Original Article

Comparison of Fibrinogen Level and Factor VIII in Single and Multiple Vessels Ischemic Heart Disease

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ABSTRACT

Objective: To determine the levels of fibrinogen and FVIII in single and multiple vessels ischemic heart disease patient's.

Study Design: Cross sectional / comparative study**.**

Place and Duration of Study: This study was conducted at the Department of Pathology, Post Graduate Medical Institute and Punjab Institute of Cardiology, Lahore from 24th October 2014 to 20th April 2015.

Materials and Methods: The study included 80 diagnosed ischemic heart disease patients who were divided into three groups, group 1 comprised of 40 patients with single vessel disease followed by group 2a with double vessel and group 2b were with multiple vessel disease. The parameters studied in these groups were risk factors like age, gender, hypertension, smoking, positive family history; number of vessels and the level of FVIII and fibrinogen and the subsequent data was recorded. Mean ± standard deviation, frequency distribution and percentages were calculated. SPSS version 20 was utilized to obtain statistical significance. Pearson's chi-square and Fisher's exact test were applied.

Results: In the present study, there were 80 diagnosed IHD patients out of which 40 (50%) had single vessel disease and 40(50%) had double and multiple vessels disease. Mean ± SD of fibrinogen was 305.1± 56.7 with a p- value of 0.85. Mean ±SD of FVIII was 191.2 ± 48.2 with a p- value of 0.80.

Conclusion: In the present study the levels of fibrinogen was raised in single vessel disease and FVIII were increased in multiple vessel disease patients. Hence it was concluded that these patients can be screened out on the basis of these two haemostatic parameters as they play a significant role in ischemic heart disease patients.

Key Words: Ischemic heart disease (IHD), Factor VIII (FVIII), Fibrinogen.

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INTRODUCTION

Ischemic heart disease (IHD) is a leading cause of global morbidity and mortality which accounts for 17.3 million deaths worldwide and is expected to raise by 2030 to 23.3 million[1]. It is a growing global public health problem which is contributing to 30% mortality and 10% of disease burden [2]. Worldwide it is affecting the quality and expectancy of life while placing a huge burden on the community as a whole[3-4]. IHD is growing in South Asians parallel to the industrial world; Pakistan with a population of 140 million has shown a high prevalence of over 30% of the population in over 45 years. Currently in Pakistan one in four of the middle aged adult are suffering from IHD[5]. In Pakistan the prevalence of IHD is 2.3% in male population.

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Statistics reveal that the chance of suffering from myocardial infarction in an average healthy adult before 60 years of age is one in five and the chance of dying is one in fifteen[6]. Pakistan is highly ranked in the world regarding IHD risk with 30% to 40 % mortality claiming 200,000 lives/year[7].

In IHD there is restriction to the blood flow and failure of the oxygen delivery due to accumulation of atherosclerotic plaque in the coronary arteries resulting in platelet aggregation and thrombus formation which deprives myocardial cells of oxygen[8].

Fibrinogen factor (1) is a water soluble glycoprotein with a molecular weight of 340 KDa. It is synthesized by the hepatocytes acts as an acute phase reactant and it is a key component of blood coagulation system[9-10]. Among all the coagulation factors of plasma the highest concentration is of fibrinogen[11]. Fibrinogen is the main protein of coagulation process which is converted to fibrin by the action of thrombin and forms a clot that helps to reduces blood loss and initiates repair[12]. It contributes in the formation of plaque in atherosclerosis and participates in the coagulation cascade as a precursor of fibrin, stimulates platelet aggregation, increases blood viscosity, promotes smooth muscle proliferation, migration and regulates cell adhesion[9].

Multiple Metaanalysis based on the growing number of prospective epidemiological studies reported fibrinogen having a direct, independent statistically significant association with IHD. Elevated fibrinogen level also contributes to the premature development of IHD in 25-37 years and in < 45 years of age group. Caerphilly study conducted in South Wales concluded that fibrinogen has the potential to increase the prediction of IHD in middle aged men. Angloscandinavian Cardiac Outcome Trails (ASCOT) concluded that fibrinogen is a strong independent predictor of IHD[9].

Meadle has reported the association between hemostatic parameters like elevated fibrinogen with increased mortality rate in IHD individuals. Lowe has emphasized on the fact that high fibrinogen levels have been seen in cardiac patients with multiple stenosed vessels as compare to single stenosis or absent stenosis[13].

FVIII a β_2 - globulin is produced in the liver, spleen and lymph nodes. In plasma 95% of FVIII circulates in a FVIII-vWf complex. FVIII plays a role in activating FX which directly generates thrombin, to produces stable fibrin and also it participates in clot formation. FVIII-vWf complex provide help in adhesion of platelet to the arterial subendothelial while resulting in its increased concentration in damaged vessel regions[14].

In the coagulation cascade FVIII acts as a cofactor with FIX to activate FX. It plays an active role in the formation of thrombin activation and generation of a fibrin-rich thrombus[15]. Multicenter Progetto Lombardo Athero-Thrombos (PLAT) study suggested that elevated clotting factors like FVIII, fibrinogen, vWf and /or leucocytosis leads to ischemic event[14].

Result of Northwick Park Heart Study indicated that in one third of the population with highest FVIII levels, the risk of IHD will be 44 % compared to one third with the lowest FVIII level. Infarction caused increase in FVIII level and the extent of elevation might be a reflection of infarction size, thus offering an alternative explanation than hypercoagulability for the prognostic values of FVIII level after heart injury[16]

MATERIALS AND METHODS

The study was conducted at the Department of Pathology, Post Graduate Medical Institute (PGMI) Lahore from 24.10.2014 to 20.4.2015. Diagnosed cases of IHD who underwent coronary angiography were selected from Punjab Institute of Cardiology. Forty single vessels and forty multiple vessels IHD patients were taken in which obstructive lesions was >70% in any one coronary artery.

The patients were informed and consent was taken before blood sampling. A questionnaire was filled for each patient, samples were collected and tests were performed to collect the required data.

Blood was drawn from the ante-cubital veins. 9 parts of blood and 1 part of 3.8% trisodium –citrate was centrifuged for ten minutes at room temperature at 2500xg. The supernatant plasma was placed in 1.5ml tubes and the sample was frozen at -20°C.Test were performed on the sample after thawing at 37°C.Test was performed on an Automated Blood Coagulation Analyzer Sysmex CA- 550. According to the standard procedure laid down in the literature of the FVIII Kit and fibrinogen kit (Clauss quantitative assay).

Inclusion criteria:

1. Age >25 years
2. All diagnosed cases of ischemic heart disease undergoing angiography.

Exclusion criteria: Patients suffering from any of the following were excluded from the study

1. Peripheral arteriopathy
2. Acute pulmonary, liver and renal diseases
3. Pregnancy
4. Coagulation disorders
5. Venous thromboembolism
6. Disseminated malignancy
7. Patients who are on drugs like anticoagulant and oral contraceptive pills (OCP's)
8. Diabetes Mellitus

RESULTS

Age Distribution in the Study Groups: The minimum age in the study group was 30 years and maximum age was 80 years with a Mean ± SD 54.5±9.49. Age distribution showed that (42.5%) of the patients were between 51-60 yrs and (22.5%) were above 60 yrs. (Table 1)

Table No. 1: Age Distribution in the Study Groups

Age group	1 (1VD)	2a (2VD)	2b (3VD)	%age	Total
<40years	5	0	1	7.5	6
41-50 years	11	5	6	27.5	22
51-60 years	17	5	12	42.5	34
>60 years	7	1	10	22.5	18
Total	40	11	29	100	80

Key: 1 (1VD) = group 1 with one vessel disease 2a (2VD) = group 2a with two vessel disease, 2b (3VD) = group 2b with multiple vessel disease. n=frequency and %=Percentage Using Fischer exact test, p value = 0.25 (Non significant)

Table No. 2: Gender Distributions in the Study Groups

Sex	1 (1VD)	2a (2VD)	2b (3VD)	%age	Total Freq. (n)
Male	35	10	26	88.8	71
Female	5	1	3	11.3	9
Total	40	11	29	100	80

Key: 1=group1 with one vessel disease (1VD),2a group2 with 2vessel disease,2bgroup with 3vessel disease. Using Fischer exact test, p value = 0.93(Non significant)

Gender Distributions in the Study Groups: The study population is divided into three groups those in group1 with single vessel were 35 male followed by 5 females. In group 2a are IHD patients with double vessel involvement while group 2b represents multiple vessel involvement 26 male patients (Table 2)

Hypertension in the Study Groups According to the Number of Vessels Involved IHD patients on antihypertensive were 28/80 out of which 13 patients had single vessel disease (Table 3)

Table No. 3: Hypertension in the Study Groups According to the Number of Vessels Involved

Hypertension	1(1VD)	2a(2VD)	2b (3VD)	Total
No	27	8	17	52
Yes	13	3	12	28
Total	40	11	29	80

Key: 1=group1 with one vessel disease (1VD),2a group2 with 2vessel disease,2bgroup with 3vessel disease. Using Fischer exact test, p value = 0.68(Non significant)

Assessment of Smokers According to the Number of Vessels Involved IHD 19 had single vessel disease whereas 15 had multiple vessel disease (Table 4)

Table No. 4: Assessment of Smokers According to the Number of Vessels Involved

History of smoking	1 (1VD)	2a(2VD)	2b(3VD)	Total
No	21	5	14	40
Yes	19	6	15	40
Total	40	11	29	80

Key: 1=group1 with one vessel disease (1VD),2a group2 with 2vessel disease,2bgroup with 3vessel disease. Using Pearson Chi-Square, p value = 0.90(Non significant)

Fibrinogen Level in the Study Groups: The Fibrinogen level in 80% of the ischemic heart disease patients was within normal range as none of them had any acute episode during the chronic phase of the disease. Hyperfibrinogenemia was reported in only 20% of study group (Table 5)

Table No. 5: Fibrinogen Level in the Study Groups

Fibrinogen(mg/dl)	1(1VD)	2a(2VD)	2b(3VD)	Freq. & %age n
Normal (181-350mg/dl)	31	9	24	64 (80)
High (>350 mg/dl)	9	2	5	16 (20)
Total	40	11	29	80 (100)

Key: 1=group1 with one vessel disease (1VD),2a group2 with 2vessel disease,2bgroup with 3vessel disease. n=frequency and %= percentage. Using Fischer exact test, p value =0.85

Fviii Level in the Study Groups: FVIII level was elevated in 11 patients of group 1, 3 patients of group 2a and in 10 patients of group 2b with had multiple vessel disease. Elevated FVIII level was observed only in 30% of the study population whereas 70% had FVIII level within the normal range (Table 6)

Table No. 6: Fviii Level in the Study Groups

FVIII (%)	1 (1VD)	2a (2VD)	2b (3VD)	Freq. & %age
<200%	29	8	19	56 (70)
>200%	11	3	10	24 (30)
Total	40	11	29	80 (100)

Key: 1(1VD) = group1with one vessel disease, 2a (2VD) = group 2a with two vessel disease, 2b (3VD) = group 2b with three vessel disease. Using Fischer exact test, p value=0.80 (Non significant)

DISCUSSION

The aim of the present study was to find out the levels of fibrinogen and FVIII in angiographically diagnosed IHD patients and to compare these levels in single and multiple coronary vessels. As stated in the literature review many haemostatic abnormalities have been reported to be associated with IHD. The abnormal activation leads to increase in the blood procoagulant which causes the clotting dysfunction. Due to the activation of platelet and the coagulation system there is marked shift of the haemostatic balance towards hypercoagulability. It has been observed in previous studies that FVIII and fibrinogen level increase with the formation of atherosclerosis.

In the present study, age distribution in group1, 2a and 2b did not show any significant difference. Regarding age the study was in accordance with the study conducted by Bhalli et al., 2011[17]. The IHD patients were divided in the following age groups in the present study (≤ 40 years7.5%, 41-50years 27.5%, 51-60years 42.5% & >61 years 22.5%) which resembles the age groups studied by Bhalli et al., 2011.The mean ± SD in the present study was 54.5±9.49 which was in accordance to Bhalli et al., 2011 was observed to be 54.26±11.60. The p-value regarding age was found to be non significant P=0.25 and this finding was consistent with the study conducted by Saruc et al., 1999 p>0.05.

In the present study fibrinogen levels was studied in 80 diagnosed IHD patients. Hyperfibrinogenemia was observed in 16 patients out of which 9 patients were of group1 as compared to 7 group 2a & 2b it was similar to the study conducted by Shi et al., 1999[18] in both the studies it is emphasized that those cardiac patients with stenosed vessels display elevated fibrinogen levels as compared to those with absent stenosis. Hence it is proved that elevated fibrinogen level can be taken as an independent risk factor of IHD and stroke.

The present study was in accordance to the study done by Shi et al., 2010.[19] The Mean ±SD 305±56.7 compared to 302±90 mg/dl.

Evidence suggests that fibrinogen is an acute phases reactant being a very effective predictor of clinical events, it plays a role in early stage of plaque formation and late complications of IHD but in the present study the cases selected were all stable chronic IHD patients who came for angiography after a couple of months so it was not an emergency or any acute episode of angina were fibrinogen is markedly raised .Its elevated levels can be taken as a complication of the disease but not as a cause of disease.

In the present study high level of FVIII with Mean ±SD 191.24±48.2 was observed in 24 patients with 11/40 group1 and 13/40 group2a & 2b.It was in accordance with Martinelli et al., 2010[20] Mean±172±55.It was found in both the studies that the baseline elevation of FVIII is due to recurrent venous thrombotic events as compared to single events. So the severity of disease can be accessed by the raised FVIII level and number of vessel involvement.

FVIII assessment is not helpful in chronic stable IHD patients. It is only raised in acute atherosclerotic episodes where it forms a complex with vWF and carries it to the site of vessel injury where it results in the formation of occlusive thrombi. As it is an acute phase reactant it has a significant role in acute coronary artery disease.

CONCLUSION

1. IHD was seen to be more common in middle age group i.e. between 51 to 60 years.
2. Hyperfibrinogenemia was commonly found in IHD patients with single vessel disease.
3. Elevated FVIII levels was found in double and multiple vessel disease. So it can guide in assessing the disease severity.
4. It was observed that Fibrinogen and FVIII levels cannot be taken as parameters to assess the severity of disease in chronic ischemic heart disease patients they are only helpful in acute episodes of the ischemic heart disease.

Recommendations: Research should be undertaken on a larger scale with a larger sample size, so that population based results may be derived.

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