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RESEARCH ARTICLE
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ASSESSMENT OF PROTEIN S LEVELS IN YOUNG PATIENTS (20-45YEARS) WITH MYOCARDIAL INFARCTION REPORTING TO SHAIKH ZAYED HOSPITAL LAHORE

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ABSTRACT

Background: Free protein S is a physiological inhibitor of coagulation. In many studies involving, especially young subjects, decreased fibrinolysis has been observed to be related to a high risk of intravascular arterial thrombosis. This study was planned to assess young patient's thrombotic risk potential for myocardial ischemia and infarction and preventive measures can be taken well in time in young patients with protein S deficiency.

Objective: To determine the proportion of protein S deficiency in young patients diagnosed with myocardial infarction (age 20 to 45 years).

Methodology:

This descriptive observational study was carried out at the Department of Haematology, Shaikh Zayed Medical Complex, Lahore. The duration of the study was one year after approval of the synopsis. After meeting inclusion and exclusion criteria, 75 patients with myocardial infarction were enrolled. Informed consent and demographic details were taken. Venous blood samples were taken and stored in a blue top vacuum tube. If protein S levels were less than 70 U/dL, then protein S deficiency was labeled.

Results: In our study among myocardial infarction patients the protein S deficiency was noted in 21(28%) patients. In diabetic patients, protein S deficiency was noted in 18 (36.7%) patients, and in non-diabetic patients, it was noted in 3 (11.5%) patients (p-value = 0.021).Among smokers, protein S deficiency was noted in 13 (44.8%) patients and in non-smokers, it was noted in 8 (17.4%) patients (p-value = 0.010) and in patients with a family history of MI, protein S deficiency was noted in 20 (55.6%) patients and in patients without a family history of MI, it was noted in 1 (2.6%).

Conclusion: The proportion of protein S deficiency in young patients diagnosed with myocardial infarction (age 20 to 45 years) is 28%, whereas factors like diabetes mellitus, smoking status, and family history of MI are associated with protein S deficiency in the patients.

Keywords: Protein S Deficiency, Myocardial Infarction, Young Patients

INTRODUCTION

Free protein S is a physiological inhibitor of coagulation and a thrombophilia marker. It potentiates activated protein C causing the inactivation of coagulation cofactors V (a) &VIII (a). Enhanced fibrinolysis is caused by the inactivation of tissue plasminogen activator inhibitor. Free protein S also inhibits factor X and prothrombin acts as a cofactor of tissue factor pathway inhibitor causing decreased thrombin formation. All these mechanisms increase susceptibility to venous and arterial thrombosis (Usman et al., 2007)[1]

Protein S, an anticoagulation factor produced in the liver, endothelial cells, and megakaryocytes, is a vitamin K-dependent plasma glycoprotein that serves as a cofactor for protein C thereby promoting anticoagulation and its deficiency dramatically increases the risk of thrombus formation. Protein S deficiency is sometimes linked to pregnancy as it is a hypercoagulable state. Numerous reports associate protein S deficiency with venous thrombosis but very few are available relating protein S deficiency to arterial thrombosis and myocardial infarction (Lee et al., 2008)[2].

In many studies involving, especially young subjects, decreased fibrinolysis has been observed to be related toa high risk of intravascular arterial thrombosis. Surprisingly, with regards to arterial occlusion and thrombosis plasma concentration of individual components of the fibrinolytic system have either not been studied extensively or were not consistently associated with it (Meltzer et al., 2010)[3].

Many risk factors for arterial thrombosis are due to the development of atherosclerosis. According to certain suggestions hereditary decrease in protein S levels are linked with myocardial infarction and arterial thrombosis due to an enhanced genetic predisposition to decreased fibrinolysis and an increased tendency for atherosclerotic plaque formation (Larsen et al., 2010)[4].

METHODOLOGY

Study Design: Descriptive observational study

Study Place: Department of Haematology, Shaikh Zayed Medical Complex, Lahore.

Duration of study: One year i.e.

Study Population: Department of Cardiology, Shaikh Zayed Medical Complex Lahore.

Sample Size: By using WHO calculator, sample size of 75 patients is calculated with 10% margin of error, confidence level of 95%, and 24% of protein S deficiency among young patients presenting with myocardial infarction (Ben et al., 2012) by using following formula:

$$n = Z^2_{1-\alpha/2} P(1-P)/d^2, \text{ where,}$$

Z1-α/2 = 95 % = 1.96.

d = margin of error = 0.10

Expected percentage of protein S deficiency in cases of myocardial infarction (P) = 24%.

Sampling Technique: Non-probability, consecutive sampling.

SELECTION CRITERIA

Inclusion Criteria:

- Age 20 to 45 years.
- Both male and female patients.
- Patients presenting with myocardial infarction (as per operational definition).

Exclusion Criteria:

- Pregnant females.
- Patients taking anticoagulants or vitamin K antagonist drugs like warfarin.
- Patients taking oral contraceptive pills.

- Patients with serum creatinine > 1.5 mg/dl, severe inflammatory infections, malignancy, chronic liver disease or acute venous thromboembolism.
- Patients with sickle cell anemia.

Seventy-five participants fulfilling selection criteria were included in the study from Department of Cardiology, Shaikh Zayed Medical Complex Lahore. A written informed consent was taken from all participants. Demographic details and risk factors were noted including name, age, sex, duration of symptoms, profession, socioeconomic status, diabetes, lifestyle (exercise), smoking, hypertension and positive family history. A clean venipuncture was done and while maintaining sterile conditions, 2.7 ml whole blood (venous) sample was taken in light blue top;
Within 4 to 6 hours of sample collection, a batch of collected samples were brought to laboratory, where at room temperature they were placed in for double centrifugation at 6000 rpm for at least 10 - 15 minutes. Minimum of 0.5 ml to 1.5ml plasma was removed and transferred to BCS sample cups; compatible to be used with Sysmex CS-1600 fully automated coagulation analyzer. Plasma samples were aliquoted, labelled, placed in freezer racks with numbering and then stored at -70 ˚C.
Sysmex CS-1600 fully automated blood coagulation analyzer was used to determine protein S levels. Reports were assessed and protein S level if less than 70 U/dL was labeled as protein S deficiency. All this information was recorded on proforma. Care was taken to avoid any pre analytical and analytical errors regarding use of improper tube, running clotted samples / overfilled and under filled tubes at the time of sample processing.

STATISTICAL ANALYSIS:
Data analysis was performed by using SPSS 25.0. Shapiro-Wilk test was applied to determine the normality of data. Mean and Standard Deviation was calculated for continuous variables like age, duration of symptoms and protein S level, if not normally distributed, then median (IQR) was calculated. Frequency and percentage was calculated for qualitative variables like gender, profession, diabetes, smoking, lifestyle (exercise), hypertension, socio-economic status, positive family history, and protein S deficiency. Data was stratified for duration of symptoms, profession, age, gender, diabetes, smoking, lifestyle (exercise), hypertension, socio-economic status and positive family history. Post-stratification, chi square test was applied to compare the protein S deficiency in stratified groups. A p-value$\leq$ 0.05 was considered as significant.

RESULTS
In this study, the mean age of the participant were 34.64 ± 7.21 years.
According to this study 52 (69.33%) patients were male and 23 (30.67%) patients were females. Male to female ratio of the patients was 2.3:1.
In this study 27 (36%) patients were from low SES group, 46 (61.33%) patients were from middle and 2 (2.67%) patients were from high SES group.
In our study diabetes mellitus was noted in 49 (65.3%) patients in which 26 (53.1%) patients had controlled and 23 (46.9%) patients had uncontrolled diabetic mellitus status.
In our study 29 (38.67%) patients were smokers.
According to this study active lung disease was noted in 7 (9.33%) patients.
The study results showed that 64 (85.3%) patients were hypertensive in which 44 (66.7%) patients had controlled and 20 (31.25%) patients had uncontrolled status of hypertension.
In our study family history of MI was seen in 36 (48%) patients.
The mean value of free protein S of the patients was 81.09 ± 31.63 u/dl with minimum and maximum values of 11 & 138 u/dl respectively.
According to this study protein S deficiency was noted in 21 (28%) patients.
In patients having age ≤ 30 years protein S deficiency was noted in 9 (42.9%) patients and in patients having age >30 years it was noted in 12 (22.2%) patients. Comparison of age between protein S deficiency status was statistically insignificant i.e. p-value = 0.074.

In male patients, protein S deficiency was noted in 18 (34.6%) patients and in female patients it was noted in 3(13%) patients. Comparison of gender between protein S deficiency status was statistically insignificant i.e. p-value=0.055.
In patients from low SES group, protein S deficiency was noted in 9 (33.3%) patients, in patients from middle SES group it was seen in 12 (26.1%) patients and in patients from high SES group it was noted in 0 (0%) patients. Comparison of SES between protein S deficiency status was statistically insignificant i.e. p-value = 0.330.
Among diabetic patients, protein S deficiency was noted in 18 (36.7%) patients and in non-diabetic patients it was noted in 3 (11.5%) patients. In diabetic patients, protein S deficiency significantly higher as compared to non-diabetic patients i.e. p-value = 0.021.
Among smokers, protein S deficiency was noted in 13 (44.8%) patients and in non-smokers it was noted in 8 (17.4%) patients. Comparison of smoking status between protein S deficiency status of the patients showed statistically significant difference i.e. p-value = 0.010.
In hypertensive patients, protein S deficiency was noted in 20 (31.2%) patients and in non-hypertensive patients it was noted in 1 (9.1%) patient. This difference was statistically insignificant i.e. p-value = 0.166.
Among active lung disease patients, protein S deficiency was noted in 3 (42.9%) patients and in patients without active lung disease it was noted in 18 (26.5%) patients. The difference between active lung disease and protein S deficiency was statistically insignificant i.e. p-value = 0.392.
In patients with family history of MI protein S deficiency was noted in 20 (55.6%) patients and in patients without family history of MI it was noted in 1 (2.6%) patient. In patients with family history of MI, protein S deficiency was significantly higher as compared to patients presented with without history of MI. i.e. p-value = < 0.01.

Table 1: Comparison of Protein S Deficiency between Age Groups

		Protein S Deficiency		Total	p-value
		Yes	No		
Age Groups	≤ 30	9	12	21	0.074
		12 %	16 %	28 %	
	>30	12	42	54	
		16 %	56 %	72 %	
Total		21	54	75	
		28.0%	72.0%	100.0%	

Table 2: Comparison of Protein S Deficiency between Genders

		Protein S Deficiency		Total	p-value
		Yes	No		
Gender	Male	18	34	52	0.055
		24 %	45.3 %	69.3 %	
	Female	3	20	23	
		4 %	26.7 %	30.7 %	
Total		21	54	75	
		28.0%	72.0%	100.0 %	

Table 3; Comparison of Protein S Deficiency in DM Patients

		Protein S Deficiency		**Total**	**p-value**
		Yes	**No**		
DM	**Yes**	18	31	49	0.021
		24 %	41.3 %	65.3 %	
	No	3	23	26	
		4 %	30.7 %	34.7%	
Total		21	54	75	
		28.0%	72.0%	100.0%	

Table 4: Comparison of Protein S Deficiency between Hypertension

		Protein S Deficiency		Total	p-value
		Yes	No		
Hypertension	Yes	20	44	64	0.166
		26.7 %	58.7 %	85.3 %	
	No	1	10	11	
		1.3 %	13.3 %	14.7 %	
Total		21	54	75	
		28.0%	72.0%	100.0%	

DISCUSSION

This descriptive observational study was carried out at department of Haematology, Shaikh Zayed Medical Complex, Lahore to determine the proportion of protein S deficiency in young patients diagnosed with myocardial infarction (age 20 to 45 years) and to stratify the Protein S deficiency by age, gender, diabetes, smoking, lifestyle (exercise), hypertension, socio-economic status, positive family history, duration of symptoms, and profession.

After acute myocardial infarction, cardiac tissue undergoes certain pathological changes like ventricular or cardiac remodeling involving changes in size, shape and function of heart. Following myocardial ischemia and necrosis, a systematic and an aggressive inflammatory response is initiated which includes in itself all segments and components of innate or natural immune system, influencing cells of both cardiac and non cardiomyocyte origin(Seropian et al., 2014)[5].

In our study among myocardial infarction patients, the protein S deficiency was noted in 21(28%) patients. In diabetic patients protein S deficiency was noted in 18 (36.7%) patients and in non-diabetic patients it was noted in 3 (11.5%) patients (p-value = 0.021).Among smokers, protein S deficiency was noted in 13 (44.8%) patients and in non-smokers it was noted in 8 (17.4%) patients (p-value = 0.010) and In patients with family history of MI protein S deficiency was noted in 20 (55.6%) patients and in patients without family history of MI it was noted in 1 (2.6%) patients (p-value = <0.001).

Prompt thrombolysis in such patients with thrombolytics like streptokinase infusion reduces the size of infarct, decreases mortality, and henceforth safeguards left ventricular function(Bendary et al., 2017)[6].

Deficiency of protein C, protein S, antithrombin III or presence of Factor V Leiden mutation (mutation in factor V gene; FVR506Q) predisposes individual to thrombophilia. These patients with genetic predisposition are at increased risk of acute thrombosis. In general population prevalence of hereditary thrombophilia due to protein S deficiency is 0.2 %, 0.02 % for antithrombin III deficiency, 4 % to 5 % for Factor V Leiden mutation and it varies from 0.2 % to 0.4 % for protein C deficiency(Ali et al., 2014)[7]

It is found that a myocardial infarction in a young male adult with no other cardiovascular risk factors might be explained by a combination of genetic abnormalities and anticoagulation linked protein S deficiency.(Klincheva et al., 2016)[8].

Patients with combined thrombophilia are at great risk of developing acute myocardial infarction and so these patients ought to be completely evaluated to rule out atherosclerosis in case of coronary thrombosis. Latest noninvasive imaging techniques like CT coronary angiography can also be very useful to detect coronary arterial atherosclerosis which has remained undetected otherwise by standard routine investigations like angiogram. All of these affect patient management as antiplatelet therapy and anticoagulation becomes essential if atherosclerosis or any thromboembolic event is detected (Hubert et al., 2018)[9].

cardiac Infarction with Non-Obstructive Coronary Arteries (MINOCA) and thrombophilia. The prevalence reaching up to 1 % and 2.6 % of protein C deficiency in general population and Myocardial Infarction with Non-Obstructive Coronary Arteries patients, respectively. Whereas for mutation in factor V Leiden, prevalence rate is up to 7 % and 12 % in population (of western nations) and

Myocardial Infarction with Non Obstructive Coronary Arteries patients, respectively (Pasupathy et al., 2016)[10].

In a 2018 study, researchers showed that although isolated protein C insufficiency was not linked to an increased risk of stroke, there was a significant link between borderline low levels of Protein C and cardiovascular events (Zakai et al., 2018)[12]. .Acute thromboembolism risk in protein C, S, and antithrombin deficiency was also evaluated, along with the importance of a prior venous thromboembolism positive history, in a cohort research (Mahmoodi et al., 2010)[11].

CONCLUSION:

From the findings of this study, we may conclude the proportion of protein S deficiency in young patients diagnosed with myocardial infarction (age 20 to 45 years) is 28%, whereas factors like history of diabetes mellitus, smoking status and family history of MI is associated with protein S deficiency of the patients.

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