Hemostatic Risk Factors Of Coronary Artery Disease And Their Importance In Predicting The Extent Of Coronary Vessel Occlusion

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Summary:

Background: Recent epidemiological studies found that there is a strong association of hemostatic factors with ischaemic heart disease. Increased levels of certain hemostatic factors may play a part in the development of acute coronary syndromes and may be associated with an increased risk of coronary events in patients with angina pectoris. The aim of this study is to assess the influence of hemostatic changes on the extent of coronary artery disease. Methods: Forty patients with coronary artery disease (mean age: 61.7±7 years) and ten healthy controls (mean age: 62±8 years) were included into the study. The existence and extent of coronary artery disease were documented by angiography in both groups. The patients group was divided into two subgroups according to the extent of coronary artery disease. Activities of protein C (PC) and protein S (PS), concentration of serum fibrinogen (F), prothrombine time (PT) and activated partial thromboplastin time (APTT) were assessed. Results: PC (70±14% vs. 89±22%), PS (54±16% vs. 79±33%) (p=0.001); and PT (12. 4±1 sec. vs. 13.8±1.1 sec.) (p=0.000) were significantly lower and F (432±53 mg/ml vs. 394±80 mg/ml) was significantly higher (p=0.000) in patients with coronary heart disease than in controls. These parameters also showed significant difference between the subgroups of double-triple vessel disease and single vessel disease patients. There was no difference regarding APTT between the groups. Conclusions: Our findings suggest a significant relation between the occurrence of coronary artery disease and hemostatic parameters including serum fibrinogen levels, prothrombin times and protein C and protein S activities. These parameters were also showed to have special importance in predicting the extent of coronary vessel occlusion. Fibrinogen, protein C and prothrombin time may be considered as cardiovascular risk markers in patients with manifest coronary heart disease. This should be accounted for in future intervention trials.

Key words: Coronary heart disease, protein C, protein S, fibrinogen, prothrombin time, risk factor.

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Introduction:

Recent epidemiological studies[1-4] found that there is a strong association of hemostatic factors with ischaemic heart disease. Increased levels of certain hemostatic factors may play a part in the development of acute coronary syndromes and may be associated with an increased risk of coronary events in patients with angina pectoris[1].

The growing number of prospective studies[2-4] that have included fibrinogen measurements consistently show a direct, independent and statistically significant association between fibrinogen level and the subsequent incidence of ischaemic heart disease, this association being about as strong as the relation between cholesterol and ischaemic heart disease, for example. The fibrinogen level is also associated with the recurrence of ischaemic heart disease in those who have survived a myocardial infarction and with the onset and recurrence or progression of cerebrovascular disease and lower extremity arterial disease[2,3,5].

Although levels of coagulation factor VII and fibrinogen are well documented to have predictive value of ischaemic heart disease[2,3,5,6], relatively little data is available about the association between prothrombin time and ischaemic heart disease. There are studies[7] in the literature claiming the presence of a strong association between prothrombin time and ischaemic heart disease and accepting that also prothrombin time has a predictive value for ischaemic heart disease.

Both protein C and protein S are vitamin K-dependent proteins that are central to the natural anticoagulant pathway involving activated protein C[8]. This pathway not only inhibits blood coagulation but also stimulates fibrinolysis[8]. That is why the presence of a relaltion between ischaemic heart disease and activity of protein C may be expected. Many studies[9-11] in the literature support this approach, but there are some other study results[12] revealing no significant differences in the levels of protein C between patients with and without ischaemic heart disease.

The aim of our study was to assess the influence of hemostatic changes on the extent of coronary artery disease.

Patients and Methods:

We evaluated the hemostatic parameters of our patients with chest pain who underwent coronary angiography. Forty patients aged 46 to 74 years (29 men and 11 women; mean age: 61.7±7 years) and ten normal, control group aged 48 to 72 years (7 men and 3 women, mean age: 62±8 years) were included into the study. The existence and extent of coronary artery disease were documented by angiography in both groups. The patients group was divided into two subgroups according to the extent coronary artery disease. Group A was consisted of the patients with single vessel disease. The patients with multiple vessels disease were collected in the group B. We defined exclusion criteria for all groups as having any coagulation disorder, acute myocardial infarction, unstable angina, severe essential hypertension or secondary hypertension. We also excluded the patients receiving any drug that might effect hemostatic parameters. The levels of protein C (PC), protein S (PS) fibrinogen (F), prothrombin time (PT) and activated partial thromboplastin time (APTT) were assessed by the use of Coulter IL-ACL-200. For each parameter, appropriate commercial assays were used.

All data are shown as mean±SEM. The differences in hemostatic parameters between the control and patients groups, and also subgroups were examined by

TABLE-1

Clinical characteristics of the patients and control groups

	Patients group	Control group	p value
n	40	10	p>0.05
Age (years)	61.7±7	62±8	p>0.05
Male	28	7	p>0.05
Female	12	3	p>0.05
Smoker	16	4	p>0.05

the unpaired t-test and SPSS computer program. P<0.05 was considered statistically significant.

Results:

There was no difference between the patients and control groups according to age and sex (p>0.05), as shown in table-1. Sixteen patients in the patients group and 4 from the control group were cigarette smokers (p>0.05). Clinical characteristics of the patients and control groups are shown in table-1.

Forty patients with arteriographically proved coronary heart disease were divided into two subgroups as having single vessel disease or double-triple vessel disease. Eighteen patients had single vessel disease (group A), and 22 patients had double or triple vessel disease (group B). Ten controls were documented angiographically to have normal coronary vessels.

TABLE-2

Hemostatic parameters of control group and patients group

	Normal (n:10)	CAD (n:40)	Group A (n:18)	Group B (n:22)
PC (%)	89±22	70±14*	83.5±13	59±9**
PS (%)	79±33	54±16*	72±15	52±28**
F (mg/ml)	245±49	394±80*	388±54	432±53**
PT (sec.)	13.8±1.1	12.4±1*	12.8±1.7	11.4±1.4**
APTT (sec.)	30.4±6.1	31.1±7.2	31.2±10	30.4±6.5

* p<0.05 compared with normal group; ** : p<0.05 compared with single vessel disease group. CAD : Coronary artery disease; Group A : single vessel disease group; Group B : Double or triple vessel disease group.

Mean protein C activities (PC) were found as 89±22% in the control group and 70±14% in the coronary heart disease group. There was significant statistical difference between two groups according to the PC (p=0.001). Serum protein S activities (PS) were found as 79±33% in the control group and 54±16% in the patients group. These values also showed statistically significant difference between two groups (p=0.001). Regarding to serum fibrinogen levels (F), values were 245±49 mg/ml and 394±80 mg/dl respectively in the control group and patients group. There was very significant difference of the serum fibrinogen levels between the patients and control groups (p=0.0001). The mean of prothrombin time (PT) was found as 13.8±1.1 seconds in controls and 12.4±1 seconds in the patients. These values revealed very significant difference between the control and patients group too (p=0.0001). Activated partial thromboplastin times (APTT) were 30.4±6.1 seconds and 31.1±7.2 seconds respectively in the control and patients groups. There was no statistically significant difference between two groups (p=0.779).

PC, PS and PT were significantly lower; and F was significantly higher in patients with coronary heart disease than in controls. These parameters also showed very significant difference between the subgroups of patients with single vessel disease (group A) and subgroups of patients with double or triple vessel disease. All findings of our study is summarized in table-2.

Discussion:

Increased levels of certain hemostatic factors may play a part in the development of coronary artery disease and may be associated with the extent of coronary arterial involvement. Thompson et al.[1] studied hemostatic parameters of 3043 patients with angina pectoris who underwent coronary angiography and followed them for two years. They revealed that the levels of fibrinogen, von Willebrand factor antigen and tissue plasminogen activator antigen in patients with angina pectoris were independent predictors of subsequent acute coronary syndromes.

Fibrinogen enhances the risk of cardiovascular disease in hypertensives, diabetics, and cigarette smokers[13]. Kannel et al.[13] found approximately half of the cardiovascular risk of cigarette smoking was due to the higher fibrinogen values. They documented that each standard deviation increase in fibrinogen was associated with a 30% increment of coronary heart disease in men and a 40% increase in women.

The metaanalysis of seven prospective, epidemiological studies[6] indicates plasma fibrinogen levels (over 300-350 mg/dl) as an important, independent cardiovascular risk factor for subsequent myocardial infarction and stroke. Furthermore, several

clinical studies[2,3,5,14] like ours revealed an association between fibrinogen and both the angiographic and clinical degree of coronary heart disease. In addition, a significant relation of fibrinogen with the number of occluded coronary vessels was found. The following pathophysiologic mechanism are of particular importance: Fibrinogen is a main determinant of plasma viscosity and red cell aggregation. Both phenomena deteriorate blood fluidity especially in the microcirculation. Fibrinogen plays a central role in platelet aggregation and performs an essential substrate in the coagulation cascade[6]. Thus high fibrinogen levels may favour a hypercoagulable state resulting in final thrombotic events of cardiovascular disease[3,6]. Fibrinogen is also involved in atherogenesis by

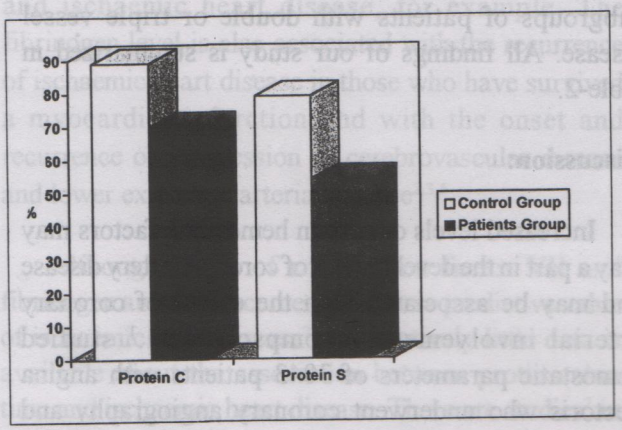

Fig. 1.
Protein C and S activities of control and patients groups.

stimulating proliferation and migration of smooth muscle cells[1,15]. Several determinants of fibrinogen levels are known[1,6,13]. Smoking is the strongest one in healthy persons[6]. This clinically important effect is dose related.

A "hematological stress syndrome" in atherosclerosis has been described[16], and a variety of stress conditions like positive energy balance, smoking, high blood pressure, diabetes mellitus, inflammation and older ages have been shown to change hemostatic parameters, creating a prone to hypercoagubility[17].

The Atherosclerosis Risk in Communities Study (ARIC)[9], whose major objectives included investigating etiologic factors associated with atherosclerosis and its clinical outcomes researched hemostatic parameters including protein C in the patients with vascular disease. There are some other studies[9,10] in the literature claiming that patients with stable coronary heart disease have lower protein C levels than that of healthy controls. A good correlation between the levels of protein C and apolipoprotein B made some authors to be in agreement that this interrelationship was particularly typical of early stages of coronary heart disease[11].

But, Iso et al.[12] evaluated the hemostatic parameters of patients with coronary heart disease. They found no significant differences in mean levels of protein C between controls and patients. There is no clinical data concerning protein S activity in patients with atherosclerosis. But in our previous study[18], we demonstrated that protein S and protein C levels were lower in the patients with essential hypertension than the normal subjects, but only protein S levels showed statistically significant difference between the two groups. We concluded that essential hypertension itself might cause cerebral and coronary ischaemia, and other vascular complications by increased coagubility as a result of the decreased protein C and protein S activities.

Fredman et al.[7] studied the relation of prothrombin times to coronary heart disease risk factors among men aged 31-45 years. They found the mean prothrombin time was shorter among whites than among blacks and was shorter among current cigarette smokers than among men who had never smoked. Inverse associations were also seen with relative weight and with levels of total cholesterol and triglycerides which were risk factors for atherosclerosis.

It is now clear that some risk factors for coronary heart disease, such as cigarette smoking and high plasma lipid levels, affect the hemostatic process[19]. Human gelatinous and fibrous plaques are rich in fibrinogen, fibrin, and fibrin(ogen) degradation products[20,21]. Fibrinogen and fibrin are involved in tissue proliferation[22] and patients with some qualitative abnormalities of fibrinogen are prone to thrombosis[23] which is a major determinant of myocardial ischaemia[24]. Drugs that affect hemostatic parameters reduce the recurrence of the two major ischaemic complications of atherosclerosis, stroke and myocardial infarction[25]

Our findings suggest a significant relation between

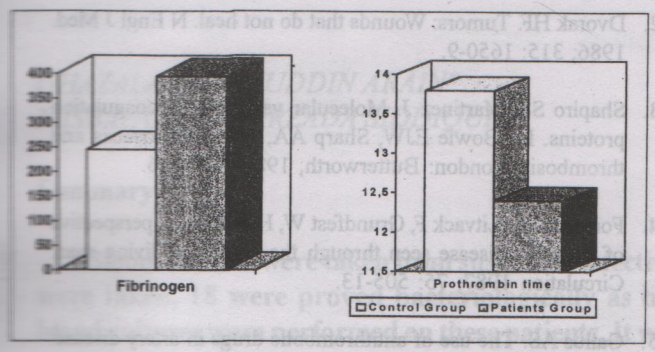

Fig. 2.
Serum fibrinogen levels (mg/ml) and prothrombin time values (seconds) of the patients and control groups.

the occurrence of coronary artery disease and hemostatic parameters including serum fibrinogen levels, prothrombin times and protein C and protein S activities. These parameters were also showed to have special importance in predicting the extent of coronary vessel occlusion. But regarding to APTT, no significant relationship was determined with ischaemic heart disease. In accordance with the results of prospective population studies, fibrinogen, protein C and prothrombin time may be considered as cardiovascular risk markers in patients with manifest coronary heart disease. This should be accounted for in future intervention trials.

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