Annals of the Rheumatic Diseases 1995; **54**: 726–729

Lp(a) lipoprotein levels as a predictor of risk for thrombogenic events in patients with Behçet's disease

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Abstract

***Objectives*—To investigate whether plasma levels of Lp(a) lipoprotein (Lp(a)) are predictors of defective fibrinolytic activity, leading to thrombosis, in patients with Behçet's disease.**

***Methods*—Plasma Lp(a) was measured by enzyme linked immunosorbent assay, lipids and lipoproteins by enzymatic methods, and apolipoproteins A-I and B, fibrinogen (turbidimetric method), tissue plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1), and D-dimer levels by enzyme immunoassay. Their levels and interactions were evaluated in 33 patients with Behçet's disease (including five with thrombotic complications) and 30 healthy control subjects.**

***Results*—Plasma Lp(a) concentration was significantly greater in the patients than in controls. Nine patients (27%) had levels > 0·30 g/l. There was no correlation between Lp(a) and other lipids and lipoproteins apart from apolipoprotein B. Lp(a) showed inverse correlation with t-PA ($r = -0·34$, $p < 0·05$) and D-dimer ($r = 0·35$, $p < 0·05$). Patients with thrombotic complications had significantly greater Lp(a) and PAI-1, and lower D-dimer concentrations than control subjects.**

***Conclusions*—Measurement of plasma Lp(a) levels in patients with Behçet's disease may provide useful information regarding the potential development of thrombotic events, because of its possible role in defective fibrinolysis.**

(*Ann Rheum Dis* 1995; **54**: 726–729)

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Accepted for publication
28 April 1995

Behçet's disease, first described in 1937,[1] is characterised by oral and genital ulcers and eye inflammation; other features include arthritis, thrombophlebitis, neurological abnormalities, and skin lesions including erythema nodosum and papulopustular lesions.[2] Vascular manifestations, especially venous thrombosis, arteritis, and aneurysm formation are not uncommon.[2] Thrombosis is predominantly venous and is seen in about 33% of the patients,[3] but the basis of the thrombosis in these patients remains unclear, even though several explanations have been put forward. Endothelial dysfunction is believed to be caused by immunological mechanisms leading to deficient synthesis or release of tissue plasminogen activator (t-PA) and, possibly, deficient endothelial heparin like activity.[4] In addition, low levels of protein S and protein C in patients with Behçet's disease were suggested to be important in the promotion of thrombosis.[4–6] Defective fibrinolysis is believed to be one contributory factor for the development of thrombotic events in Behçet's disease,[7] but may not be involved directly.[6] Several studies have indicated that reduced fibrinolysis may be related to decreased production of t-PA by endothelial cells and increased concentration of plasminogen activator inhibitor-1 (PAI-1) in patients with Behçet's disease,[6–8] and similar findings have been reported in other conditions associated with vasculitis.[6] Changes in endothelial cell mediated production and release of substances as a result of vasculitic damage have been reported to be related to disease activity.[3]

Lp(a) lipoprotein (Lp(a)) is newly recognised as a cardiovascular risk factor with implications in atherogenic and thrombogenic processes.[9] The protein moiety of human Lp(a) is composed of apolipoprotein B_{100} and the unique, highly glycated glycoprotein, apolipoprotein(a), which is heterogeneous in size. Both protein moieties are linked by disulphide bridges. The apolipoprotein(a) gene is highly homologous with plasminogen and contains multiple repeats of a kringle 4 motif. It exhibits a striking size polymorphism, its isoproteins ranging in approximate size from 420 to 840 kDa. It is inherited in an autosomal codominant fashion, and its gene size is an important factor in determining plasma Lp(a) concentration: there is an inverse correlation between the size of the isoprotein and plasma Lp(a) concentration.[10 11] Thus plasma Lp(a) levels are very significantly genetically determined, while remaining little influenced by diet, age, gender or treatment with lipid decreasing drugs.[12 13] However, Lp(a) is known to be an acute phase protein and is significantly correlated with acute phase reactants.[14 15] There are several reports indicating that it is influenced by disease states such as rheumatoid arthritis and cancer.[15–17] Because of the striking similarity between apolipoprotein(a) and plasminogen, Lp(a) was suggested to act within the fibrinolytic system, by competing with plasminogen for its binding sites in a dose

dependent manner and inhibiting plasminogen activation.[18 19] Increased plasma levels of Lp(a) thus favour receptor occupancy by the lipoprotein particle and are associated with increased risk of thrombosis. In our previous study, we suggested that increased concentrations of Lp(a) in patients with Behçet's disease may be a predictor of risk for development of thrombotic events.[20] The aim of the present study was to investigate whether plasma Lp(a) levels have an effect on fibrinolytic activity in patients with Behçet's disease.

Subjects and methods

The study group included 33 patients with Behçet's disease (19 men and 14 women; mean age 29·1, range 18–55 years) and 30 healthy volunteers (15 men and 15 women; mean age 31·7, range 18–50 years). Mean body mass was similar in both groups. All the patients were diagnosed separately by the Internal Medicine, Dermatology, and Ophthalmology Departments. The diagnosis of Behçet's disease was made according to criteria from the International Study Group for Behçet's Disease.[21] Oral aphthous lesions and genital ulcerations were found in all patients. Uveitis was present in eight patients (24%) and dermatological lesions in 13 (39%). Five of the patients (15%) had thrombotic lesions such as superficial thrombophlebitis, involving different extents of segmentally thrombosed veins, located on the lower extremity; there was no deep vein thrombosis. At the time of the study, the patients were being treated with colchicine (n = 6) or non-steroidal anti-inflammatory drugs (NSAIDs) (n = 11), or both (n = 5); the remaining 11 patients were receiving no systemic medication. Approximately 33% of the patients were cigarette smokers, including three patients with thrombotic complications.

Subjects remained in a sitting position for 15 minutes before venepuncture. Blood samples were drawn by venepuncture in the morning after an overnight fast, into tubes containing 3·8% sodium citrate (1:9 ratio (v/v)) for measurement of fibrinolytic parameters, and into tubes without anticoagulant for other analyses. Anticoagulated blood was immediately centrifuged at 1500 *g* for 15 minutes at 4°C and the plasma samples obtained stored at −70°C until required for assay of fibrinolytic components (within three months). Blood without anticoagulant was allowed to clot at room temperature for one hour and serum samples obtained by the same centrifugal process. The serum samples were divided into two aliquots: one was immediately stored at −70°C until the time of Lp(a) measurement (within three months); the other was immediately analysed for lipids and apolipoproteins A-I and B.

Serum total cholesterol was measured by a cholesterol oxidase enzymatic method, triglycerides by a glycerol oxidase enzymatic method, high density lipoprotein cholesterol (HDL-C) by a cholesterol oxidase enzymatic method in the supernatant obtained after precipitation with phosphotungstic acid-magnesium chloride, and apolipoproteins A-I and B by immunoassay (Sera-Pak Immuno Apo AI (Code No 6821)/Apo B (Code No 6822), Ames, Canada). All determinations were by autoanalyser (Technicon Axon). Low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula.[22] Lp(a) was measured using a commercial antiapolipoprotein(a) polyclonal capture enzyme linked immunosorbent assay (TintElize lipoprotein(a); catalogue No 610220, Biopool AB, Umea, Sweden) according to the manufacturer's instructions. Using the method described for analysis for Lp(a), an intra-assay coefficient of variation of 5·5% was obtained with Lp(a) concentrations of 0·31 g/l (n = 10). Fibrinogen was measured by a turbidimetric method using a commercial kit (Instrumentation Laboratory Test, catalogue No 84691-10, Milan, Italy).

t-PA (the major activator of the fibrinolytic system in blood), PAI-1 (the major inhibitor of fibrinolysis), and D-dimer (split products of cross linked fibrin) were measured by microplate enzyme immunoassay using the respective monoclonal antibodies. Briefly, the t-PA, PAI-1, and D-dimer measurements were as follows: wells of the polystyrene microplate strip were coated with mouse monoclonal anti-t-PA, anti-PAI-1, or anti-D-dimer, which constituted the solid phase antibodies. The test sample or standard solutions were incubated in the wells at 37°C for two hours (D-dimer) or one hour (t-PA and PAI-1). Subsequently, respective mouse monoclonal antibodies, labelled with the enzyme horseradish peroxidase, were added and became bound to any solid phase antibodies which remained free. Labelled antibodies, not bound to the solid phase antibodies, were then removed by further washing. Incubation with enzyme substrate (tetramethylbenzidine dissolved in dimethyl sulphoxide) produced a blue colour in the test wells, which became yellow when the reaction was stopped with sulphuric acid. The final coloured product was measured by absorbance reading at 450 nm. Test kits were supplied by Innogenetics, N W Zwijndrecht, Belgium (lot Nos 30524644 A, 31125746, and 31223785).

STATISTICAL ANALYSIS

Plasma concentration of the lipids and lipoproteins in the patients and controls were compared by the Mann-Whitney *U* test or Student's *t* test. Relationships between two variables were examined by linear regression analysis.

Results

Table 1 shows the concentrations of Lp(a), lipids, lipoproteins and components of fibrinolysis in patients with Behçet's disease and the control group. Plasma Lp(a) concentrations were significantly greater in the patients than in controls. Nine of the patients (27%) had levels > 0·30 g/l. Apolipoprotein A-I, HDL-C, and triglyceride concentrations were lower in

Table 1 Concentrations of plasma Lp(a), lipids, lipoproteins, fibrinogen and fibrinolytic components in patients with Behçet's disease and a control group

Variable	Control group (n = 30)	Patients (n = 33)
Apolipoprotein A-I (g/l)	1·35 (0·32)	1·01 (0·19)**
Apolipoprotein B (g/l)	0·77 (0·18)	1·05 (0·21)**
Total cholesterol (mmol/l)	4·89 (1·01)	4·83 (0·92)
Triglycerides (mmol/l)	1·41 (0·44)	1·07 (0·36)***
HDL-C (mmol/l)	1·38 (0·10)	1·18 (0·09)**
LDL-C (mmol/l)	2·93 (0·98)	2·96 (0·92)
D-dimer (ng/ml)	486 (106)	463 (97)
t-PA (ng/ml)	5·8 (2·1)	4·2 (1·2)*
PAI-1 (ng/ml)	58·1 (21·2)	63·8 (27·9)
Fibrinogen (g/l)	3·10 (0·61)	3·52 (0·78)*
Lp (a) (g/l)	0·18	0·30†
(Median)	(0·12)	(0·18)
(Range)	(0·02–0·55)	(0·05–1·20)

Values are mean (SD) except as indicated. HDL-C, LDL-C = High and low density lipoprotein cholesterol; t-PA = tissue plasminogen activator; PAI-1 = plasminogen activator inhibitor-1; Lp(a) = Lp(a) lipoprotein.
*p < 0·05, **p < 0·01, ***p < 0·001 (Student's *t* test); †p < 0·05 (Mann-Whitney *U* test).

patients than in controls, but apolipoprotein B and fibrinogen levels were greater. There was no correlation between concentrations of Lp(a) and lipids or lipoproteins (other than apolipoprotein B: $r = 0·52$, $p < 0·01$), but Lp(a) showed inverse correlation with t-PA ($r = -0·34$, $p < 0·05$) and D-dimer ($r = -0·35$, $p < 0·05$). Plasma concentrations of t-PA were lower in patients than in controls. There was no significant difference between the groups in PAI-1 and D-dimer levels, and no correlations among t-PA, PAI-1, and D-Dimer levels. Haemostatic variables did not correlate with lipoproteins, apart from a negative correlation between PAI-1 and apolipoprotein A-1.

Table 2 shows the plasma Lp(a), D-dimer, t-PA, PAI-1, and fibrinogen levels in the five patients with thrombotic complications. These patients had significantly greater Lp(a) and PAI-1 levels, and lower D-dimer levels than the remaining Behçet's disease patients. Fibrinogen levels in the patients with Behçet's disease were significantly higher than in controls, but the values in patients with thrombotic complications were not different from controls. There was a positive correlation between smoking and fibrinogen concentration, and a negative correlation between smoking and HDL-C. Lp(a) and PAI-1 levels in the patients with thrombotic complications were greater than those in the other Behçet's patients, but D-dimer levels were lower. There was no correlation with haemostatic variables in patients with thrombotic complications.

Table 2 Details of patients with thrombotic complications

Patient	Sex (M/F)	Age (yr)	Lp(a) (g/l)	D-dimer (ng/ml)	t-PA (ng/ml)	PAI-1 (ng/ml)	Fibrinogen (g/l)
EV	M	27	1·20	321	3·57	102	3·19
YK	M	38	0·55	378	5·45	96	2·75
MK	M	32	0·39	395	6·70	81	3·30
SS	F	28	0·22	415	4·55	91	4·56
IM	F	42	0·23	388	3·65	46	4·04
Mean			0·52**	378*	4·78	83*	3·57
Median			(0·39)	(388)	(4·55)	(91)	(3·19)
Range			(0·22–1·20)	(321–415)	(3·57–6·70)	(46–102)	(2·75–4·56)
Other Behçet's patients							
Mean			0·26	471	4·63	59·4	3·32
Median			(0·21)	(427)	(4·42)	(52·5)	(3·01)
Range			(0·05–0·64)	(388–620)	(3·01–8·21)	(22·3–92·0)	(2·28–4·50)

Lp(a) = Lp(a) lipoprotein; t-PA = tissue plasminogen activator; PAI-1 = plasminogen activator inhibitor-1.
*p < 0·05, **p < 0·01 (Mann-Whitney *U* test).

Discussion

It has been reported in in vitro studies that high plasma levels of Lp(a) can interfere with the process of plasminogen-plasmin conversion, resulting in decreased generation of plasmin and attenuation of clot lysis at the endothelial surface.[23] Previous studies have shown that Lp(a) competes with plasminogen for binding to the surface of fibrin or fibrin fragments located in the plasma membrane of endothelial cells, platelets and macrophages.[18 24 25] The effects of Lp(a) on secretion of PAI-1 and t-PA in human endothelial cells remain controversial. Etingin *et al* found that Lp(a) caused twofold enhancement of PAI-1 antigen secretion from human endothelial cells in culture, while having no effect on t-PA production;[26] however, these findings were not confirmed by other groups.[27 28] Studies of patients with Behçet's disease have suggested that reduced t-PA and increased PAI-1 secretion in endothelial cells as a result of vascular damage may be responsible for diminished fibrinolysis in these patients.[6 7] In the present study, plasma Lp(a) levels in the patients were found to be different from those in control subjects. Plasma Lp(a) levels are under genetic control and the distribution of values is highly skewed, both in individuals in the same population and between populations.[29] Nine of our patients had Lp(a) concentrations greater than 0·3 g/l—the value at which excess risk for cardiovascular disease is ascribed to Lp(a).[30] We also observed that five patients with thrombotic complications had Lp(a) levels more than twice as great as those in the remaining Behçet's patients. A similar observation was reported by Glueck *et al* in patients with a history of thrombophlebitis, leading them to speculate that Lp(a) levels might be related to the pathophysiology of thrombophlebitis in certain instances.[31] Plasma concentrations of Lp(a) in all patients were significantly correlated (inversely) with t-PA and D-dimer; levels of D-dimer did not differ between patients and control subjects. No correlation was found between t-PA, PAI-1 or D-dimer and fibrinogen levels. These results suggest that high plasma levels of Lp(a) in patients with Behçet's disease may be a contributory factor in their decreased fibrinolytic activity, though increased Lp(a) may be considered unlikely to have a unique role in the development of this decreased activity; other unidentified factors also may have an important role in this process.

All patients in the present study, including those with thrombotic complications, suffered various degrees of vascular damage and had differing levels of endothelial secretion of t-PA and PAI-1, making it difficult to evaluate their haemostatic variables. Increased plasma concentrations of PAI-1 in the patients with thrombotic complications were associated with increased Lp(a) concentrations; Etingin *et al* showed that PAI-1 secretion from endothelial cells was stimulated by Lp(a),[26] and reduced t-PA and increased PAI-1 secretions from endothelial cells in patients with Behçet's disease were reported by Aitchison *et al.*[7] In

view of these observations, significantly decreased concentrations of D-dimer in patients with thrombotic complications may indicate decreased fibrinolytic activity resulting from increased levels of either Lp(a) or PAI-1. These two effects may cause decreased fibrinolytic activity independently, or in combination. Further studies are required to examine the effects of Lp(a) on fibrinolysis and any relationships between Lp(a) and haemostatic variables in patients with Behçet's disease.

Plasma fibrinogen levels in the patients with Behçet's disease were greater than those in control subjects, as reported by others,[3 6 32] but there was no further increase in the patients with thrombotic complications. Those patients who smoked had greater fibrinogen and lower HDL-C concentrations than those who did not. High fibrinogen levels in the patients may have been associated with disease activity, because fibrinogen is an acute phase protein. There is no reason to suppose that the differences were caused by thrombosis or necessarily indicate a risk of thrombosis.[33 34]

HDL-C, LDL-C, total cholesterol, triglycerides and apolipoprotein B did not show any correlation with haemostatic variables. Apolipoprotein A-I had a weak correlation with HDL-C. The increased levels of apolipoprotein B in patients compared with controls are interesting, but cannot be explained by the (weak) correlation between Lp(a) and apolipoprotein, as Lp(a) values were only slightly increased in the patient group. Because total cholesterol and LDL were unchanged, the increase in apolipoprotein may have reflected a change in the LDL particle towards a smaller, more dense LDL which is more atherogenic. We cannot explain, however, why triglyceride levels then remained low; further studies of lipoprotein lipase activity, complemented by analysis of the lipid composition of lipoprotein, are required to explain the decrease in triglycerides.

In conclusion, we suggest that measurement of plasma concentrations of Lp(a) in patients with Behçet's disease may provide useful information regarding the potential for development of thrombotic events, because of the possible role of this lipoprotein in defective fibrinolysis.

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