Comparative Study of D-Dimer and Hs-CRP as Biomarkers in Various Types of Coronary Heart Diseases

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Abstract

Background: Coronary heart disease is one of the leading cause of mortality in the world. D-dimer is direct marker of on going coagulation with fibrinolysis and high sensitive-C reactive protein not only marker of low grade chronic systemic inflammation but also directly involved in atherosclerosis.

Objectives: The aim of present was to investigate the diagnostic potential of the plasma D-Dimer and high sensitive-C reactive protein as inflammatory markers in Coronary heart disease.

Methods: In present case-control study 265 with various types coronary heart disease (age range 26 to 75) and 120 healthy age and sex matched volunteers formed the control group. Nyco Card reader was used for plasma D-Dimer estimation whereas high sensitive C-reactive protein was estimated by Latex turbidimetric method. Statistical software SYSTAT version-12 was used to analyze the data. Values were expressed as mean ± standard deviation and Comparisons of study groups and study groups to control groups were done by applying Z test. one way analysis of variance (ANOVA) test and tukey-Kramer multiple comparison test were used comparison.

Results: Plasma D-Dimer and high sensitive C-reactive protein levels were significantly higher (p<0.01) in patients with Coronary heart disease like Stable Angina, Unstable Angina and Myocardial Infacrction as compared to healthy controls.

Conclusion: D-Dimer seems to be independent cardiovascular risk factors, which might add relevant information. Circulating level of hs-CRP was significantly increased in patients with all types of Coronary heart disease but patients with Stable Angina had low level of high sensitive-C reactive protein as compared with patients with Unstable Angina and Myocardial infarction which shows that its role as acute inflammatory marker.

Keywords: Coronary Heart Disease; D-Dimer; High Sensitive C-Reactive protein.

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INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of mortality and morbidity of over the

world including India. coronary heart disease (CHD), congestive heart failure, carotid artery disease, peripheral artery disease, heart failure are encompassed in it.[1] World health organization has reported that nearby a 17.9 million people die every year due to cardiovascular diseases but out of, 85% deaths are due to heart attack and stroke so early diagnosis of coronary disease is important fact.[2]

Prevention of CHD can be approached in many ways including health promotion campaign, specific protection strategies, life style modification programs, early detection and control of risk factors and constant vigilance of emerging risk factors.[3]

D-Dimer is the primary degradation product of cross linked fibrin and therefore serves as a direct marker of on going coagulation with fibrinolysis.[4] In the caerphilly prospective study, Gordon DO Lowe *et al.* have showed that, there is strong and independent association of D-Dimer with incident Ischemic heart disease.[5] John Danesh *et al.* have suggested that, there may be an association between circulating D-Dimer values and CHD that seems largely independent of classic risk factors.[6]

C-Reactive Protein (CRP) is an acute phase protein which produced predominantly by hepatocytes under the influence of cytokines such as interleukin - 6 and Tumor Necrosis Factor alpha (TNF-α).[7] Inflammation manifested by elevated serum levels of CRP measured by high sensitivity CRP assay (hs-CRP). It is associated with an increased risk of cardiovascular events mainly CHD.[8] It is believed that, hs-CRP protein not only marker of low grade chronic systemic inflammation but also directly involved in atherosclerosis.[9] It is increased in CHD subjects which can be used as a diagnostic tool for CHD patient.[10]

As view of above information and numerous risk of complication, it is valuable to examine whether increased amounts of hs-CRP and D-Dimer are detectable in various stage of CHD as well as to find out hs-CRP as inflammatory marker and D-Dimer as marker of fibrinolysis in addition to establish possible relationship between these parameters and severity of CHD.

MATERIAL AND METHOD

The present case control study was conducted at Department of Biochemistry PDVVPF's Medical College Ahmednagar and Swasthya Hospital and Research Centre, Ahmednagar, Maharashtra in collaboration with Department of Biochemistry, B. J. Medical College and Sassoon General Hospital (S.G.H) Pune. The Ethics Committee of B.J.M.C. and S.G.H. Pune was approved this study. All participants had provided informed consent and according to the declaration of Helsinki 1975, care was taken during experimental procedure.

Study Duration: 4 years and 6 months.

Study Design:

Type: Analytical case control study.

Population: Total 385 subjects were enrolled in the present study. of which Stable angina = 55, Unstable Angina - 100, Myocardial infarction - 110 and controls - 120.

Sampling: Simple random sampling

Sample size calculation:

Present study was quantitative study thus the sample size calculated by using the following formula.

Sample size $n = 4x\sigma2/E2$

n = sample size, σ = Standard deviation in population E = Allowable error.

Control Group

120 healthy age and sex matched individuals without any evidence of CHD as per clinical examinations were taken as control subjects.

Patients Group

The study included total 265 patients between age group 26 to 75 years of CHD. of these, patients of Myocardial Infarction (MI) and Unstable Angina (UA) had taken from Intensive Cardiac Care Unit (ICCU) having chest pain. Patients of stable angina had taken from out patients attending the cardiology department of same hospitals. The patients were diagnosed by physicians.

Inclusion Criteria

The diagnosis of all patients of CHD was made by physicians, and Patients, who had typical symptoms of CHD like chest pain, sweating, breathlessness, etc. and particular defects seen on electrocardiogram, higher cardiac markers were encompassed in the present study.

Exclusion Criteria

- All patients having heart disease like congenital heart disease, diseases of heart valves & myocardium.

- Confounding factors which could interfere in the biochemical analyses of study subjects and

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alter the results were diabetes mellitus, renal insufficiency, hypertension, hepatic disease, inflammatory disease, history of recent infection, febrile disorders.

Collection of specimen:

Criteria for blood collection were different for different groups.

- For control and stable angina, 2 ml blood was collected between 9.00 to 11.00 am after fasting from 10.00 pm from previous day.

- For unstable angina and myocardial infarction, 2 ml blood was collected with in 12 hours after admission in the ICCU.

Ethylene Damine Tetracetic Acid (EDTA) vaccutainer (Yucca Diagnostic) was used for assessment of hs-CRP and Sodium citrate vaccutainer was used for measurement of D-Dimer.

After an hour, the samples were centrifuged at 3000 rpm for 10 minutes to separate plasma. The separated plasma were collected in polythene tube with cork and stored at 20°C (precaution were taken to avoid the hemolysis) and used for analysis of respective parameter.

Quantitative determination of D-dimer by using nycocard reader II: [11]

Nycocard D-Dimer test was based upon an immunometric flow through principle. Test well of the device was used where plasma sample was applied. D-Dimer molecules were trapped on a membrane carrying D-Dimer specific monoclonal antibodies.

The conjugate solution then added which contain D-Dimer specific monoclonal antibodies and it conjugated with ultra small gold particles. The D-Dimer on the membrane was bind the gold antibody conjugate in a sand wich type reaction. By using washing solution, the excess conjugate was removed from the membrane.

In the presence of D-Dimer levels above of 0.1 mg/L in the sample the membrane appears red dish with colour intensity proportional to the D-Dimer concentration. The colour intensity was evaluated using Nycocard *Reader* II.

Quantitative determination of high sensitive c-reactive protein by using Latex turbidimetric method.[12]

Low level of C-reactive protein (hs-CRP) in human serum or plasma was determined by using hs-CRP ultrasensitive turbidimetric test. Sample containing hs-CRP was mixed with Latex particle coated by specific anti-human hs-CRP, plasma Hs-CRP were agglutinated. The agglutination causes an absorbance change which depends upon the hs-CRP content of the patient sample that can be measured by comparison from a calibrator of known hs-CRP concentration.

Statistical Analysis

Statistical software SYSTAT version - 12 (by Cranes Software, Bangalore) was used to analyze the data. The results were expressed in Mean ± Standard Deviation.

Data was analyzed by descriptive statistics as mean, SD, percentage etc. Comparisons of study groups and study groups to control groups were done by applying Z test of difference between two sample means at 5% (p, 0.05) and 1% (p, 0.01) level of significance.

Different parameters were measured in four different groups i.e. compared variable between the different groups. Thus one way analysis of variance (ANOVA) test was used to find out any significant difference between the means of different variables in four different groups. Tukey-Kramer multiple comparison test is specific for unequal group size and determine which specific group differed from each other therefore it was applied to compare all groups together in respect to all parameters under study.

RESULTS

As shown is Table 1 plasma levels of D- Dimer and Hs-CRP were significantly higher as compared to controls. By applying 'Z' test of difference

Table 1: Biochemical changes in CHD and controls

Variable	Controls (n=120) Mean ± SD	CHD		
		Stable Angina (n=55) Mean ± SD	Unstable Angina (n=100) Mean ± SD	Myocardial Infarction (n=110) Mean ± SD
D-Dimer (mg/l)	0.22±0.108	0.70±0.46**	1.13±0.98**	2.14±1.54**
Hs-CRP(mg/l)	0.80±0.61	2.33±1.26**	3.20±1.53**	5.17±2.37**

Values were expressed in mean with Standard Deviation (Mean±SD), **p<0.01- considered as highly significant

between two means there was a significant difference between mean values of D-Dimer and hs-CRP when healthy control group compared with all CHD groups as stable angina, unstable angina and myocardial infarction individually (p<0.01).

And by applying 'Z' test of difference between two means there was a significant difference between mean values of D-Dimer and hs-CRP when all CHD groups compared with each other (p<0.01).

Table 2 showed that the ANOVA test.

Hypothesis of ANOVA Test: The means of D-Dimer and hs-CRP in SA, UA, MI and controls are equal.

Alternative Hypothesis: At least one mean is different.

Interpretation of ANOVA Table 2: Value of 'F' of ANOVA test is 159.30 But here Critical f-value of

Table 2: ANOVA

Source of Variation	d.f.	Sum of Squares	Mean Square
Treatment (between columns)	7	1967.1	281.02
Residuals (within columns)	756	1333.8	1.764
Total	763	3300.8	

Value of 'F' = 159.30, p<0.01, highly significant
Hypothesis of ANOVA Test: The means of D-Dimer and hs-CRP in SA, UA, MI and controls are equal.
Alternative Hypothesis: At least one mean is different.

ANOVA test was 2.66 Thus test statistic is much superior than the critical value. So we rejected the hypothesis of equal population means and concluded that there was a statistical significant difference among means of D-Dimer and hs-CRP, in SA, UA, MI and controls. Test statistic was significant (P<0.01) at that level.

DISCUSSION

The main cause of CHD is primarily constant progression of coronary atherosclerosis. Atherosclerosis is a focal intimal disease of large and medium sized arteries extending from the aorta to the epicardial coronary arteries. Coronary arteries are susceptible to atherosclerosis. The focal nature of the intimal lesions which consist of variable quantities of lipid and collagen is called atherosclerotic plaque.[16]

Acute coronary syndromes are owing to an acute or subacute primary decrease of myocardial oxygen supply provoked by disruption of an atherosclerotic plaque associated with inflammation, thrombosis, vasoconstriction and microembolization.

The lipid core is extremely thrombogenic because of tissue factor released by macrophages and smooth muscle cells stimulates the coagulation cascade. The disrupted plaque provokes both thrombosis and coagulation. D-Dimer is the break down product formed when plasmin action on cross linked fibrin therefore it can be considered as a marker of fibrin production and plasmin activity.[13]

Lowe GDO *et al.* have stated that, defective fibrinolysis might play a role in initial progression of atherosclerosis lesion in addition to the clinical CHD events.[5]

D-Dimer antigen remains undetectable until it releases from cross linked fibrin by the action of plasmin. It is usually measurable one hour after the formation of the thrombus with a half life time of 4-6 hours.[13]

As shown in Table 1 plasma D-Dimer levels were increased significantly (p<0.01) in patients with CHD like SA, UA and MI as compared to controls group (0.22±0.11). Similarly, there was a significant difference between mean D-Dimer when all CHD groups compared with each other (p<0.01).

By applying the ANOVA test and Tukey-Kramer multiple comparison test, the means of D-Dimer in all types of CHD and controls significantly differed than expected by chance (p<0.01).

In the present study, higher levels of plasma D-Dimer were seen in all stages of CHD as compared to healthy controls. Our results are strongly supported by previous studies,[6,14] where extremely high plasma D-Dimer levels were noted, which may reflect systematic prothrombic state and possibly focal vessel wall related to fibrin formation i.e. D-Dimer with unstable atherosclerotic plaque activity.

Kruskal J B *et al.* have found that, there is increased concentration of D-Dimer and other fibrin related antigen in patients, studied within an hour after angina pain. The elevated D-Dimer concentration in patients with UA at rest is most likely due to enhanced formation of cross linked fibrin clot to intracoronary thrombosis and to the continuous breakdown of cross linked fibrin.[15] Tataru MC *et al.* have studied the plasma D-Dimer in relation to the severity of atherosclerosis in patients with stable angina pectoris after MI. They found that, plasma

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concentration of D-Dimer increases with age in CAD and are dependent on the amount of fibrin associated with arteriosclerotic thrombus.[16]

John Danesh has suggested that, there may be an association between circulating D-Dimer values and CHD, that seems largely independent of classical risk factors.[6] Ajay K Singh *et al.* have established that, there is significantly higher plasma D-Dimer in patients with CAD as well as IHD. They concluded that, D-Dimer can be regarded as a global marker of the turn over of cross linked fibrin and of activation of the hemostatic system. So in contrast to numerous other markers of hemostasis, D-Dimer assay is more appropriate and useful to measure and therefore may be chiefly suitable from a diagnostic point of view for physicians in emergency department when patients with chest pain.[17]

In large case control study, Koenig W *et al.* have investigated that, plasma D-Dimer levels were higher in stable CAD as compared with controls. According to their judgment, plasma D-Dimer levels are strongly and independently associated with the presence of CAD in patients with stable angina pectoris and these results support the concept of a contribution of intravascular fibrin to thrombogenesis.[18]

In the present study, the plasma D-Dimer level was significantly enhanced in all types of CHD as compared to controls, which conclude that, D-Dimer seems to be independent cardiovascular risk factors, and it might add relevant information in addition to lipid variables and other classical risk factors. Consequently D-Dimer acts as marker of fibrinolysis, which can constitute a good screening test to add a current emergency protocol, in the management of chest pain of possible coronary origin.

CRP is an acute phase reactant which is released in the circulation in response to inflammation and tissue damage. Recently numbers of researcher have focused on the use of hs-CRP, a marker of inflammation in the detection of subjects who are at increased risk for CVD.[19]

In January 2003, joint guidelines from the CDC and AHA have named hs-CRP as the inflammatory marker of choice to assess cardiovascular risk. Hs-CRP is not only a indicator of vascular inflammation, but also shows significant role in atherogenesis. At early stages of plaque development, hs-CRP is noticeable so prove that it involved in atherogenic process. Elevated hs-CRP has been shown to be a strong predictor of future cardiovascular risk in patients with established CHD with or without previous MI.[20]

In current study, we have examined the levels of hs in SA, UA, MI and normal healthy controls. The results of the present study showed highly significant (p<0.01) mean levels of hs-CRP in SA, UA and MI as compared with healthy controls. Similarly, there was a significant difference between mean hs-CRP when all CHD groups compared with each other (p<0.01). Table No. 1 Mean levels of hs-CRP were significantly increased (p<0.01) in MI patients without survival as compared with MI with survival. By applying the ANOVA test and Tukey-Kramer multiple comparison test, the means of hs-CRP in all types of CHD and controls significantly differed then expected by chance (p<0.01).

Result of the present study are in agreement with earlier work done by Shishir Kumar Basak *et al.*, Eun Jin Choi *et al.*[21] [22] Teresa Lozano *et al.* have evaluated the hs-CRP in patient with acute chest pain patients. According to their study, hs-CRP showed a marked increase in patients with a final diagnosis of CAD, when compared with those with chest pain not attributable to cardiac ischemia. Thus measurement of the hs-CRP level is useful in patients with acute chest pain of likely coronary origin.[23] Patients with ST-elevated MI treated by percutaneous coronary intervention with high serum hs-CRP concentration is at a high risk of prolonged hospitalization and long term events.[24]

Po-Cheng Chang *et al.* have studied hs-CRP in patients who received coronary angiography for stable angina. Elevated hs-CRP in stable CAD and subclinical atherosclerosis plaques has confirmed the association between increase CRP production and subclinical atherosclerosis.[25]

In seven years follow up study, Minna Soinio *et al.* found an independent association between CHD death and elevated hs-CRP in patients with type 2 diabetes, without MI at baseline suggesting that inflammation also plays important role in this high risk group before severe clinical outcomes of CHD have occurred. There are many possible mechanisms by which hs-CRP enhances atherosclerosis. Hs-CRP activates the complement pathway by human endothelial cell. It has been found to play a role in monocytes recruitment into the arterial wall. It enhances the entry of LDL particle into macrophages and it has been found to induce plasminogen activator inhibitor-1 expression. [26]

Reza Madadi *et al.* have established that, patients

with MI had higher levels of hs-CRP than subjects with UA. Hs-CRP levels equal to or higher than 3.27 mg/L are more likely to be associated with MI. The study has recommended that, to test this biomarker in all patients with ACS.[27]

CONCLUSION

D-Dimer is the primary degradation product of cross linked fibrin and therefore it can be regarded as a global marker of the turn over of cross linked fibrin and of activation of the hemostatic system. A D-Dimer level seems to be independent of other cardiovascular risk factors, which suggests that they might add relevant information in addition to lipid variables and other classical risk factors. In current study, circulating level of hs-CRP was significantly increased in patients with all types of CHD but patients with SA had low level of hs-CRP as compared with patients with UA and MI which shows that totally occluded lesions with no visible thrombus had low hs-CRP suggesting its role as acute inflammatory marker. Consequently inflammation can be implicated in transformation of stable coronary plaque rupture to unstable plaque rupture and thrombus. Identification of markers indicating susceptibility of plaque rupture is of clinical importance. Single measurement of hs-CRP or D-Dimer may be simple and valuable in this regard and their combination can be even more powerful. These may be clinically prevention measures.

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