EXTENDED REPORTS

Increased concentrations of serum Lp(a) lipoprotein in patients with primary gout

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Abstract

Objectives—To investigate if serum Lp(a) lipoprotein (Lp(a)), a risk factor for atherosclerotic diseases, increases in patients with gout, who frequently also have atherosclerotic disease.

Methods—Fasting blood samples were taken for measurement of Lp(a) and other variables in 175 male patients with primary gout. Serum concentrations of Lp(a) were measured by enzyme linked immunosorbent assay. The median value and frequency distribution of Lp(a) in gout patients were compared with those in 172 control male subjects. In addition, we examined the effect of niceritorol on serum Lp(a) values in gout patients in whom the Lp(a) concentration was greater than 20 mg/dl.

Results—Serum Lp(a) was significantly higher in patients with gout than control subjects (median 15.5 mg/dl v 8.6 mg/dl; $p < 0.01$). The frequency distribution of Lp(a) in gout was significantly shifted towards greater concentrations compared with control, although skewed distribution was noted in both groups. Serum Lp(a) concentration was not related to age, body mass index, alcohol intake, creatinine, fasting blood sugar or uric acid in patients with gout. Niceritorol decreased the serum concentrations of Lp(a) in gout.

Conclusions—These observations suggest that serum Lp(a) concentrations are increased in patients with gout and may play a role as one of the risk factors for atherosclerotic diseases in gout. Niceritorol seems effective in decreasing high levels of Lp(a) in patients with gout without detrimental influence on serum uric acid concentration.

(*Ann Rheum Dis* 1995; 54: 90-93)

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Accepted for publication 1 September 1994

In recent years, atherosclerotic diseases including ischaemic heart disease have become important causes of death in patients with gout. A previous in vitro study¹ demonstrated that uric acid provokes the proliferation of vascular smooth muscle cells, resulting in arteriosclerosis. However, it remains undetermined whether or not hyperuricaemia per se is an independent risk factor for arteriosclerosis. In contrast, it is well known that lipid abnormalities such as hypercholesterolaemia, decreased concentrations of high density lipo-

protein cholesterol (HDL-C), hypertriglyceridaemia and increased serum apolipoprotein B concentrations are important risk factors for atherosclerosis. Previous studies have demonstrated that serum concentrations of both triglyceride and apolipoprotein B were greater in patients with gout than in normal subjects, while HDL-C was decreased in patients with gout.²⁻³ Thus gout patients share some of the characteristics of the so called 'multiple risk factor clustering syndrome'.

Lp(a) lipoprotein (Lp(a)) is a plasma lipoprotein similar to LDL because apolipoprotein(a) is linked to apolipoprotein B-100 by a disulphide bond. Lp(a) was first discovered in plasma in 1963 by Berg;⁴ thereafter its concentration was demonstrated to be increased in patients with myocardial infarction.⁵ Since then, many studies have demonstrated that Lp(a) is related to the development of atherosclerotic diseases.⁶⁻⁷ However, to our knowledge, only one study has investigated serum Lp(a) concentration in patients with gout,⁸ but in a small number of subjects. Therefore we measured the serum concentration of Lp(a) and that of lipids in a relatively large number of patients with gout, and compared them with control subjects in an attempt to investigate if Lp(a) contributes to the high incidence of atherosclerotic diseases in gout.

Subjects and methods

SUBJECTS

The subjects were 175 male patients with primary gout, aged 20-81 years (mean 49.1 (SE 1.0) years) and 172 control male subjects aged 23-88 (mean 48.5 (0.8) years). All patients met the criteria on primary gout as outlined by the American Rheumatism Association.⁹ After informed consent was obtained, any medication affecting serum lipid profiles was withheld from at least six months before the study. Subjects who had diseases known to cause hyperlipidaemia, such as diabetes mellitus, renal or hepatic diseases, were excluded from the study. Control male subjects were selected randomly from applicants for an annual medical check-up and had normal results on urine analysis, complete blood counts and routine biochemical analyses which included a 75 g oral glucose tolerance test. Information on frequency, quantity and type of alcohol intake was obtained by questionnaire and converted to a measure of daily alcohol consumption according to Thomson and Majumdar.¹⁰

Table 1 Clinical features and laboratory data of the subjects

	Gout (n = 175)	Control (n = 172)	p
Age (yr)	49.1 (1.0)	48.6 (0.8)	NS
BMI (kg/m ²)	24.0 (0.2)	24.2 (0.2)	NS
Alcohol intake (g/day)	21.1 (1.6)	19.9 (1.5)	NS
SBP (mm Hg)	135.6 (1.3)	126.8 (1.2)	<0.01
DBP (mm Hg)	80.7 (0.7)	80.4 (0.8)	NS
Uric acid (mg/dl)	8.8 (0.1)	5.5 (0.1)	<0.01
ALT (KU)	23.5 (0.8)	23.3 (0.8)	NS
AST (KU)	22.9 (0.5)	22.7 (0.6)	NS
γ-GTP (IU/l)	46.1 (2.2)	44.5 (2.4)	NS
FBS (mg/dl)	98.0 (1.2)	98.5 (0.8)	NS
Creatinine (mg/dl)	1.0 (0.0)	1.0 (0.0)	NS

Mean values (SE). BMI = Body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; ALT = alanine aminotransferase; AST = aspartate aminotransferase; γ-GTP = γ-glutamyl transpeptidase; FBS = fasting blood sugar; NS = not significant.

Table 2 Serum concentrations of Lp(a), lipids and apolipoproteins in patients with gout and control subjects

	Gout (n = 175)	Control (n = 172)	p
Lp(a) (mg/dl)	15.5 (1.0–90.5)†	8.6 (1.0–61.4)†	0.01
T-cholesterol (mg/dl)	19.9 (1.2)	12.7 (0.9)	NS
Triglyceride (mg/dl)	209.7 (2.8)	207.4 (2.9)	NS
Phospholipid (mg/dl)	197.5 (11.1)	154.5 (10.9)	<0.05
HDL-C (mg/dl)	237.7 (3.7)	233.8 (3.2)	NS
Apo A-I (mg/dl)	47.8 (0.9)	51.1 (1.1)	<0.05
Apo A-II (mg/dl)	131.8 (1.9)	130.0 (1.7)	NS
Apo B (mg/dl)	37.6 (0.7)	33.1 (0.4)	<0.01
Apo C-II (mg/dl)	108.5 (1.8)	99.6 (1.9)	<0.01
Apo C-III (mg/dl)	5.6 (0.2)	4.3 (0.2)	<0.01
Apo E (mg/dl)	15.1 (0.6)	11.6 (0.5)	<0.01
	6.8 (0.2)	5.1 (0.2)	<0.01

†Median and range; other values mean (SE). Lp(a) = Lp(a) lipoprotein; HDL-C = high density lipoprotein cholesterol; Apo = apolipoprotein; NS = not significant.

Table 3 Multiple regression analysis of serum Lp(a) on selected independent variables in 175 patients with gout

Variable	Partial regression coefficient	Standard regression coefficient	Partial correlation coefficient	Partial F value	p
Age	0.113854	0.0972779	0.0884821	1.32567	NS
BMI	0.309675	0.0554656	0.0541423	0.49392	NS
Alcohol intake	-0.0491642	-0.0663583	-0.0654893	0.72363	NS
Creatinine	-11.9794	-0.133279	-0.123932	2.62057	NS
Uric acid	-1.1129	-0.0985665	-0.0957275	1.55375	NS
FBS	0.0193369	0.0197248	0.0190495	0.0609864	NS

BMI = Body mass index; FBS = fasting blood sugar; NS = not significant.

NICERITOROL

Fifteen subjects in whom the Lp(a) concentration was greater than 20 mg/dl were treated with nickeritorol 750 mg/day for 5 months and their serum Lp(a) concentration was measured at 1, 3 and 5 months.

MEASUREMENTS

Blood samples were obtained after an overnight fast. Serum Lp(a) was determined by enzyme linked immunosorbent assay (ELISA)¹¹ using Tint ELISA Lp(a) kit (Biopool International AB, Umea, Sweden). Serum total cholesterol and triglyceride concentrations were measured by enzymatic methods. HDL-C was measured by the heparin calcium precipitation method.¹² Serum apolipoproteins A-I, A-II, B, C-II, C-III and E were determined by the single radial immunodiffusion method, using the respective kits (Daiichi Pure Chem Co. Ltd, Tokyo, Japan).

STATISTICAL ANALYSES

With the exception of Lp(a), data were expressed as the mean (SE); the non-parametrically distributed Lp(a) concentrations were expressed as medians and ranges. Wilcoxon-Mann-Whitney rank sum test was used to compare the significance of any differences in medians of Lp(a) values between patients and controls. Other data on laboratory and clinical features were tested by Student's *t* test for significance. Comparison of Lp(a) distribution frequency between gout and control was made by the Kolmogorov-Smirnov test. Multiple regression analysis was used to assess the association between serum Lp(a) concentration and other measured variables. A *p* value less than 0.05 was considered statistically significant.

Results

SUBJECTS AND CLINICAL FEATURES

Table 1 shows the clinical features and laboratory data of the subjects. Body mass index, age, and alcohol intake were not different between gout and control groups. Serum uric acid and systolic blood pressure values were significantly greater in patients than in normal controls (*p* < 0.01), while serum alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase, fasting blood sugar and creatinine values were not different between the two groups.

SERUM LP(A), LIPIDS AND APOLIPOPROTEINS

Table 2 shows the concentrations of serum Lp(a), lipids and apolipoproteins. Serum concentrations of Lp(a), triglyceride, apolipoproteins A-II, B, C-II, C-III and E were significantly greater in patients with gout than in normal controls, while the HDL-C concentration was significantly less in patients than in normal controls. Serum total cholesterol values did not differ between the two groups. Multiple regression analysis demonstrated that Lp(a) was not related to all the variables tested (table 3). The distribution of Lp(a) concentrations in gout patients was significantly different from that in control subjects (*p* < 0.01) (fig 1).

EFFECT OF NICERITOROL ON LP(A) CONCENTRATION

In the 15 gout subjects with Lp(a) concentrations greater than 20 mg/dl who were treated with 750 mg/day nickeritorol, serum concentrations of Lp(a) decreased significantly after 1, 3 or 5 months (fig 2).

Discussion

The present study demonstrated an increase in Lp(a) concentrations in patients with gout. The skewed distribution of the concentrations was in agreement with previous reports suggesting that the major determinants of Lp(a) concentrations are common for both gout and control subjects. However, the

Figure 1 Distribution frequency of serum Lp(a) lipoprotein concentrations in patients with gout ($n = 175$) (▨) and control subjects ($n = 172$) (□). The distribution frequency of serum Lp(a) lipoprotein concentrations in gout was significantly different from that in control, although skewed distribution was noted in both gout and control.

Figure 2 Mean (SE) changes in serum Lp(a) lipoprotein concentration after administration of 750 mg/day nicositol. * $p < 0.05$; ** $p < 0.01$ compared with before nicositol. $n = 15$.

frequency distribution of Lp(a) in gout was significantly different from that in controls: fewer patients with gout had Lp(a) concentrations less than 10 mg/dl, and more patients with gout had Lp(a) concentrations greater than 20 mg/dl compared with control subjects.

Regarding correlations with other lipids, inverse relationship between serum Lp(a) and triglyceride concentrations have been reported by several workers.^{13, 14} However, in spite of greater serum triglyceride concentrations in gout as described previously, Lp(a) concentrations were also significantly higher. Therefore increased triglyceride concentration may have little influence on the regulation of Lp(a) concentration in gout. The rate of production of Lp(a) has also been reported to be a major determinant of differences in Lp(a) concentrations,^{15, 16} but in the present study there was no evidence for an increased rate of production of Lp(a) in patients with gout. Increased concentrations of Lp(a) in gout may be attributable to acute gouty arthritis, as Lp(a) is known to be an acute phase reactant, as indicated by a study of acute myocardial infarction.¹⁷ However, in the present study, blood samples were obtained from the patients when they did not have acute gouty arthritis. Differences between subject populations

regarding age, alcohol consumption, gender, and ethnic background may also contribute to the different Lp(a) concentrations in patients with gout and control subjects, but in the present study groups were matched for these factors. Some as yet unknown mechanism must play a role in the increased serum Lp(a) concentration. A possible explanation for the increased Lp(a) concentrations could be that gout patients are more likely to have smaller apolipoprotein(a) isoforms, because subjects possessing such isoforms generally have greater concentrations of Lp(a). Further studies including investigation of genetic markers for apolipoprotein(a) isoforms will be needed to clarify the underlying mechanism for increased Lp(a) concentrations in patients with gout.

Together with low HDL-C and high triglyceride and apolipoprotein B concentrations, an increase in serum Lp(a) concentration may contribute to the development of atherosclerosis in primary gout. As Lp(a) is not correlated with other risk factors for atherosclerosis, and is minimally influenced by nutrition or the variables we investigated (table 3), we consider it to be an independent risk factor for atherosclerosis in patients with gout which warrants therapeutic intervention. Unfortunately, hydroxymethyl glutaryl coenzyme A reductase inhibitor¹⁸ or probucol¹⁹ have not been found to be effective for this purpose. Large doses of nicotinic acid²⁰ or nicositol (a nicotinic acid derivative)²¹ have been reported to be effective, but can increase the serum uric acid concentration, which is disadvantageous in gout patients. We administered moderate doses of nicositol to 15 patients and found reductions in Lp(a) concentration after 1, 3 or 5 months without significant increases in serum uric acid concentration, which suggests that nicositol may be useful to control the increased Lp(a) concentrations and hypertriglyceridaemia which are frequently seen in patients with gout.

In conclusion, because lipid abnormalities including increased Lp(a) concentrations accelerate atherosclerosis in patients with gout, it seems to be important to measure serum Lp(a) in addition to lipids and apolipoproteins routinely in patients with this condition, and to decrease Lp(a) concentrations by drug therapy in order to prevent atherosclerotic complications. A prospective study is required to elucidate whether reduction of the Lp(a) concentration would effectively decrease the incidence of atherosclerotic diseases.

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