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Fibrinogen Predicts Mortality in High Risk Patients with Peripheral Artery Disease

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Objective: *Fibrinogen plays a key role in the pathogenesis of atherosclerosis and complications of atherothrombotic disease. We investigated the prognostic impact of fibrinogen levels on mortality of high risk patients with peripheral artery disease (PAD).*
Methods: *We studied 486 patients with PAD and several cardiovascular comorbidities. Atherosclerotic risk factors and fibrinogen levels were determined at initial presentation and patients were followed for median 7 years (IQR 6–10) for all-cause and cardiovascular mortality. Multivariate Cox regression analysis was applied to assess the predictive value of fibrinogen levels (in quartiles) on patients' outcome.*
Results: *Cumulative survival rates at 1, 3, 5 and 10 years were 96, 91, 83 and 67%, respectively. Overall, 138 patients (28%) died, 70% of these patients died of cardiovascular complications ($n = 96$). Patients with fibrinogen levels 10.2–12.2 μmol/l (third quartile) and patients with fibrinogen levels above 12.2 μmol/l (fourth quartile) had a significantly increased adjusted risk for all-cause mortality (hazard ratios [HR] 1.87 and 1.90, $p = 0.025$ and $p = 0.020$, respectively) compared to patients in the lowest quartile (fibrinogen below 8.6 μmol/l). A consistent effect was observed for cardiovascular causes of death. Diabetes mellitus and critical limb ischemia were the only other independent predictor variables (HR 2.08, $p < 0.001$ and 1.88, $p = 0.001$, respectively).*
Conclusion: *Elevated fibrinogen levels in high risk patients with PAD indicate an increased risk for poor outcome, particularly for fatal cardiovascular complications.*

Key Words: Fibrinogen; Atherosclerosis; Mortality.

Introduction

Complications of atherosclerosis are the most common causes of death in Western societies.[1] Although atherosclerosis was formerly considered a bland lipid storage disease, substantial advances in basic and experimental science have illuminated the role of inflammation and the underlying cellular and molecular mechanisms that contribute to atherogenesis.[1,2] Compelling evidence for the importance of inflammation and atherosclerosis at both the basic and clinical level has evolved in parallel. Accumulating data indicate that insights gained from the link between inflammation and atherosclerosis can yield predictive and prognostic information of considerable clinical utility.[3] In broad outline, atherosclerosis can be considered to be a form of chronic inflammation resulting from interaction between modified lipoproteins, monocyte-derived macrophages, T-cells, and the normal cellular elements of the arterial wall.[4] This inflammatory process can ultimately lead to the development of complex lesions, or plaques, that protrude into the arterial lumen.[1] Plaque rupture and thrombosis may result in the clinical complications of stroke or myocardial infarction.[4]

Fibrinogen is essential for fibrin formation under the influence of thrombin, and forms the basic plug of plasmatic coagulation and platelet aggregation.[5,6] Furthermore, fibrinogen synthesis is stimulated by cytokines from activated megacaryocytes thus acting as an acute phase reactant and a mediator of inflammatory processes. In particular, it is a ligand for cellular integrins and increases the binding of platelets, endothelial cells and leukocytes to each other which in turn causes activation of leukocytes and platelets, and release of mediators from these cells.[7,8] Fibrinogen, therefore, can be considered as a key molecule in the cascades of inflammation and coagulation and supposedly is involved in the pathogenesis of atherosclerosis and occurrence of atherothrombotic complications.[9,10] Recently, fibrinogen was described as a risk factor particularly for the development of

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peripheral artery disease (PAD)[11] and was suggested to be associated with an increased risk of short-term mortality.[12] However, the predictive value of fibrinogen on the long-term outcome of high risk patients with PAD has not been assessed as yet.

We hypothesized that elevated fibrinogen levels would be associated with an increased risk of long term mortality in patients with pre-existing, severe atherosclerosis. Therefore, the aim of the present study was to investigate the prognostic impact of fibrinogen on 10 year all-cause and cardiovascular mortality of high risk patients with PAD.

Methods

Study design, inclusion and exclusion criteria

We analyzed the data of all inpatients with symptomatic PAD Fontaine stages IIa, IIb, III and IV who were admitted to the Angiology department of a tertiary care university hospital from January 1, 1990 to December 31, 1992. PAD was assessed by clinical evaluation, ankle brachial index measurements, duplex sonography and confirmed by lower limb angiography in all patients. Patients were identified using our registry database, which prospectively recorded these patients' data. Furthermore, data were completed by systematic chart review. The main outcome measure was mortality until December 31, 1999. The study complied with the Declaration of Helsinki.

Definitions

Diabetes mellitus was defined as fasting blood glucose levels above 110 mg/dl measured at three different occasions, pathologic oral glucose tolerance tests and glycated hemoglobin (HbA1c) $>6.0\%$. Hyperlipidemia was defined as fasting total serum cholesterol >200 mg/dl, LDL cholesterol >130 mg/dl or serum triglycerides >180 mg/dl and was assumed to be present in all patients on lipid lowering medication. Arterial hypertension was defined as blood pressure values above 140/90 mmHg in repetitive measurements and was considered to be present in all patients with a history of hypertension taking anti-hypertensive medication.

Patient data

At admission patients medical history and data from physical examination were recorded using a standard questionnaire. Laboratory examination included complete blood count, global coagulation tests, HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, lipoprotein (a), and serum uric acid. Clinical history and physical examination were evaluated with special attention to cardiovascular risk factors and comorbidities: age, gender, hyperlipidemia, hypertension, diabetes mellitus, coronary artery disease, history of cerebrovascular events, current medication, and smoking habits at the time of admission in categories (non-smoker, 1–9 cigarettes daily, 10–19 cigarettes daily, 20 or more cigarettes daily).

Laboratory investigations

For measurement of fibrinogen *Fibrinogen Clauss*® (Stago, Roche) with a sensitivity of 0.6 μmol/l, a normal range of 4.4–10.3 μmol/l, and a coefficient of variation of 5.2% was used, since the automated Clauss assay has been established as the standard for measurement of fibrinogen.[13]

Follow-up

Patients were followed for case fatality until December 31, 1999. The Austrian Central Statistical Office provided data of patients who died within that period (day and cause of death, ICD 9).

Statistical analysis

Continuous data are presented as the median and the interquartile range (IQR, range from the 25th to the 75th percentile). Discrete data are given as counts and percentages. The Chi-square test was used to compare proportions and the Mann–Whitney U Test was applied for univariate comparison of continuous data. Mortality rates according to the fibrinogen level (in quartiles) are presented as a Kaplan–Meier curve and compared by means of the Log Rank test. Multivariate Cox regression analysis was applied to assess the independent effect of fibrinogen on all-cause and cardiovascular mortality, and to adjust for confounding effects of other atherosclerotic risk factors. Results of the Cox logistic regression model were presented as the hazard ratio (HR) and the 95% confidence interval (95% CI). Multiplicative interaction terms and log likelihood ratio Chi-square tests were used to test for interactions between predictor variables. A two sided p-value <0.05 was considered as statistically significant. All calculations were

performed with SPSS for Windows (Version 10.0, SPSS Inc, Chicago, IL, USA).

Results

We included 486 patients with PAD in the present analysis. The median age was 72 years (IQR 64–79), and 296 patients were male (61%). Fibrinogen values at the time of initial presentation were median 10.2 μmol/l (IQR 8.6–12.2). According to the reference values of our laboratory, 256 patients (53%) had a normal fibrinogen level (4.4–10.3 μmol/l), 228 patients (47%) had an elevated fibrinogen level (>10.3 μmol/l) and two patients (0.4%) had a lower than normal fibrinogen (<4.4 μmol/l).

Mortality

The median follow-up period was 89 months (i.e. 7.3 years) (IQR 72–119 months). Cumulative survival rates at 1, 3, 5 and 10 years were 96, 91, 83 and 67%, respectively. During the follow-up period until December 31, 1999, overall 138 patients (28%) died. Median survival time in non-survivors was 67 months (i.e. 5.5 years) (IQR 39–93 months). We found predominately cardiovascular causes of death (myocardial infarction and stroke) in these patients (96 of 138, 70%). Twenty-three patients (17%) died because of carcinomas, the remaining 19 patients (14%) died following traumas, infectious diseases and respiratory insufficiency due to chronic obstructive pulmonary diseases and renal insufficiency. Demographic data and clinical characteristics of survivors and non-survivors are given in Table 1. Non-survivors were older, had more frequently diabetes mellitus, arterial hypertension and critical limb ischemia.

Fibrinogen and mortality

Fibrinogen values were divided into quartiles to analyze its potential impact on patients' outcome. Compared to patients in the lowest quartile ($n = 122$, fibrinogen <8.6 μmol/l), patients in the second ($n = 121$, fibrinogen 8.6–10.2 μmol/l), third ($n = 122$, fibrinogen 10.2–12.2 μmol/l) and fourth quartile ($n = 121$, fibrinogen >12.2 μmol/l) had a cumulatively increasing risk for mortality ($p = 0.0014$, Fig. 1).

We then applied a multivariate Cox proportional hazard model to assess the independent effect of fibrinogen on all-cause mortality and adjust for the confounding effects of other baseline variables. Patients in the third and fourth quartile of fibrinogen values had a significantly increased adjusted risk for mortality compared to patients in the lowest quartile (Table 2). The final model adjusted for age (in quartiles), sex, smoking (in categories), diabetes mellitus, hyperlipidemia, arterial hypertension and critical limb ischemia (vs. intermittent claudication). Although patients with diabetes mellitus showed significantly higher fibrinogen values compared to non-diabetic patients ($p = 0.001$), we observed no significant interaction between fibrinogen and diabetes or any other baseline variable, indicating that fibrinogen is an independent predictor of mortality in these patients. In particular, we found no significant interaction between fibrinogen, smoking habits and death, and there were no significant differences of fibrinogen levels between non-smokers and smokers (in categories) ($p = 0.47$). Diabetes mellitus and critical

Table 1. Demographic data and clinical characteristics of 486 patients presenting with peripheral artery disease: comparing long-term survivors and non-survivors.

	Survivors ($n = 348$, 72%)	Non-survivors ($n = 138$, 28%)	p-value
Age (years)	71 (61–79)	74 (69–80)	<0.001
Male sex	212 (61%)	84 (61%)	0.99
Smoking at admission			0.16
Non-smoker	140 (40%)	70 (51%)	
1–9 cigarettes daily	128 (37%)	44 (32%)	
10–19 cigarettes daily	46 (13%)	16 (12%)	
20 or more cigarettes daily	34 (10)	8 (6%)	
Diabetes mellitus	102 (29%)	76 (55%)	<0.001
Arterial hypertension	147 (42%)	77 (56%)	0.007
Hyperlipidemia	301 (87%)	110 (80%)	0.062
Critical limb ischemia	62 (18%)	45 (33%)	<0.001
Coronary artery disease	176 (51%)	69 (50%)	0.97
History of myocardial infarction	54 (16%)	29 (21%)	0.57
History of stroke	17 (5%)	7 (5%)	0.93

Continuous data are given as median and interquartile range (range from the 25th to the 75th percentile).

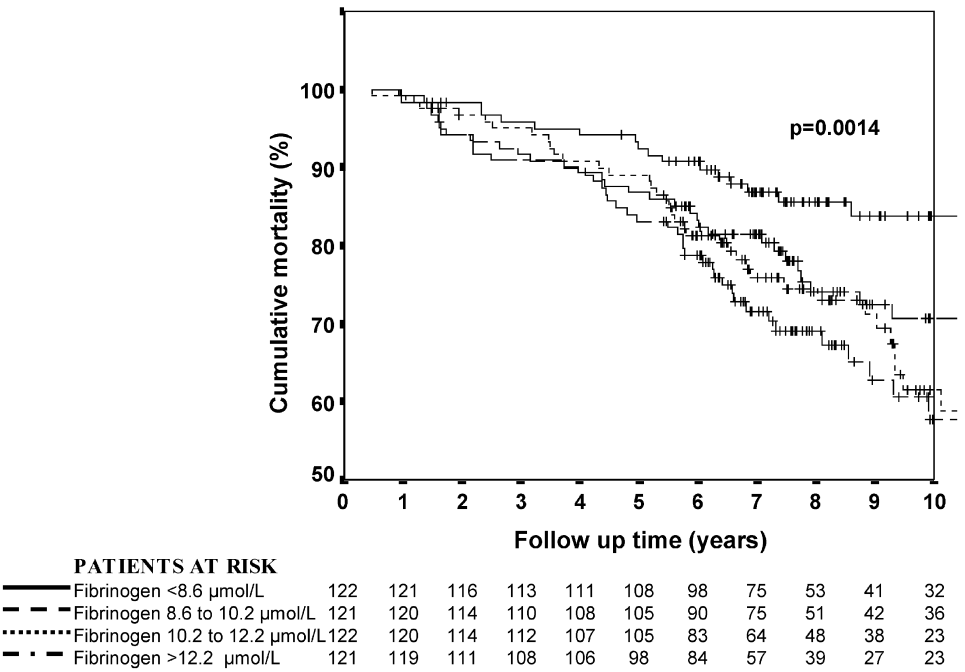

Fig. 1. Cumulative mortality of 486 patients with peripheral artery disease according to the fibrinogen level at initial presentation.

limb ischemia were the only other independent predictors of death in these patients.

Assessing the risk for cardiovascular death according to patients' baseline fibrinogen level, we found that patients in the second (adjusted HR 1.99, 95% CI 1.07–4.08, $p = 0.031$), third (adjusted HR 2.66, 95% CI 1.37–5.10, $p = 0.007$) and fourth quartile (adjusted HR 2.68, 95% CI 1.39–5.16, $p = 0.003$) had an increased risk for poor outcome compared to patients in the lowest quartile of fibrinogen levels, adjusting for age (in quartiles), sex, smoking (in categories), diabetes mellitus, hyperlipidemia, and arterial hypertension and critical limb ischemia.

Discussion

We found that higher fibrinogen levels were associated with a significantly increased risk for 10-year-mortality in patients with PAD. Particularly, fatal cardiovascular complications frequently occurred in these patients. This association was independent of any other atherothrombotic risk factor.

Table 2. Cox proportional hazard model to assess the predictive value of fibrinogen on 10 year mortality of patients with peripheral artery disease adjusting for confounding factors.

	Hazard ratio	95% Confidence interval	*p*- value
Fibrinogen			
First quartile (<8.6 µmol/l)	1.0	–	–
Second quartile (8.6–10.2 µmol/l)	1.47	0.85–2.56	0.17
Third quartile (10.2–12.2 µmol/l)	1.87	1.09–3.23	0.025
Fourth quartile (>12.2 µmol/l)	1.90	1.11–3.41	0.020
Male sex	1.22	0.85–1.76	0.31
Age (in quartiles)	1.17	0.97–1.38	0.13
Smoking (in categories)			
Non-smoking	1.0	–	–
1–9 cigarettes daily	1.22	0.77–1.93	0.40
10–19 cigarettes daily	1.22	0.65–2.27	0.53
20 or more cigarettes daily	0.80	0.35–1.80	0.58
Hyperlipidemia	0.80	0.45–1.17	0.18
Diabetes mellitus	2.25	1.51–3.36	<0.001
Arterial hypertension	1.30	0.89–1.90	0.17
Critical limb ischemia	1.88	1.30–2.74	0.001

Atherosclerosis has been demonstrated to be related to an inflammatory process in the vascular wall.[2,3,14,15] The activity of the disease and the likelihood of its progression are influenced by the extent of the vascular inflammatory process.[14,15] In this context, a close association between atherosclerosis and increased levels of fibrinogen have been described,[16,17] presumably indicating underlying vascular inflammation. Fibrinogen is a marker of acute phase response and provides an indirect measure of a cytokine dependent inflammatory process of the arterial wall. The molecule is a ligand for cellular integrins and increases the binding of platelets, endothelial cells and leukocytes to each other which in turn causes activation of leukocytes and platelets, and release of mediators from these cells.[7,8] Furthermore, fibrinogen plays a key role in the coagulation cascade serving as a ligand for the platelet GPIIb/IIIa receptor. Such a pivotal role in platelet physiology and development of arterial thrombosis parallels the consistency of clinical studies, which showed an increased cardiovascular risk for elevated fibrinogen levels.[9,10,12,18–20] Another causal mechanism for fibrinogen involvement in atherosclerosis is the promotion of endothelial damage and diffuse intimal thickening early during the disease's course.[10] Putting these findings together, it seems reasonable to speculate that fibrinogen levels potentially reflect the activity of the atherosclerotic process and are a surrogate marker for the individual's risk for poor outcome. Previously in cardiologic patients, elevated fibrinogen was reported to increase the risk of short term mortality.[12] Analysing mortality rates in the present study according to the baseline fibrinogen level (Fig. 1), it becomes obvious the Kaplan Meier curves markedly diverge after 3–5 years, indicating that elevated fibrinogen was mainly associated with increased long-term rather than early mortality in this groups of high risk patients with peripheral atherosclerosis.

Considering the prognostic impact of fibrinogen for the occurrence of future cardiovascular or all-cause mortality, one has to recognise that the effect size in terms of the hazard ratios was rather small, suggesting that this measurement adds little to risk prediction of adverse events in clinical practice. However, patients with atherosclerosis and hyperfibrinogenaemia may be good candidates for treatment with fibrates, which in contrast to statins combine lipid-lowering with beneficial fibrinogen-lowering effects.[21] Nevertheless, it has to be acknowledged that statins have a larger effect on the reduction of cardiovascular and all-cause mortality[22] and, therefore, should be used preferentially or in controlled combination.

Remarkably, in the present patient series, smokers and patients with hyperlipidemia exhibited reduced mortality rates in univariate analysis. This may be explained by an interaction with patients' age, since current smokers and hyperlipidemic patients were significantly younger. Indeed, we found no significant influence of these variables on outcome when adjusting for patients' age in the multivariate model. Patients with diabetes mellitus, in contrast, had an increased mortality during the follow up period. These patients also had significantly higher fibrinogen levels at initial presentation, presumably due to enhanced inflammatory activity. Nevertheless, no effect modification was observed testing for interaction between fibrinogen and diabetes and both variables independently predicted patients' mortality.

Limitations

We are aware of the limitations of a retrospective study design. In a non-randomised setting it is very difficult to account for the effects of changing medication during a study period of 10 years. Certainly, the increasing use of statins and ACE inhibitors during the recent years may influence mortality rates of these patients, but these data hardly can be acquired retrospectively. However, due to the careful and standardised patient evaluation with respect to cardiovascular risk factors and the complete follow-up data which were obtained via an independent institution, the interpretation of our findings seem valid.

Conclusion

Elevated fibrinogen levels in patients with PAD indicate an increased risk for poor outcome, particularly for fatal cardiovascular complications. Patients with hyperfibrinogenaemia, therefore, may be considered for close monitoring of cardiovascular comorbidities, aggressive treatment of concomitant risk factors and potentially for fibrinogen-lowering therapeutic approaches.

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