

Lipoprotein (a) in patients with aortic aneurysmal disease

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Objective: Lipoprotein (a) is an independent risk factor for atherosclerosis. Atherosclerotic degeneration is usually found in abdominal aortic aneurysms (AAAs), whereas thoracic aortic aneurysms (TAAs) caused by aortic dissection are not suggested to be linked pathogenetically to atherosclerosis. Lipoprotein (a) was analyzed in patients with AAA and TAA and in healthy individuals in relation to the extent of atherosclerosis.

Methods: Included in the case control study were patients with AAA (n = 75) and TAA with dissection (n = 39) and healthy control subjects (n = 43), for a total of 157 participants. Serum lipoprotein (a) was measured with nephelometry. Lipoprotein (a) levels were compared between age-matched and gender-matched paired samples of the three groups, and an association of lipoprotein (a), aortic aneurysm, and the extent of atherosclerosis was determined in multivariate analysis.

Results: Median lipoprotein (a) levels of patients with AAA and TAA and of control subjects were 18.9 mg/dL (interquartile range [IQR], <9.6 to 40.5), less than 9.6 mg/dL (IQR, <9.6 to 16.7), and less than 9.6 mg/dL (IQR, <9.6 to 16.3), respectively. Lipoprotein (a) was positively associated with the extent of atherosclerosis in patients and control subjects ($P < .0001$). Lipoprotein (a) levels of patients with AAA were significantly higher compared with patients with TAA ($P < .0001$) and control subjects ($P < .0001$). Multivariate analysis confirmed an independent association between lipoprotein (a) and AAA ($P = .009$). No significant differences of lipoprotein (a) were found between patients with TAA and control subjects ($P = .3$).

Conclusion: The lipoprotein (a) serum level, an indicator of atherosclerosis, is significantly elevated in patients with abdominal aneurysms independently of cardiovascular risk factors and the extent of atherosclerosis. Patients with TAAs caused by dissection have lipoprotein (a) levels comparable with healthy individuals. (*J Vasc Surg* 2002;36:25-30.)

Aortic aneurysm and aortic dissection are characterized as two distinct disease entities. Evidence from epidemiologic, experimental, and genetic investigations suggests that the pathogenesis of abdominal aortic aneurysms (AAAs) is related to atherosclerosis risk factors and atherosclerotic plaque formation.¹⁻⁴ However, additional risk factors and potential alternative pathomechanisms for development of abdominal aneurysms are discussed,^{5,6} and particularly matrix metalloproteinases may play a pivotal role in aneurysmal disease.⁷⁻¹¹ In contrast, the initiation of nontraumatic dissection of the thoracic aorta and subsequent aneurysmal dilation is not suggested to be linked pathogenetically to the process of atherosclerosis.¹²⁻¹⁴

Lipoprotein (a) is a cholesterol-rich lipoprotein consisting of one molecule of apolipoprotein B-100 linked to a molecule of apolipoprotein (a) by a disulfide bridge.¹⁵ High plasma levels of lipoprotein (a) are strongly associated with coronary artery disease, stroke, and peripheral artery

disease. Lipoprotein (a) thus was been established as an independent risk factor and marker for atherosclerosis.¹⁶⁻²¹ Lipoprotein (a) has a high affinity for proteoglycans, which is probably why it is found in high amounts in atherosclerotic plaques of the human aorta.^{22,23} Elevated serum levels of lipoprotein (a) have been reported in small patient series with AAAs.^{23,24} However, no data on lipoprotein (a) values of patients with thoracic aortic aneurysms (TAAs) or dissection have been published to date, and whether lipoprotein (a) is coincidentally elevated in patients with AAAs because of concomitant atherosclerotic comorbidities or independently indicates an increased risk for aneurysm formation is unknown. Elevated levels of lipoprotein (a) cause endothelial and intimal damage and thus may increase the susceptibility for intimal injury and initiation of aneurysm formation. Because TAAs from aortic dissection and atherosclerotic abdominal aneurysms are considered as two distinct disease entities, differences in lipoprotein (a) serum levels may be expected between these groups.

The aim of this study was to investigate lipoprotein (a) serum levels in patients with atherosclerotic AAAs and TAAs caused by aortic dissection and in healthy individuals. We hypothesized that abdominal aneurysms are associated with increased lipoprotein (a) serum levels because atherosclerosis may be involved. Patients with TAA with dissection were expected to have lipoprotein (a) levels similar to healthy control subjects because atherosclerosis is not suggested to play a pathogenetic role for this disease.

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Competition of interest: nil.

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Table I. Clinical characteristics of patients with AAA and TAA with aortic dissection and healthy control subjects

	AAA (n = 75)	TAA (n = 39)	Control subjects (n = 43)	P value
Age (years; median, IQR)	72 (66 to 78)	64 (56 to 74)	70 (59 to 76)	.01
Male gender	61% (81%)	25% (64%)	30% (70%)	.2
Arterial hypertension	42% (65%)	29% (74%)	0	<.0001
Hyperlipidemia	50% (67%)	6% (15%)	0	<.0001
Smoking	33% (44%)	11% (28%)	0	<.0001
Diabetes mellitus	15% (20%)	1% (3%)	0	<.0001
Cerebrovascular disease	57% (76%)	12% (31%)	0	<.0001
CAD	39% (52%)	8% (21%)	0	<.0001
PAD	39% (52%)	5% (13%)	0	<.0001

METHODS

Study design. The study was designed as a case control study. We prospectively included 75 consecutive patients with AAA, 39 consecutive patients with TAA dissection and aneurysmal dilation, and 43 healthy individuals without aortic aneurysms, without any atherothrombotic risk factor, and without a history of atherosclerotic disease. The study was performed according to the Declaration of Helsinki. All patients gave their written informed consent.

Patients. Consecutive patients with TAAs or AAAs admitted from January 1 to December 31, 2000, to the Department of Emergency Medicine and the Department of Angiology of a tertiary care university hospital were eligible for the study. Patients with inflammatory aortic aneurysms²⁵ (n = 2) and luteic aortic aneurysms (n = 0) were excluded. Inflammatory aneurysms were diagnosed with computed tomographic (CT) scan in conjunction with surgical findings (n = 2), and luteic aortic aneurysms were excluded with clinical history, routine serologic tests, and CT scans. One patient with penetrating atherosclerotic aortic ulcer^{26,27} with diagnosis during a surgical procedure also was excluded. Patients with hereditary defects of connective tissue, like Marfan's syndrome, were not eligible for the study (n = 3). Patients with thoracic aortic dissection were only eligible when aneurysmal dilation was coincidentally present. Patients with traumatic aneurysms or dissection were not eligible for the study. Healthy individuals without aortic aneurysm, without atherothrombotic risk factor (diabetes mellitus, smoking, arterial hypertension, hyperlipidemia), and without medical history and clinical signs of atherosclerotic disease were recruited at the outpatient ward of the emergency department within the same time interval.

Definitions. An *aneurysm* was defined as a permanent dilatation of the aorta, with a diameter of at least 50% greater than the proximal neck.²⁸ The diagnosis was established with color-coded duplex sonography, transthoracic and transoesophageal echocardiography, and CT scan. Surgery and autopsy reports and angiographic findings were used to confirm data from the clinical investigation. All diseases were confirmed with a combination of at least two independent examinations: the diagnosis of AAA was settled in 42 patients with CT scan plus surgery (additional

angiography in 32 of these patients), in 30 patients with CT scan in conjunction with angiography, and in three patients with autopsy. The diagnosis of TAA and dissection was made in 18 patients with CT scan plus surgery, in two patients with echocardiography plus surgery, in 15 patients with combination of CT scan, echocardiography, and angiography, and in four patients with autopsy. All radiographic procedures were performed and evaluated by independent radiologists. *Diabetes mellitus* was defined as fasting blood glucose levels of more than 110 mg/dL measured three times and pathologic oral glucose tolerance tests and hemoglobin A1c (glycosylated hemoglobin) more than 6.5 mg/dL. *Hyperlipidemia* was defined as fasting total serum cholesterol level more than 200 mg/dL, low density lipoprotein cholesterol level more than 130 mg/dL, or serum triglyceride level more than 180 mg/dL and all patients on lipid-lowering medication. *Arterial hypertension* was diagnosed according to the World Health Organization criteria.²⁹ Patients who were smoking more than three cigarettes per day were regarded as current smokers. The diagnosis of cerebrovascular atherosclerotic disease (CVD) of the extracranial carotid artery was assessed with duplex sonography and confirmed with angiography. Peripheral artery disease (PAD) was evaluated clinically, with ankle brachial index measurements, duplex sonography, and peripheral angiography in selected cases. Coronary artery disease (CAD) was diagnosed with clinical history, in conjunction with treadmill exercise testing, myocardium scintigraphy, and coronary angiography in selected patients. Patients were grouped according to the extent of atherosclerotic disease into atherosclerosis in one vessel area (CVD, or PAD, or CAD), into atherosclerotic disease in two vessel areas, or into generalized atherosclerosis in three vessel areas (concomitant CVD, CAD, and PAD).

Blood samples. Antecubital venous blood samples were collected at initial presentation of the patient at the emergency department or at the outpatient ward of the angiology department. Samples were centrifuged immediately and then frozen at -80°C until use. In previous experiments, we ascertained that freezing once did not affect the assay performed.¹⁵ Serum lipoprotein (a) was measured with nephelometry on a Behring Nephelometer Analyzer II with the N Latex Lipoprotein (a) reagent

(Dade Behring, Marburg, Germany), according to the manufacturer's instructions. The lower detection level of the used method was less than 9.6 mg/dL, and the coefficient of variation was 2.1%.

Statistical analysis. Continuous data are presented as the median and the interquartile range (IQR; range from the 25th to the 75th percentile). Percentages were determined for dichotomous variables. The Kruskal-Wallis test was used to compare lipoprotein (a) serum levels of patients with thoracic and AAAs and healthy control subjects overall. Patients of the three groups then were individually matched. Matching was performed blinded with respect to patient data. A difference of less than 5 years was accepted for matching patient age. The Wilcoxon paired rank test was applied to compare continuous variables of age-matched and gender-matched patients. A multivariate logistic regression model was applied to assess the independent association of lipoprotein (a) serum levels and AAAs compared with TAAs. Results of the logistic regression model are given as the odds ratio and the 95% confidence interval. The Hosmer-Lemeshow test was used to assess the model fit. All *P* values are two-sided. A *P* value of less than .05 was considered as statistically significant. Calculations were performed with MS Excel for Windows 2000 and SPSS (Version 10.0, SPSS Inc, Chicago, Ill) for Windows.

RESULTS

Overall, 157 individuals were included in the study: 75 patients with AAA, 39 patients with TAA, and 43 healthy control subjects. Clinical characteristics of patients and control subjects are given in the Table. Patients with AAA exhibited the highest cumulative frequency of atherosclerotic risk factors and atherosclerotic comorbidities, except for arterial hypertension, which was found most frequently in patients with TAA. All women included in this analysis were postmenopausal. Sixteen patients (21%) with AAA had a coincident abdominal aortic dissection. In all 39 patients with TAA, presence of dissection was confirmed, in 26 patients (67%) in the ascending aorta and in 13 patients (33%) in the descending aorta.

The median lipoprotein (a) level of patients with AAA was 18.9 mg/dL (IQR, <9.6 to 40.5), in patients with TAA less than 9.6 mg/dL (IQR, <9.6 to 16.7), and in healthy individuals less than 9.6 mg/dL (IQR, <9.6 to 16.3; Fig 1). Overall, patients with AAA had significantly higher lipoprotein (a) serum levels compared with patients with TAA and healthy individuals (Kruskal-Wallis, *P* < .0001). No significant differences of lipoprotein (a) serum levels were found between patients with (n = 16) and without (n = 59) dissection of AAAs (*P* = .7) and between patients with dissection of the ascending (n = 26) and descending (n = 13) thoracic aorta (*P* = .5).

Lipoprotein (a) serum levels in the sample of 157 individuals were significantly associated with the extent of atherosclerosis as indicated by the number of affected vessel areas (*P* < .0001). Patients with more extensive atherosclerotic disease had the highest lipoprotein (a) serum levels, and healthy subjects had the lowest lipoprotein (a) serum

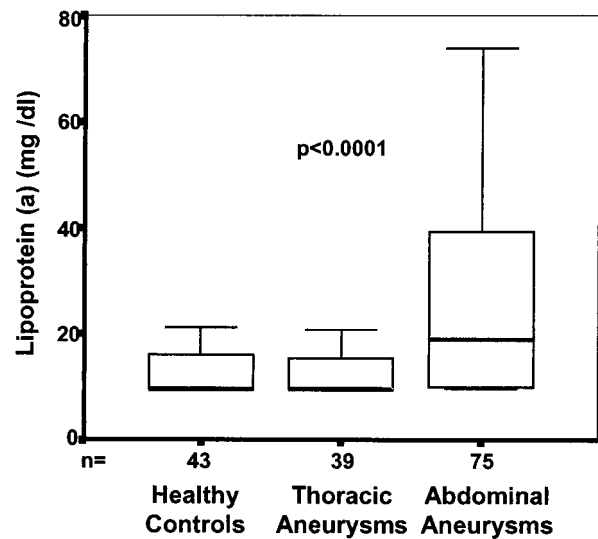


Fig 1. Serum levels of lipoprotein (a) in patients with AAA (n = 75) and thoracic aortic disease (n = 39) and healthy control subjects (n = 43). Box plots indicate median, IQR (range from 25th to 75th percentile), and range.

levels. Consistent findings were observed in patients with AAA (*P* < .0001) and TAA (*P* = .003; Fig 2).

Furthermore, age-matched and gender-matched paired samples of patients with AAA and TAA and control subjects were analyzed with respect to differences of lipoprotein (a) levels. No significant differences of age and gender were found between these groups of paired samples. Patients with AAA had significantly higher lipoprotein (a) levels compared with age-matched and gender-matched patients with TAA (38 matches; median, 27.5 mg/dL; IQR, 14.4 to 54.7; versus median, <9.6 mg/dL; IQR, <9.6 to 16.9; Wilcoxon, *P* < .0001) and compared with healthy individuals (41 matches; median, 31.7 mg/dL; IQR, 16.6 to 61.9; versus median, <9.6 mg/dL; IQR, <9.6 to 17.7; Wilcoxon, *P* < .0001). No significant differences were observed between patients with TAA and healthy individuals (35 matches; median, <9.6 mg/dL; IQR, <9.6 to 13.8; versus median, <9.6 mg/dL; IQR, <9.6 to 17.7; Wilcoxon, *P* = .3). Stratified analysis was performed to adjust for patient gender. In both strata, male and female, patients with AAA had higher serum levels of lipoprotein (a) compared with patients with TAA (*P* = .009 and *P* = .02, respectively) and compared with healthy subjects (*P* < .0001 and *P* = .01, respectively). Patients with TAA had similar lipoprotein (a) levels compared with healthy subjects in the male and female stratum (*P* = .5 and *P* = .3, respectively).

A multivariate logistic regression model was applied to assess the independent association of AAAs and lipoprotein (a) serum levels in the groups of patients with AAA and TAA. Patient age, gender, arterial hypertension, smoking, hyperlipidemia, diabetes mellitus, and extent of atherosclerosis (number of affected vessel areas) were entered into the

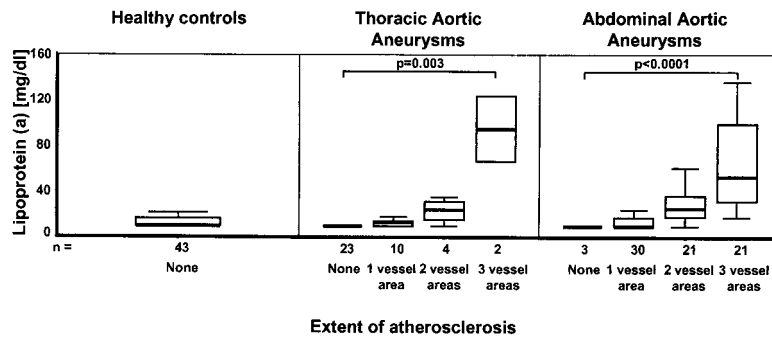


Fig 2. Serum levels of lipoprotein (a) according to extent of atherosclerotic disease in subgroups of patients with AAA (n + 75) and thoracic aortic disease (n = 39) and healthy control subjects (n = 43). Box plots indicate median, IQR (range from 25th to 75th percentile), and range.

model as possible confounding variables. Healthy control subjects were not included in this model because of the collinearity between the group classification and these possible confounding variables. Multivariate analysis confirmed an independent association between lipoprotein (a) and AAA: patients with higher lipoprotein (a) serum levels had a significantly increased risk for having an AAA (odds ratio, 1.1; 95% confidence interval, 1.0 to 1.1; $P = .009$). The final model had an acceptable fit ($C = 4.0$, $df = 8$, $P = .9$).

DISCUSSION

We found that patients with AAAs had significantly elevated lipoprotein (a) serum levels, whereas patients with thoracic aortic disease had lipoprotein (a) serum levels comparable with healthy individuals. The association between lipoprotein (a) and AAA was independent of atherosclerotic risk factors and the extent of atherosclerosis, although lipoprotein (a) serum levels were significantly associated with atherosclerosis in patients and control subjects.

The physiologic role of lipoprotein (a) has not been entirely determined yet. One of the main sites of catabolism is the kidney. We could recently show that fragments of lipoprotein (a) were excreted via the urine and that decreased kidney function led to an accumulation of these apo(a) fragments in the plasma and to increased plasma lipoprotein (a) levels.³⁰⁻³⁴ It also has been speculated that lipoprotein (a) is involved both in tissue synthesis and tissue repair. In patients with aortic aneurysms, it was suggested to play a role in thrombus formation and reinforcement of the aortic wall,²³ which might explain its elevation, particularly in patients with abdominal aneurysms where mural thrombus formation frequently occurs. However, lipoprotein (a) elevation also was found in patients with intracranial aneurysms without clinically significant atheromatous disease.^{35,36}

Lipoprotein (a) values of patients with AAAs in this patient series compare well with previous findings.²⁴ However, Fig 1 shows a rather wide variability of lipoprotein (a)

values in the group of patients with AAA. The extent of concomitant atherosclerosis seems to be the major determinant for this variability (Fig 2). The predictive value of lipoprotein (a) has not been determined yet, although Watt et al³⁷ reported that elevated plasma levels of lipoprotein (a) were not a risk factor for aneurysm rupture. Further longitudinal observations will be necessary to investigate whether excessively high lipoprotein (a) values are of prognostic importance.

Lipoprotein (a) has repetitively been shown to be associated with the presence of clinically significant atherosclerosis in the coronary, peripheral, and cerebral vessels.¹⁶⁻²¹ We believe our study to be the first demonstration that patients with more extensive atherosclerotic disease indicated by the number of affected vessel areas exhibit the highest lipoprotein (a) levels, whereas healthy individuals free of atherosclerosis had the lowest lipoprotein (a) values. Because several risk factors for atherosclerosis and abdominal aneurysms are identical, an association between lipoprotein (a) and AAA has already been assumed previously.³⁸ Lipoprotein (a) is significantly associated with the extent of atherosclerosis, and patients with AAA are likely to have several atherosclerotic comorbidities. Therefore, higher lipoprotein (a) values in patients with AAA may be explained by a high prevalence of concomitant atherosclerosis. However, the findings of the multivariate analysis suggest that these lipoprotein abnormalities are associated with the pathophysiology of abdominal aneurysms independently of cardiovascular risk factors and atherosclerosis.

Atherosclerosis per se is not the exclusive explanation for the development of AAAs.^{5,6,39} It is widely recognized that a chronic transmural vascular inflammatory process and destruction of connective tissue proteins within the outer aortic wall play a role in the initiation and progression of aortic disease.⁴⁰⁻⁴⁴ The development of aneurysmal dilatation is attributed to the depletion of medial and adventitial elastin, whereas rupture of the aneurysm is generally thought to involve the additional degradation of adventitial collagen. In particular, matrix metalloproteinases, zinc-dependent enzymes that are capable of degrading collagen,

elastin, and gelatin, have been detected in aortic aneurysmal tissue and evaluated in their role in aneurysmal development by several recent studies⁷⁻¹¹: metalloproteinase 2 and metalloproteinase 9 have been identified in increased levels within aortic aneurysm and may be responsible for aneurysm formation and expansion. It may be worth examining whether lipoprotein (a), which causes endothelial dysfunction and intimal damage, facilitates or contributes to the vascular inflammatory process of aneurysm formation.

In this study, lipoprotein (a) was significantly elevated in patients with abdominal aortic disease, whereas patients with TAAs caused by dissection had lipoprotein (a) serum levels similar to healthy individuals. We have included only patients with TAA caused by dissection on purpose because in these patients the cause for aneurysmal dilation seems to be the weakening of the wall by the dissecting membrane and atherosclerosis as a potential cause can be widely excluded. Therefore, these patients seemed to be a homogeneous comparison group. Different patterns of atherosclerosis, various hemodynamic factors, and intrinsic anatomic differences of the proximal and distal aorta contribute to the development and progression of aortic aneurysms in the thoracic and abdominal part of the vessel.^{45,46} Our findings suggest that lipoprotein (a), a marker for atherosclerosis risk, is not associated with the development of TAAs caused by dissection. In these patients, processes other than lipoprotein abnormalities and atherosclerosis initiate aortic dissection, which subsequently leads to aneurysmal dilation. On the other hand, in patients with abdominal aneurysms, no differences of lipoprotein (a) were found in patients with and without dissecting membrane. Dissection of the abdominal aorta may occur as a complication of the aneurysmal process rather than the cause for initiation of aortic dilation.

It is known that lipoprotein (a) levels vary during and after menopause. However, all women in this study were postmenopausal, and therefore, we cannot comment on this issue.

The case control study design implies some limitations; in particular, a causal relationship between lipoprotein (a) and AAA cannot be proven from these data. This issue has to be addressed in longitudinal studies, which include large numbers of subjects without AAA, follow the subjects, and determine whether elevated lipoprotein (a) is predictive of the development of AAA.

CONCLUSION

Lipoprotein (a) serum level, an indicator of atherosclerosis, is significantly elevated in patients with abdominal aneurysms independently of cardiovascular risk factors and the extent of atherosclerosis. Elevated lipoprotein (a) thus may be a risk factor for AAA. Patients with TAAs with dissection have lipoprotein (a) levels comparable with healthy individuals.

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