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Impact of elevated serum lipoprotein (a) concentrations on the risk of coronary heart disease in patients with type 2 diabetes mellitus

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Abstract

Type 2 diabetes mellitus is associated with a marked increase of coronary heart disease (CHD). We aimed to assess the impact of elevated serum lipoprotein (a) (Lp[a]) concentrations on the risk of CHD in patients with type 2 diabetes mellitus. A consecutive series of 352 outpatients was investigated. We determined the serum lipid profile and checked the patients for a history of CHD and of its traditional risk factors. Furthermore, the patients were divided into 3 groups according to the degree of elevation of the serum Lp(a) concentration: serum Lp(a) concentrations greater than 50 mg/dL, between 30 and 50 mg/dL, and less than 30 mg/dL, a presumed high normal value; and the prevalence of CHD was compared among the 3 groups. The serum Lp(a) concentrations in the subjects varied widely from 0.4 to 163.6 mg/dL. Patients with CHD had significantly higher serum Lp(a) concentrations than those without CHD ($P = .0045$). Logistic regression analysis to identify factors associated with the presence of CHD revealed that elevated serum Lp(a) is a significant risk factor ($P = .0246$). The prevalence of CHD increased with increasing serum Lp(a) concentrations ($P = .048$). Patients with serum Lp(a) concentrations greater than 50 mg/dL had a significantly higher prevalence of CHD than those with serum Lp(a) concentrations less than 30 mg/dL: the odds ratio of an elevated serum Lp(a) concentration was 3.346 ($P = .039$). In conclusion, elevated serum Lp(a) is a significant risk factor; and the risk of CHD appears to increase with increasing serum Lp(a) concentrations. Serum Lp(a) concentration of 50 mg/dL might represent a threshold level in relation to the risk of CHD in patients with type 2 diabetes mellitus.

1. Introduction

Type 2 diabetes mellitus is associated with a marked increase in the risk of cardiovascular diseases, in particular, of coronary heart disease (CHD) [1,2]. The traditional risk factors for CHD, namely, hypertension, elevated serum cholesterol, and smoking habit, do not explain the excessive prevalence of CHD among diabetic patients. We considered that one possible factor that may increase the risk of CHD in diabetic patients might be elevated serum lipoprotein (a) (Lp[a]) concentrations.

Lipoprotein (a) is a low-density lipoprotein–like particle linked by a disulfide bond to the glycoprotein apolipoprotein (a) [3-5]. Since the discovery of the Lp(a) system by Berg [3] in 1963, this lipoprotein has attracted much attention as a potential risk factor for atherosclerotic cardiovascular diseases. A number of case-control studies [5-8] and prospective studies [9] have indicated that elevated serum Lp(a) concentrations are a risk factor for CHD in the general population. However, the situation may be different in patients with diabetes mellitus. Studies of the serum Lp(a) concentrations in patients with type 2 diabetes mellitus are limited, and the significance of elevated serum Lp(a) concentrations in patients with type 2 diabetes mellitus remains inconclusive: some studies have indicated a direct association between elevated serum concentrations of Lp(a) and the risk of CHD in these patients [10], whereas others have shown discrepant results [11]. The results of prospective studies are also conflicting [12-14]. Although the exact reasons for the conflicting reports are not clear, special attention must be paid to the fact that the distribution of the serum Lp(a) concentrations in the population differs greatly

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from those of other lipids: it is broad, with an extremely wide range of variations from less than 0.2 mg/dL to more than 200 mg/dL [5], and shows striking skewing toward lower concentrations, with 90% of the population having concentrations less than 30 mg/dL [5], which may sometimes complicate data analysis.

Previously, we reported a positive association between high serum Lp(a) concentrations and the risk of cardiovascular events in diabetic patients, based on the results of a prospective study [12]. Very recently, we demonstrated that markedly elevated serum Lp(a) concentrations (≥100 mg/dL) are associated with a 5-fold or greater increase in the CHD risk in patients with type 2 diabetes mellitus, as well as in patients with familial and nonfamilial hypercholesterolemia [15]. The aim of the present study was to demonstrate the impact of elevated serum Lp(a) concentrations on the risk of CHD in patients with type 2 diabetes mellitus.

2. Subjects and methods

2.1. Study subjects

A consecutive series of 352 patients (236 men and 116 women, 33-85 years of age) with type 2 diabetes mellitus who visited our Diabetes and Lipid Outpatient Clinic was enrolled in the present study. The duration of diabetes in the study subjects was 15 ± 9 years. About half of the patients, that is, 173 of the 352 patients, were receiving medications for diabetes (insulin in 46 and oral hypoglycemic agents in 127); and 62 patients (17.6%) were receiving lipid-lowering agents. Patients with end-stage renal disease and nephrotic syndrome, both of which have been reported to be associated with significant increase of the serum Lp(a) levels and increased risk of CHD [5,15], were not included.

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

Blood samples were collected for measurement of fasting blood glucose; glycosylated hemoglobin (HbA_{1c}); and the serum cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), and Lp(a) concentrations. The serum Lp(a) concentrations were measured by the latex immunosorbent assay method described previously [16], and the other parameters mentioned were determined by routine laboratory methods.

2.3. CHD and its traditional risk factors

We obtained a careful history of CHD and of its traditional risk factors, including dyslipidemia, hypertension, and history of smoking, from the subjects.

2.3.1. Coronary heart disease

Subjects with a previous history of myocardial infarction and/or of having undergone coronary bypass grafting or percutaneous transluminal coronary angioplasty were considered to have definite CHD.

2.3.2. Dyslipidemia

Serum cholesterol, triglyceride, and HDL-C concentrations of ≥220, ≥150, and <40 mg/dL, respectively, were considered to represent dyslipidemia. Subjects who were taking lipid-lowering agents were also counted as having dyslipidemia.

2.3.3. Hypertension

Subjects with blood pressure values greater than 140/90 mm Hg and also those who were taking antihypertensive medication were considered to have hypertension.

2.3.4. Smoking habit

Subjects who smoked more than 10 cigarettes per day were designated as smokers. Both past and current smokers were included.

2.4. Risk factor analysis

The risk factors for CHD were scored as follows: sex: 1 for male and 0 for female; age: 1 for male subjects ≥45 years old and female subjects ≥55 years old, and 0 for male subjects <45 years old and female subjects <55 years old; dyslipidemia, hypertension, and smoking habit: 1 for "+" and 0 for "−."

In the analysis conducted to identify independent factors, 3 lipid parameters (ie, HDL-C, non–HDL-C, and triglycerides) were entered in place of dyslipidemia. Because Lp(a) contains about 45% cholesterol [17,18], Lp(a)-cholesterol ([Lp[a]-C) values may reach considerably high values at concentrations greater than 50 mg/dL; and the contribution of Lp(a) to the total cholesterol level should be taken into account. Therefore, non-HDL, non-Lp(a) cholesterol values were obtained by calculating Lp(a)-C (Lp[a] mass × 0.45) and then subtracting HDL-C and Lp(a)-C from the total cholesterol level; and this was designated as the "corrected" non–HDL-C values.

2.5. Statistical analysis

Results were expressed as the frequency or mean ± SD. Comparisons between groups were performed using Student t test for continuous variables, whereas for the serum Lp(a) concentrations, the comparisons were conducted using Mann-Whitney U test. Category comparison was performed by the χ^2 test. The odds ratios and 95% confidence intervals were calculated using StatView, version 5.0, for Macintosh computer (SAS, Cary, NC). Logistic regression analysis was conducted to estimate the association of CHD with potential risk factors, including the age, sex, HbA_{1c}, serum Lp(a), serum lipid levels (HDL-C, corrected non–HDL-C, and triglycerides), hypertension, and smoking habit. The serum Lp(a) concentrations were log-transformed before the logistic regression analysis. In all the analyses, P values less than 0.05 were considered to represent significance.

Table 1
Characteristics of the study patients with and without CHD

	CHD (+)	CHD (−)	*P* value
n	25	327	
Age (y)	65 ± 9	62 ± 10	NS
Sex (M/F)	18:7	218:109	NS
Duration of diabetes (y)	19 ± 9	15 ± 9	.0381
HbA_{1c} (%)	7.7 ± 1.7	7.3 ± 1.5	NS
Lp(a) (mg/dL)	21.9 (5.4-163.6)	13.9 (0.4-140.3)	.0045
Cholesterol (mg/dL)	221 ± 34	215 ± 38	NS
HDL-C (mg/dL)	46 ± 12	54 ± 17	.0124
Corrected non–HDL-C (mg/dL) [a]	161 ± 32	152 ± 38	NS
Triglycerides (mg/dL)	117 ± 42	124 ± 97	NS
Hypertension (%)	72	63.9	NS
Smoking habit (%)	80	41	.0002

Data are means ± SD. For Lp(a), the data represent the median (range); and the statistical test used is Mann-Whitney *U* test. The Lp(a)-C was obtained by calculating Lp(a) × 0.45. NS indicates not significant.

[a] Corrected non–HDL-C = total cholesterol − HDL-C − Lp(a)-C.

The study was conducted with the approval of the institutional review board.

3. Results

3.1. Baseline characteristics of the study patients

The study patients were mostly nonobese, with a body mass index of 21.7 ± 2.6. The fasting blood glucose and HbA_{1c} values were 138 ± 38 mg/dL and 7.4% ± 1.5%, respectively. The median serum Lp(a) concentration was 14.5 mg/dL (range, 0.4-163.6 mg/dL). The serum concentrations of total cholesterol, triglycerides, and HDL-C were 216 ± 38, 123 ± 95, and 53 ± 17 mg/dL, respectively, although many patients (62/352, 19.6%) were taking lipid-lowering agents, including statins and fibrates.

3.2. Comparison of the characteristics of patients with and without CHD

The overall prevalence of CHD in the study subjects was 7.8% (25/352). The baseline characteristics of the patients who did and did not have CHD are shown in Table 1. The mean age was similar in the subject groups with and without CHD. There was no sex-related difference in the prevalence of CHD (18/236 and 7/116 in men and women, respectively).

The duration of diabetes was longer in the subject group with CHD as compared with that in the subject group without CHD. Glycemic control, as evaluated by the HbA_{1c} values, was similar between the 2 groups of patients. The proportion of subjects receiving insulin or oral hypoglycemic agents was similar in the subject groups with and without CHD. The proportion of subjects taking lipid-lowering agents was significantly higher in the subject group with CHD than in the subject group without CHD (12/25 vs 50/327, $P < .0001$). Serum Lp(a) concentrations are also known to be elevated in patients with end-stage renal disease and nephrotic syndrome [5,15]. In the 25 patients with CHD in the present study, the serum creatinine and blood urea nitrogen concentrations were in the range of 0.7 to 1.3 mg/dL (0.9 ± 0.2 mg/dL) and 12 to 34 mg/dL (18 ± 5 mg/dL), respectively. Urinary albumin excretion was negligible (<30 mg/g creatinine) and minimal (microalbuminuria, <300 mg/g creatinine) in 11 and 10 patients, respectively, with the remaining 4 patients showing clinical proteinuria (84-168 mg/dL).

Patients with a history of CHD had significantly higher serum concentrations of Lp(a) than those without a history of CHD. The serum corrected non–HDL-C and triglyceride concentrations were similar in the 2 groups, whereas the serum HDL-C concentrations were significantly lower in the patients with CHD than in those without CHD.

3.3. Risk factor analysis

Logistic regression analysis to identify factors associated with the presence of CHD revealed that elevated serum Lp(a) concentrations as well as smoking habit and reduced serum HDL-C concentrations were statistically significant independent risk factors (age, $P = .8418$; sex $P = .6168$; HbA_{1c}, $P = .5375$; Lp[a], $P = .0246$; HDL-C, $P = .0424$; corrected non–HDL-C, $P = .0911$; triglycerides, 0.0867; hypertension, $P = .4129$; smoking, $P = .0033$).

3.4. Prevalence of CHD in relation to the degree of elevation of the serum Lp(a) levels

The subjects of the study were then divided into 3 groups according to the degree of elevation of the serum Lp(a) concentrations: group A, Lp(a) ≥50 mg/dL; group B, 30 to <50 mg/dL; and group C, <30 mg/dL. Because 30 mg/dL is the presumed high normal value [4], group C was assumed as a disease control. The baseline characteristics of these

Table 2
Baseline characteristics of the 3 groups of patients with type 2 diabetes mellitus

Lp(a) (mg/dL)	n	M/F	Age (y)	HbA_{1c} (%)	Triglycerides (mg/dL)	Corrected non–HDL-C (mg/dL) [a]	HDL-C (mg/dL)	Risk Factors (n) [b]
Group A (≥50)	31	16:15	65 ± 11	7.6 ± 1.3	121 ± 48	147 ± 37	52 ± 14	3.4 ± 0.8
Group B (30-<50)	45	25:20	65 ± 11	7.7 ± 1.4	101 ± 48	153 ± 30	55 ± 16	3.4 ± 1.1
Group C (<30)	276	195:81	62 ± 10	7.3 ± 1.6	127 ± 104	154 ± 39	53 ± 17	3.3 ± 1.1

[a] Corrected non–HDL-C = total cholesterol − HDL-C − Lp(a)-C. Lipoprotein(a) cholesterol was obtained by calculating Lp(a) × 0.45.

[b] Risk factors: sex, 1 for male and 0 for female; age, 1 for male subjects ≥45 years old and female subjects ≥55 years old, and 0 for male subjects <45 years old and female subjects <55 years old; hypertension and smoking habit, 1 for "+" and 0 for "−."

Table 3
Prevalence of CHD in relation to the degree of elevation of the serum Lp(a) concentration

Lp(a) (mg/dL)	n	CHD (+)	Odds ratio	95% CI	*P* value
Group A (≥50)	31	5	3.346	1.126-9.947	.039
Group B (30-<50)	45	5	2.175	0.749-6.312	.175
Group C (<30)	276	15	1		

CI indicates confidence interval.

3 groups of patients are shown in Table 2. There were no significant differences between the 3 groups in regard to the age, sex ratio, HbA_{1c}, serum lipid profile (corrected non–HDL-C, HDL-C, and triglycerides) or the number of risk factors for CHD.

A comparison of the prevalence of CHD in the 3 groups is shown in Table 3; the prevalence increased steadily with increase in the serum Lp(a) concentration (group C to group A) ($P = .048$). As compared with that in the control group (group C), a trend toward an increase in the prevalence of CHD among the subjects with slight elevation of the serum Lp(a) concentrations (group B), and a significant increase in the prevalence of CHD among the subjects with more marked elevation (≥50 mg/dL) of the serum Lp(a) concentrations were observed (group A).

4. Discussion

The present study showed that diabetic patients with CHD had significantly higher serum Lp(a) concentrations than those without CHD. Logistic regression analysis to identify factors associated with the presence of CHD revealed that the serum Lp(a) concentration is a risk factor for CHD. Results of the prevalence of CHD in relation to the degree of elevation of the serum Lp(a) concentration revealed a steady increase in the prevalence of CHD with an increase in the serum Lp(a) concentration, and serum concentrations greater than 50 mg/dL were associated with a 3.3-fold increase in the risk of CHD. The results of the present study strongly indicate that elevated serum Lp(a) concentrations represent a significant risk factor for CHD, and the concentration of 50 mg/dL may represent an apparent threshold value in relation to the risk of CHD in patients with diabetes.

Although the clinical significance of the serum Lp(a) concentration is well recognized in the general population [5-9], information about its significance in diabetic patients is still limited; and the results are conflicting: some studies have indicated an association between elevated serum Lp(a) concentrations and the risk of CHD [10,12,13], whereas others have demonstrated the absence of any such association [11,14]. The precise reason for this discrepancy is not certain; however, this may arise, at least in part, from the fact that the distribution of serum Lp(a) concentrations is broad, with an extremely wide range of variations from less than 0.2 mg/dL to more than 200 mg/dL, and shows striking skewing toward lower values [5]. A review of the literature indicates that sometimes subjects with markedly elevated serum Lp(a) concentrations have been excluded from studies because of the extreme deviations of the Lp(a) values [5]. A recent report addressing the role of Lp(a) in patients with type 2 diabetes mellitus studied only patients with serum Lp (a) concentrations less than 30 mg/dL [14]. In addition, we must recognize that because Lp(a) particles contain about 45% cholesterol [17,18], the Lp(a)-C values should reach considerably high values at high serum Lp(a) concentrations. Thus, when serum Lp(a) concentrations are elevated, conventional "calculated low-density lipoprotein cholesterol (LDL-C)" values might be overestimated; and this may obscure the significance of elevated serum Lp(a). Almost none of the previous cardiovascular complication studies appear to have taken the contribution of Lp(a)-C to total cholesterol into account.

The results of our logistic regression analysis indicated that elevated serum Lp(a) concentrations as well as reduced serum HDL-C concentrations and smoking habit were independent risk factors for CHD. There was no difference in the corrected non–HDL-C value, corresponding to the serum LDL-C, between the subject groups with and without CHD. However, the proportion of subjects taking lipid-lowering agents was significantly higher in the subject group with CHD than in the subject group without CHD; and this could be the reason why the serum "LDL-C" was not significantly different between the 2 subject groups. In the present study, no sex-related difference was observed in the prevalence of CHD. This suggests that the normal sex-related difference in the prevalence of cardiovascular diseases is eliminated in the presence of diabetes mellitus [19,20].

Kostner et al [21] reported that serum Lp(a) concentrations greater than 30 mg/dL represent a relative risk of 1.75 for myocardial infarction in normolipidemic men and that those with serum Lp(a) concentrations greater than 50 mg/dL show a 2.3-fold relative risk. From these results, they concluded that elevated serum Lp(a) concentrations represent an independent risk factor for myocardial infarction and that the concentration of 30 mg/dL represents a possible threshold for an increase in the risk in the normolipidemic population [21]. In our study, the prevalence of CHD increased with increasing serum concentrations of Lp(a); and serum concentrations greater than 50 mg/dL were associated with a significant increase in the risk of CHD. We suggest that the serum concentration of 50 mg/dL represents a threshold in relation to the risk of CHD in diabetic subjects.

Thirty-one of the 352 subjects, that is, 8.8%, exhibited serum Lp(a) concentrations greater than 50 mg/dL. From the results of the present study, we do think that these subjects need to be treated. It is known, however, that the serum Lp(a) concentration is mostly under genetic control and that major lipid-lowering agents, including statins and fibrates, are ineffective at lowering the serum Lp(a) concentrations Nicotinic acid is known to decrease the serum Lp(a) concentration; however, this agent may worsen glycemic

control and should not be given to patients with diabetes [22]. A number of publications, including ours [23], have shown that a large dose of estrogen caused a marked reduction of the serum Lp(a) concentrations; and we hope that some derivatives without hormonal action may become available in the future.

In conclusion, the present study results showed that elevated serum Lp(a) is a significant risk factor for CHD in patients with diabetic subjects and that serum Lp(a) concentrations greater than 50 mg/dL were associated with a 3.3-fold increase in the risk of CHD, representing an apparent threshold for an increase in the risk of CHD in patients with type 2 diabetes mellitus.

References

[1] Kannel WB, McGee DC. Diabetes and cardiovascular risk factors: the Framingham study. Circulation 1979;59:8-13.

[2] Nathan DM, Meigs J, Singer DE. The epidemiology of cardiovascular disease in type 2 diabetes mellitus: how sweet it is/or is it? Lancet 1997;350(Suppl 1):S14-9.

[3] Berg K. A new serum type system in man: the Lp(a) system. Acta Pathol Microbiol Scand 1963;59:362-82.

[4] Scanu AM, Fess GM. Lipoprotein(a). Heterogeneity and biological relevance. J Clin Invest 1990;85:1709-15.

[5] Utermann G. Lipoprotein(a). In: Scriber CR, Beaudet AL, Aly WS, Vallo O, editors. The metabolic and molecular bases of inherited disease. 8th ed. McGraw-Hill; 2001. p. 2753-89.

[6] Nguyen TT, Ellefson RD, Hodge DO, Bailey KR, Kottke TE, Abu-Lebden HS. Predictive value of electrophoretically detected lipoprotein (a) for coronary heart disease and cerebrovascular disease in a community-based cohort of 9936 men and women. Circulation 1997; 96:1390-7.

[7] Marcovina SM, Koschisky ML. Lipoprotein(a) as a risk factor for coronary artery disease. Am J Cardiol 1998;82:57U-66U.

[8] Yamazaki T, Katoh K, Nakanishi S, Nishiyama S, Seki A, Okubo M, et al. Prediction of the severity of coronary artery disease by measurement of lipoprotein(a). Coron Artery Dis 1992;3:51-60.

[9] Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease: meta-analysis of prospective studies. Circulation 2000;102:1082-5.

[10] Mohan V, Deepa R, Haranath SP, Premalatha G, Rema M, Sastry NG, et al. Lipoprotein(a) is an independent risk factor for coronary artery disease in NIDDM patients in South India. Diabetes Care 1998;21: 1819-23.

[11] Haffner SM, Moss SE, Klein BEK, Klein R. Lack of association between lipoprotein(a) concentrations and coronary heart disease mortality in diabetes: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Metabolism 1992;41:149-97.

[12] Hiraga T, Kobayashi T, Okubo M, Nakanishi K, Sugimoto T, Ohashi Y, et al. Prospective study of lipoprotein(a) as a risk factor for atherosclerotic cardiovascular disease in patients with diabetes. Diabetes Care 1995;18: 241-3.

[13] Shai I, Schulze MB, Manson JE, Stampfer MJ, Rifai N, Hu FB. A prospective study of lipoprotein(a) and risk of coronary heart disease among women with type 2 diabetes. Diabetologia 2005;48:1469-76.

[14] Saely CH, Koch L, Schmit F, Marte T, Aczel S, Langer P, et al. Lipoprotein(a), type 2 diabetes and vascular risk in coronary patients. Eur J Clin Invest 2006;36:91-7.

[15] Murase T, Okubo M, Amemiya-Kudo M, Hiraga T, Oka J, Shimada M, et al. Impact of markedly elevated serum lipoprotein(a) levels (≥100 mg/dl) on the risk of coronary heart disease. Metabolism 2007; 56:1187-91.

[16] Hiraga T, Shimada M, Okubo M, Nakanishi K, Kobayashi T, Murase T. Lipoprotein(a) is an independent risk factor for multiple cerebral infarctions. Atherosclerosis 1996;122:29-32.

[17] Kostner GM, Ibovnik A, Holzer H, Grillhofer H. Preparation of a stable frozen primary lipoprotein[a] (Lp[a]) standard. J Lipid Res 1999;40: 2255-63.

[18] Marcovina SM, Albers JJ, Scanu AM, Kennedy H, Giaculli F, Berg K, et al. Use of a reference material proposed by the International Federation of Clinical Chemistry and Laboratory Medicine to evaluate analytical methods for the determination of plasma lipoprotein(a). Clin Chem 2000;46:1956-67.

[19] Sowers JR, Lester MA. Diabetes and cardiovascular disease. Diabetes Care 1990;22(Suppl 3):C14-20.

[20] Barett-Conner E Cohn BA, Wingard DL, Edelstein SL. Why is diabetes a strong risk factor for fatal ischemic heart disease in women and in men? JAMA 1991;265:627-31.

[21] Kostner GM, Avogaro P, Cazzolato G, Marth E, Bittolo-Bon G, Qunici GB. Lipoprotein Lp(a) and the risk for myocardial infarction. Atherosclerosis 1981;38:51-61.

[22] Carlson LA, Hamsten A, Asplund A. Pronounced lowering of serum Lp(a) in hyperlipidaemic subjects treated with nicotinic acid. J Intern Med 1989;226:271-6.

[23] Hiraga T, Harada K, Kobayashi T, Murase T. Reduction of serum lipoprotein(a) using estrogen in a man with familial hypercholesterolemia. JAMA 1992;267:2328.