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Plasminogen Activator Inhibitor-1 and Fibrinogen in Ischemic Heart Disease

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Abstract

Three groups were included in the study. Group I of 40 males with stable angina with mean age of (52.1 $\pm$ 5.43 yrs). Group II of 40 male patients with acute myocardial infarction (M.I) with a mean age of (51.2 $\pm$ 5.7 yrs). Control group of 10 normal males with mean age of (50.8 $\pm$ 8.04). Our results showed significant elevation of s.cholesterol in groups I & II over control group ($P < 0.0001$, - < 0.05) respectively. Triglyceride levels were elevated nonsignificantly in group I ($P > 0.05$) but showed highly significant elevation in group II over controls ($P < 0.0001$) Plasma fibrinogen levels were significantly elevated in both groups over controls ($P < 0.0001$). Plasma PAI-1 showed a non-significant difference in group I ($P > 0.05$) and a highly significant elevation group II over control group ($P < 0.0001$) Patients with acute MI (group II) showed a significant rise of triglycerides & PAI 1 over those with stable angina (group I) ($P < 0.0001$). The results of this study showed that plasma fibrinogen is a significant risk factor in both stable angina and acute MI. They also support the hypothesis that there is a significant correlation between triglycerides & PAI.1 as important risk factors only in acute MI, while serum cholesterol is rather more important as atherogenic than thrombogenic factor.

Introduction

FIBRINOLYTIC activity is impaired in many patients with coronary artery disease. It has been suggested that impaired fibrinolysis has a pathogenic role in coronary artery disease[1]. The plasmin dependent fibrinolytic pathway is an important physiologic mechanism for the removal of vascular fibrin deposits and for prevention of thrombosis[2]. It is initiated by the release from endothelium of tissue type plasminogen activator (t-PA)[3]. T-PA has a short half-life in blood due to inactivation by inhibitors. It was suggested that at least four immunologically distinct plasminogen activator inhibitors exist. Namely, types 1,2 and 3 plasminogen

activator inhibitors and protease nexin 1 [4]. The most important inhibitor is the plasminogen activator inhibitor-1 (PAI-1), which seems to be the main regulator of the fibrinolytic system under normal conditions and in relation to coronary artery disease[5]. It is also suggested that fibrinogen level is positively associated with coronary artery disease, and is at least equally predictive of ischemic events. Recent prospective investigations have reported that higher plasma fibrinogen concentration is associated with greater risk of cardiovascular diseases[6].

The aim of this work is to clarify the role of PAI-1 as one component of the fibrinolytic system, that could be involved in the pathogenesis of ischemic heart diseases whether in patients with stable angina or recent Q wave acute myocardial infarction. Also it is intended to find out if there is a conrelation between serum levels of cholesterol, triglycerides and fibrinogen as known risk factors and PAI-1 in either situations.

Material and Methods

Our work comprised three groups of patients :

Group I : Included 40 male patients with age range of (40-60) years of average weight, normotensive and non-diabetic having ischemic heart disease.

Group II : 40 male patients in the same age range as group I of average weight, normotensive and non-diabetic presented with acute myocardial infarction.

Group III : As a control group including 10 males of the same age group.

All patients were subjected to full clinical evaluation, ECG, blood urea serum creatinine, fasting and postprandial blood sugar, Serum cholesterol was determined by the enzymatic colorimetric test according to Richmond[7]. Plasma triglycindes were determined by the enzyme colorimetic test with the lipid clearing factor L.C.F. according to koditscheck et al[8].

Plasma fibrinogen was determined according to the modified Clause method [9].

Determination of PAI, 1 capacity in plasma was done according to Prolong using the chromotimer[10].

Results

Results of our study are shown in tables 1 to 4 and Fig (1). Table (1) shows the comparison between cholesterol levels in the three studied groups. Table (2) shows the comparison between mean triglyceride levels in the same groups. Table (3) includes comparison between mean plasma fibrinogen level in all groups. Table (4) shows mean PAI-1 activities in the three groups. Fig. (1) Shows the correlation between PAI -1 & serum triglycerides in patients with acute MI.

Table (1) : Comparison between Mean Cholesterol Level in all Groups.

	Control	Group 1	Group 2
Range	155-230 mg%	166-370 mg%	155-280 mg%
Mean	183.8	259.38	207.48
S.D.	± 29.91	± 53.3	± 33.09
	[P 0.0001]	[P 0.0001]	
	[P 0.05]		

Group 1: Patients with ischemic heart disease.
Group 2 : Patients with acute myocardial infarction.

Table (2) : Comparison between Triglyceride Level in all Groups.

	Control	Group 1	Group 2
Range	87-192 mg%	90-317 mg%	139-370 mg%
Mean	126.2	147.7	235.6
S.D.	± 29.91	± 51.94	± 72.32
	[P 0.05]	[P 0.0001]	
	[P 0.0001]		

Table (3) : Comparison between Fibrinogen Level in all Groups.

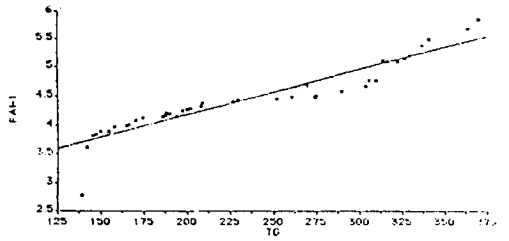
	Control	Group 1	Group 2
Range	184-362 mg%	209-570 mg%	209-673 mg%
Mean	255.23	81.48	395.15
S.D.	± 58.49	± 90.59	± 105.802
	[P 0.0001]	[P 0.5364]	
	[P 0.0001]		

Table (4) : Comparison between PAI-1 Level in all Groups.

	Control	Group 1	Group 2
Range	1.95-3.95 U/ml	1.24-4.625 U/ml	2.79-5.89 U/ml
Mean	3.11	3.512	4.463
S.D.	± 0.73	± 0.924	± 0.615
	[P 0.05]	[P 0.0001]	
	[P 0.0001]		

Fig. 1. Correlation between PAI-1 & serum Triglyceride level in Patients with acute myocardial infarction.

Y = .008× + 2.584, R-squared : .88



Correlation coefficient X1 : TG
Y1 : PAI-1
R = 0.938 P 0 0001

Discussion

Intraluminal coronary thrombosis is involved in the pathogenesis of Q-wave myocardial infarction as contrasted with stable angina; wherein thrombosis is not generally involved. The processes allowing thrombosis to proceed in certain individuals but not in others, have not been identified. Impaired fibrinolysis could contribute to thrombosis in this setting. The fibrinolytic activity of blood depends on a balance between circulating t-PA and its fast acting inhibitor PAI-1, both of which are secreted by the vascular endothelium. Both decreased release of t-PA and elevated levels of PAI-1 have been reported in patients with coronary artery disease.

The results of the present work showed a non-significant elevation of PIA-1 in the stable angina group when compared with the control group with ($P > 0.05$). Meanwhile, there was a significant elevation in patients with acute myocardial infarction when compared to either the control group or patients with stable angina ($P < 0.0001$).

Studies to determine the association between PAI.1 and coronary artery disease have yielded conflicting results. Many authors found that PAI.1 levels are increased in patients with angiographically documented coronary atherosclerosis[**14,11**]. Others stated that a higher rate of reinfarction was found in patients with coronary artery disease with high concentrations of PAI.1[**15,16**]. On the other hand Mehta et al[**17**] reported no difference in PAI.1 between men with normal coronary angiography and men with abnormal coronary angiogram. Also Osserof et al in 1989[**18**] demonstrated no correlahon between the presence of coronary artery disease and increased PAI.1

in a well defined population. However it has been found that PAI.1 activity is increased in obviously healthy individuals with increasing age[19]. Meyers et al[12] suggested that the pathogenesis of myocardial infarction might be different between older and younger individuals when they found that in older subjects there was no difference in fibrinolytic activity among healthy controls, patients with IHD and normal coronaries and patients with thrombosis associated coronary syndromes. It is to be noted, that some studies have used age-matched healthy subjects as a control population[19,11] while others have used non age matched control group[20,21]. In our study, the three groups were age-matched.

Level of plasma fibrinogen in our study showed a significant elevation in patients with myocardial infarction ($P < 0.0001$) and in patients with stable angina ($P < 0.0001$) when compared to the control group. There was no significant difference between both groups of patients.

Fibrinogen is on the cross-road between coagulation and fibrinolysis, it is also important for platelet aggregation and plasma viscosity. It is not surprising that it plays a crucial role in the development of coronary heart disease. Several authors have found high plasma fibrinogen level in patients with the main complications of atherosclerosis.

Meade et al in 1980[22] found that high fibrinogen level was an idependent risk factor for cardiovascular mortality. In 1985 Meade[23] reported fibrinogen as an obligatory mediator of platelet aggregability, also as a leading determinant of blood viscosity. In 1991 Aeron et al[6] reported that higher plasma fibrinogen concentration is associated with greater risk of coronary vascular disease. This view was strengthened by the finding of Diminno & Mancini in 1991 of fibrin deposits in arterial lesions[24].

Also, in our study, the serum cholesterol levels showed a significant elevation in patients with stable angina when compared to the control group ($P < 0.0001$), or to the group with acute myocardial infarction ($P < 0.0001$). There was a less significant, ($P < 0.05$), rise in patients with acute myocardial infarction than in the control group. Serum triglyceride level was significantly elevated in patients with acute myocardial infarction than in either stable angina group ($P < 0.0001$) or in control group ($P < 0.0001$). Meanwhile, there was a non-significant difference in serum triglyceride between group with stable angina and control group.

No correlation could be found between PAI-1 and cholesterol in either stable angina group or patients with acute M.I. ($r = 0.061$). Also, no correlation could be found between PAI-1 and triglycerides in stable angina group ($r = 0.273$). On the other hand, a strong correlation between PAI-1 and triglycerides has been found in patients with acute myocardial infarction ($r = 0.938$).

The combination of hyperlipoproteinemia and reduced fibrinolytic activity of blood has been found in several studies.

Epstein et al, in 1970[25] first drew attention to the strong association between type IV hyperlipidemia and impaired fibrinolytic activity. It has also been reported that hyperlipidemia is associated with a decrease in fibrinolytic activity when it is caused by an increase in LDL. Increased concentrations of HDI were reported to have the opposite effect[26]. Moreover, follow up studies showed that hypertriglyceridaemia was an independent risk factor for reinfarction. An association possibly connected with predisposition to thrombosis through a coexisting high concentration of PAI-1[15]. Nikkila & coworkers in 1990 [27] suggested that hypertiglyceridemia is a thrombogenic factor rather than an atherogenic factor while the overwhelming evidence stated that hypercholesterolemia is a major risk factor in atherosclerosis[28].

Conclusion :

The pathogenesis of coronary artery disease is multifactorial. The significant elevation of plasma level of PAI-1 only in group II patients in comparison to group I and control strongly suggests that it has a major role in the pathogenesis and development of acute myocardial infarction.

The elevated plasma fibrinogen in patients in either group, could represent another important risk factor for the development of the disease via thrombus formation.

Hypercholestrolemia is still one of the known risk factors that plays a crucial role in the progression of atherosclerosis with its important consequences.

The significant elevation of triglycerides and the strong correlation with PAI-1 shed some light on its possible role in the pathogenesis and development of acute myocardial infarction while cholesterol is rather more important as an atherogenic factor in the chronic stable cases.

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