these subjects have not yet been fully characterized from the clinical point of view. In the present investigation, we studied a total of 223 subjects, comprising 123 males and 100 females, with serum Lp(a) values of more than 100 mg/dL. Many of these subjects had a variety of underlying diseases, including metabolic disorders, renal diseases, and hypertension. We focused our attention on the patients with metabolic disorders, namely, familial hypercholesterolemia (FH), primary non-FH hypercholesterolemia (HC), and type 2 diabetes mellitus (DM), and conducted a comparative study of the patients of these 3 disease groups with the corresponding disease controls with serum Lp(a) levels of less than 30 mg/dL, a presumed high normal value. The frequency of markedly elevated serum Lp(a) levels in the general population has not been reported previously. We determined the frequencies in a consecutive series of patients at our Diabetes and Lipid Outpatient Clinic; the results revealed that the frequencies were 6.4% (8/125), 2.6% (6/232), and 0.9% (3/352) in patients with FH, HC, and type 2 DM, respectively. In an attempt to further demonstrate the impact of markedly elevated serum Lp(a) concentrations on the risk of coronary heart disease (CHD), we compared the prevalence of CHD among the study subjects with that among the corresponding disease controls. The results revealed a significantly higher CHD prevalence in the study subjects of all the 3 groups as compared with that in the corresponding disease controls: the odds ratios of a markedly elevated serum Lp(a) level were 5.429 (95% confidence interval [CI], 1.353-21.782), 8.243 (95% CI, 2.793-24.327), and 5.981 (95% CI, 2.530-14.139) for FH, HC, and type 2 DM, respectively. In the present study, we examined some characteristics of this rare population of subjects with markedly elevated serum Lp(a) levels and demonstrated a very high prevalence of CHD among these patients with FH, HC, and type 2 DM, strongly suggesting the significance of Lp(a) as a risk factor for CHD.

1. Introduction

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein–like particle linked by a disulfide bond to the glycoprotein apolipoprotein(a) [1-3]. Since the discovery of the Lp(a) system by Berg [1] in 1963, this lipoprotein has attracted much attention as a potential risk factor for atherosclerotic cardiovascular disease, in particular, coronary heart disease (CHD). Although numerous case-control studies [3-6] and prospective studies [7] have indicated an association between elevated serum concentrations of Lp(a) and the risk of CHD, others have reported discrepant results [8-11].

The serum concentration of Lp(a) is under genetic control [3]. In the Japanese population, the distribution of the serum Lp(a) concentrations showed skewing toward lower values, with 90% of the population having values less than 30 mg/dL; [12] this distribution is consistent with the serum concentration profile reported for whites [3]. It is also known that the distributions are broad and trail toward greater values. However, subjects with marked elevations of the serum Lp(a) concentrations, that is, ≥100 mg/dL, seem to be encountered but rarely. Although such subjects have been described in the literature [3,13,14], they have been excluded from studies because of the extreme deviations of the Lp(a) values. In the present study, we

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doi:10.1016/j.metabol.2007.04.015

specifically studied selected subjects showing markedly elevated serum Lp(a) levels and attempted to characterize the clinical features of these subjects.

In an attempt to further demonstrate the significance of serum Lp(a) as a risk factor for CHD, we selected 3 different groups among these subjects with markedly elevated serum Lp(a) levels, namely, those with familial hypercholesterolemia, those with primary hypercholesterolemia, and those with diabetes mellitus, and compared the prevalence of CHD among these subjects with that in the corresponding disease controls having serum Lp(a) values less than 30 mg/dL, a presumed high normal value.

2. Subjects and methods

2.1. Study subjects and disease controls

The study subjects were patients who visited the Toranomon Hospital (Tokyo, Japan). Their blood samples sent to the clinical laboratory center for measurement of the serum lipid were also used for measurement of the serum Lp(a). We defined serum Lp(a) concentrations ≥100 mg/dL as representing markedly elevated levels. From the records of the clinical laboratory center over a period of 5.5 years, we selected a total of 223 subjects, consisting of 123 males and 100 females, ranging in age from 14 to 80 years (58 ± 12 years), whose serum Lp(a) values exceeded 100 mg/dL. We carefully checked the hospital medical records of the selected subjects to obtain information concerning the presence of underlying metabolic disorders such as hyperlipidemia (HL) and diabetes mellitus, and on the history of CHD and its traditional risk factors including hypertension and the smoking habit.

For comparison purposes, we studied a consecutive series of patients with familial hypercholesterolemia (FH), primary non-FH hypercholesterolemia (HC), and type 2 diabetes mellitus (DM) without renal diseases who visited our Diabetes and Lipid Outpatient Clinic. (The diagnosis of FH was made on the basis of its characteristic features, ie, marked elevation of the serum low-density lipoprotein cholesterol to more than 200 mg/dL, thickening of the Achilles tendon [>9 mm], and a history of first-degree relatives with marked hypercholesterolemia or CHD.) There were 125, 232, and 352 patients with FH, HC, and type 2 DM, respectively. Among these, we selected the patients whose serum Lp(a) levels were less than 30 mg/dL as the disease controls. The study was conducted with the approval of the institutional review board.

2.2. Determination of the serum Lp(a) and lipid concentrations

The serum lipid concentrations were measured at the clinical laboratory center of the hospital, and the data were extracted from the records of the laboratory. The serum Lp(a) concentrations had been determined by a latex immunosorbent assay method described previously [15]. The serum cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol concentrations had been determined by routine laboratory methods.

2.3. Underlying metabolic disorders

2.3.1. Hyperlipidemia

Serum cholesterol and/or triglyceride concentrations of more than 240 and 150 mg/dL, respectively, were considered to represent HL. Subjects who were taking lipid-lowering agents were also counted as having HL; in fact, a significant number of patients were taking lipid-lowering agents such as statins or fibrates. Because it was difficult to differentiate HL type IIa (hypercholesterolemia alone) from HL type IIb (hypercholesterolemia with hypertriglyceridemia), we designated both as hypercholesterolemia (HC). Selective hypertriglyceridemia, classified as HL type IV, was designated as hypertriglyceridemia.

2.3.2. Diabetes mellitus

The diagnosis of diabetes mellitus was based on the World Health Organization criteria [16]. Subjects who were taking oral hypoglycemic agents or insulin were also counted as diabetic subjects for this study.

2.4. Coronary heart disease and its traditional risk factors

Subjects with a previous history of myocardial infarction, and/or of having undergone coronary artery bypass graft or percutaneous transluminal coronary angioplasty were considered to have definite CHD. Subjects with blood pressure levels of greater than 140/90 [17], and also those who were taking antihypertensive medication, were considered to have hypertension. Subjects who smoked more than 10 cigarettes per day were designated as habitual smokers.

2.5. Statistical analysis

Results were expressed as the frequency or mean ± SD. Statistical analysis to compare age, plasma lipids, and hemoglobin A_{1c} (HbA_{1c}) between the subject group and the control group was performed using Mann-Whitney *U* test. Category comparison was performed by χ^2 tests. Odds ratios and 95% confidence intervals were calculated using StatView, version 5.0, for Macintosh computer (SAS Institute, Cary, NC). Logistic regression analysis was conducted to estimate the association of CHD with potential risk factors, including age, sex, smoking habit, elevated serum Lp(a), HL, diabetes mellitus, and hypertension. In all the analyses, *P* values of less than .05 were considered to represent significance.

3. Results

3.1. Characteristics of the study subjects (Tables 1 and 2)

The serum Lp(a) concentrations in the study subjects were 133 ± 32 mg/dL (range, 101-356 mg/dL), with 80% of the subjects having values between 100 and 150 mg/dL.

Table 1
Characteristics of the study subjects with markedly elevated serum Lp(a) levels

Subjects, n (male/female)	223 (123/100)
Age (y)	58 ± 12
Lp(a) concentrations (mg/dL)	133 ± 32
Underlying disorders	
HL (n [%])	162 (72.6)
FH (n)	13
Hypercholesterolemia (IIa and IIb) (n)	126
Hypertriglyceridemia (IV) (n)	23
Diabetes mellitus[a] (n [%])	71 (31.8)
Renal diseases (n [%])	49 (22.0)
Chronic renal insufficiency (n)	31
Nephrotic syndrome (n)	22
Hypertension (n [%])	91 (40.8)

[a] Nine and 62 patients with type 1 DM and type 2 DM, respectively.

Many of the subjects had a variety of diseases, including metabolic diseases, renal diseases, and hypertension, as shown in Table 1. Among the metabolic diseases, hypercholesterolemia (n = 139) was encountered most frequently. A significant number of the subjects also had underlying diseases known to cause secondary hypercholesterolemia, such as diabetes mellitus, hypothyroidism, and renal diseases. The number of subjects without any underlying diseases known to cause hypercholesterolemia, who were assumed to have "primary" hypercholesterolemia, was 73 in this study. Among these, 13 patients had FH and 60 had HC. In contrast, the frequency of hypertriglyceridemia (n = 23) was considerably lower than that of hypercholesterolemia among the patients with markedly elevated serum Lp(a) concentrations. Many of these patients with hypertriglyceridemia had underlying disorders (n = 16) potentially influencing triglyceride metabolism, and only 7 patients were presumed to have primary HL, type IV. Diabetes mellitus was the second most frequently encountered disease; 71 patients were found to have diabetes, 9 with type 1 DM, and 62 with type 2 DM. Many of the patients with type 2 DM had renal complications, including chronic renal disease (n = 13) and nephrotic syndrome (n = 4). The remaining 43 patients were subjected to the CHD risk analyses.

Many subjects with markedly elevated serum Lp(a) concentrations had atherosclerotic cardiovascular diseases, including CHD, cerebrovascular diseases, or other cardiovascular diseases, as shown in Table 2. When attention was focused on the prevalence of CHD, 53 had definite CHD and 12 had possible CHD. When 6 young subjects (2 males and 4 females) younger than 30 years were excluded from the total number of study subjects, the prevalence of definite CHD in the subjects with markedly elevated serum Lp(a) concentrations was 24.4% (53/217). There was a sex difference in the prevalence of CHD in the study subjects (40/121 in males vs 13/96 in females; $P < .001$). Risk factor analysis was conducted in a total of 197 subjects, after excluding 6 young subjects younger than 30 years, 7 subjects for whom sufficient data concerning the risk factors were not available, and 13 patients with FH, which is already known as a strong risk factor for CHD. Logistic regression analysis of factors associated with the presence of CHD, including the age, sex, serum Lp(a) concentration, HL, diabetes mellitus, hypertension, and the smoking habit, revealed only age and the smoking habit as statistically significant independent risk factors [age, $P < .01$; smoking, $P < .01$; sex, $P = .377$; Lp(a), $P = .458$; HL, $P = .556$; diabetes mellitus, $P = .595$; hypertension, $P = .208$].

3.2. Frequencies of markedly elevated serum Lp(a) concentrations among patients with FH, HC, and type 2 DM

The frequency of markedly elevated serum Lp(a) levels in the general clinic population has not been reported previously. For reference purposes, we determined the frequency in a consecutive series of patients at our Diabetes and Lipid Outpatient Clinic, and the results revealed that 6.4% (8/125), 2.6% (6/232), and 0.9% (3/352) of the patients with FH, HC, and type 2 DM, respectively, had markedly elevated serum Lp(a) concentrations.

3.3. Comparison of the CHD prevalence in the study subjects with that in the disease controls

The baseline characteristics of the study subjects and the corresponding disease controls are shown in Table 3. The risk factors for CHD were scored as follows: sex, 1 for male and 0 for female; age, 1 for male ≥45 years old and female ≥55 years old and 0 for male <45 years old and female <55 years old; HC, type 2 DM, hypertension, and smoking habit, 1 for (+) and 0 for (−). As for the groups with FH and HL, there were no significant differences between the study group and the disease control group in regard to the sex, age, serum lipid profile, or number of risk factors for CHD. In the case of type 2 DM, the study subjects had higher serum cholesterol and lower HDL cholesterol levels than the disease controls. Other parameters including the HbA_{1c} and number of risk factors of CHD were similar between the 2 groups.

The prevalence of CHD in the study subjects was greater than that in the corresponding disease controls in all the 3 groups.

Table 2
Frequency of cardiovascular diseases among the study subjects

Total no. of subjects	223
Cardiovascular diseases	
CHD I: definite (n [%])	53 (23.8)
Previous myocardial infarction (n)	29
CABG (n)	11
PTCA (n)	13
CHD II: clinical	
Angina pectoris (n [%])	12 (5.4)
Cerebrovascular diseases	
MCI and bleeding (n [%])	18 (8.1)
Other cardiovascular diseases (n [%])	8 (3.6)
Aneurysm of the aorta (n)	6
Peripheral vascular disease (n)	2

CABG indicates coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; MCI, multiple cerebral infarctions.

Table 3
Baseline characteristics of the study subjects and the disease controls

	No.	M/F	Age (y)	HbA_{1c} (%)	Lp(a) (mg/dL)	Cholesterol (mg/dL)	Triglyceride (mg/dL)	HDL cholesterol (mg/dL)	Risk factors (n)
FH									
Subjects	13	5/8	58 ± 9		144 ± 55***	271 ± 44	159 ± 128	43 ± 15	3.4 ± 1.0
Controls	44	18/26	53 ± 9		16 ± 13	281 ± 54	112 ± 61	49 ± 13	2.9 ± 1.4
HC									
Subjects	60	24/36	58 ± 10		135 ± 23***	256 ± 43	131 ± 69	56 ± 21	2.8 ± 1.3
Controls	154	69/85	59 ± 10		15 ± 8	256 ± 29	125 ± 72	61 ± 15	2.9 ± 1.0
Type 2 DM									
Subjects	43	27/16	62 ± 11	7.5 ± 1.9	129 ± 31***	227 ± 41*	122 ± 48	47 ± 14**	4.1 ± 1.3
Controls	276	195/ 81	62 ± 10	7.3 ± 1.6	12 ± 8	212 ± 38	127 ± 103	53 ± 17	4.1 ± 1.1

* $P < .05$.
** $P < .01$.
*** $P < .0001$.

3.3.1. Familial hypercholesterolemia

The prevalence of CHD in the study subjects and the disease controls was 6 of 13 and 6 of 44, respectively ($P = .0323$), and the odds ratio was 5.4286 (95% confidence interval [CI], 1.3529-21.7819).

3.3.2. Primary non-FH hypercholesterolemia

The prevalence of CHD in the study subjects and the disease controls was 13 of 60 and 5 of 154, respectively ($P < .0001$), and the odds ratio was 8.2426 (95% CI, 2.7928-24.3274).

3.3.3. Type 2 DM

The prevalence of CHD in the study subjects and the disease controls was 11 of 43 and 15 of 276, respectively ($P < .0001$), and the odds ratio was 5.9813 (95% CI, 2.5303-14.139).

4. Discussion

Most humans have serum Lp(a) concentrations of less than 30 mg/dL, and to the best of our knowledge, there have been no reports until now specifically addressing subjects with markedly elevated serum Lp(a) concentrations of ≥100 mg/dL. Many of the subjects of this study with markedly elevated serum Lp(a) values had diverse underlying diseases, and the prevalence of CHD in these patients was very high.

The serum level of Lp(a) is under genetic control. The distribution of serum Lp(a) values in the healthy Japanese population was skewed toward lower values, with 90% of the population showing values lower than 30 mg/dL [12]; this distribution is consistent with that reported from many different populations [3,13,14]. It is also known that the distribution of the serum Lp(a) values trails toward greater values; however, only a limited number of reports have described the presence of subjects with markedly elevated serum Lp(a) levels, that is, ≥100 mg/dL [3,13,14]. The frequency of such marked elevation of the serum Lp(a) level in the general population has not yet been reported. We did not address this issue in the present study because the subjects were selected from patients who visited our hospital over a period of 5.5 years. For just reference purposes, however, we determined the frequency in specific groups of patients at our Diabetes and Lipid Outpatient Clinic, and the results revealed frequencies of 6.4%, 2.6%, and 0.9% in patients with FH, HC, and type 2 DM, respectively.

Many subjects with markedly elevated serum Lp(a) concentrations had CHD. In an attempt to confirm whether the prevalence of CHD among the subjects with markedly elevated serum Lp(a) levels was indeed high, we examined, as disease controls, patients from our Diabetes and Lipid Outpatient Clinic. As for FH and HC, the corresponding disease control groups had a comparable serum lipid profile, except for the serum Lp(a) concentration, and a comparable number of risk factors for CHD. In the case of diabetes, the study subjects had higher cholesterol and lower HDL cholesterol levels as compared with the disease controls. This means that the control group was not the most appropriate for comparisons. We have no explanations for the differences in the lipid levels observed between the 2 groups at present. However, except for this difference, there were no other significant differences between the 2 groups: glycemic control as evaluated by the serum HbA_{1c} and the number of risk factors for CHD were similar between the 2 groups. The results of the present study revealed that the prevalence of CHD in the study subjects was much greater than that in the corresponding disease controls in all the 3 groups. Again, in the case of the subjects of the 2 groups with type 2 DM, the differences in the lipid levels may have had some degree of influence; however, it is difficult to reason that such differences could have contributed in any significant manner to the substantially increased prevalence of CHD in the study subjects with markedly elevated serum Lp(a) levels.

The results of our logistic regression analysis of the study subjects indicated that only age and the smoking habit were independent risk factors for CHD. It is possible that the serum Lp(a) level of 100 mg/dL exerts a maximal effect on the CHD risk and that the risk does not increase further with further increase of the serum Lp(a) values.

In conclusion, we characterized the clinical features of 223 subjects with markedly elevated serum Lp(a) levels. Many of the subjects had a variety of underlying disorders, including FH, HC, and type 2 DM. The subjects with FH and HC, and possibly type 2 DM, with markedly elevated serum Lp(a) values had a high prevalence of CHD, strongly suggesting the significance of Lp(a), at least markedly elevated concentrations of Lp(a), as a risk factor for CHD.

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