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Original article

Role of Immunoturbidimetric plasma fibrin D-dimer test in patients with coronary artery disease as well as ischemic heart disease in emergency medicine

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ABSTRACT

The aim of the present was to assess the value of the ELISA D-dimer (hemostatic marker) assay in patients with coronary artery disease as well as ischemic heart disease presenting to the emergency department with chest pain syndrome. Methods: We measured levels of D-dimers ($\text{\AA}\mu\text{g/ml}$ by immunoturbidimetric assay) in 120 patients with angiographically proved CAD, consecutive outpatients with chest pain, arterial fibrillation, acute coronary syndromes and 240 age and sex matched healthy controls. Demographic characteristics were assessed by a standardized questionnaire, and a complete lipid profile was performed for all subjects. In addition to this inflammatory marker C-reactive protein was also measured. Result: The distribution of D-dimer levels skewed to the right, and plasma mean levels were higher in cases than in control (mean: 2.51 ± 3.60 vs. $41 \pm 59 \text{\AA}\mu\text{g/ml}$; $p < 0.001$). In contrast, correlation of D-dimer was found with C-reactive protein ($p < 0.001$) and is higher in cases than controls. Conclusion: Plasma D-dimer levels are strongly and independently associated with the presence of CAD in patients with stable angina. These results support the concept of a contribution of intravascular fibrin to atherothrombogenesis.

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of death and disability in developed nations and is increasing rapidly in the developing world, it is estimated that CVD will surpass infectious disease as the World's leading cause of death and disability [1]. Acute coronary syndromes occur when an unstable plaque ruptures and activates coagulation at the site, blocking blood flow and causing ischemic injury to the heart. Thrombogenesis is the final process whereby the exposed tissue factor triggers the activation of coagulation and the freshly formed clot fills the coronary artery lumen [2]. Several studies suggest that the likelihood myocardial infarction is higher in patient having high levels of biochemical markers of thrombus formation such as

fibrinogen, prothrombin fragment [3, 4], thrombin-antithrombin complex and fibrinopeptides [5]. It is widely accepted that thrombosis, provoked by a rupture of an atherosclerotic plaque, play key role in triggering a coronary heart disease event [6].

D-dimer is the primary degradation product of cross-linked fibrin and therefore serves as a direct marker of ongoing coagulation with fibrinolysis [7]. D-dimer level increases in patients with unstable angina pectoris (UPA) and acute myocardial infarction [8], and is an early marker of coronary ischemia in patients with chest pain [9].

2. Materials and Methods:

Patients and control were recruited between June 2008 to July 2009. Consecutive outpatients with chest pain, arterial fibrillation, acute coronary syndromes etc. admitted in the emergency department of Escort Heart Institute and Research Centre, New Delhi. Exclusion criteria were age under 18 years, use of

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anticoagulation agents, presence of primary coagulopathy or nephritic syndrome, recent surgery, infection in the month preceding the study, abnormal renal function test or liver and deep vein thrombosis in the last year. The healthy controls were selected from hospital staff without any history of diabetes mellitus, HTN and coronary heart disease. Informed consent was provided to all patients for D-dimer assay.

2.1. Sample collection and D-Dimer assays:

Fasting venous blood samples were drawn in the morning after overnight fasting under standardized condition from patients admitted in ED. Four ml of blood were collected, out of which 2 ml transfer to the gel vacutainer for estimation of other parameters (CRP, FBS, lipid profile and cardiac enzyme) and 2 ml blood mixed with 0.2 ml buffered sodium citrate and centrifuged at 3,000 rpm for 10 minutes within 30 minutes for plasma. Plasma fibrin D-dimer levels were evaluated by Latex turbidometric assay (Hitachi 917, Roche Diagnostics, Japan) according to manufacturer instructions.

The SPSS 16.0 software (Chicago, IL, USA) was used for statistical analysis. Differences in various parameters between the two groups were analyzed for significance using the student's t-test. Statistical significance was defined as $P < 0.01$

3. Results

The study included 120 consecutive patients (both male and female) mean age 56 ± 13.52 years had a positive clinical sign of coronary heart disease as well as ischemic heart disease. The characteristics of patients and controls are listed in Table 1. D-dimer and hs-CRP levels was significantly higher ($P > 0.001$) in CHD patients as compared to control subjects. Other biochemical parameters like fasting blood sugar and lipid profile (TG, HDL-C and LDL-C) were also changed significantly ($P > 0.001$) in CHD patients as compared to control subjects.

4. Discussion

For a long time progression of coronary artery disease leading to acute coronary syndrome was believed due to continuous progression of coronary atherosclerosis. Rapid progression of coronary atherosclerosis leading to complex coronary syndromes often is due to the plaque disruption. Plaques that are prone to disruption are characterized by a thin, fibrous cap with a reduced collagen content covering a large lipid pool. Acute coronary syndrome will occurs when thrombus formation lead to a severe reduction of coronary blood flow [10]. D-dimer is the breakdown product formed when plasmin act on cross linked fibrin therefore it can be considered as a marker of fibrin production and plasmin activity [11]. Originally, von Rokistsansly and later Duguid proposed that intima thickening at initial atherosclerosis results from mural thrombosis and fibrinolytic organization [12, 13]. Some other studies have supported this hypothesis [11]. The experimental finding showed elevated level of study parameters in patients as compared to the control subjects. This finding is consistent with the results of Lowe GDO et al, that shows the defective fibrinolysis may play a role in early progression of atherosclerotic lesions in additions to the clinical CHD events (UAP, Acute shock, MI) [14].

In our study higher concentration of D-dimer, hs-CRP, Lipid profile levels was found in patients with coronary heart disease as compared to controls (Shows in Table 1). In CHD as well as atherosclerosis, the plaque formation in the vessel is increased. The disruption of the plaque formed result in increase of coagulation along with fibrinolysis. Its fits well with the concept of hypercoagulable state that has been found hypothesized to proceed clinical CHD events (MI, UAP, ACS) [15]. Thus showing high turnover of fibrin in these individuals.

This is consistent with the study of Shitrit D et al, [16]. Tataru M-C et al, also reported that there is a high turnover of D-dimer level in ischemic heart diseases [17]. Higher levels of D-dimer were noted in peripheral blood of patients with UAP. In addition to this, in one study there was an approximately 5 fold increases in patients with UAP and acute MI [5]. It may reflect systematic prothrombotic state and possibly, focal vessel wall related to fibrin formation (D-dimer) with unstable atherosclerotic plaque activity [18]. D-dimer level in affected patients in the time of admission to emergency department, add information about the magnitude of UAP even with normal ECG, this happen so because the time between the appearance of symptom and admission to emergency department is long enough to normalize the ECG but the higher level of D-dimer remains unchanged and can be analyzed [16].

In arterial fibrillation higher D-dimer levels are found because of thromboembolism. The D-dimer level predicts prthrombotic states suggested by preliminary associations with venous thrombosis and other conditions associated with embolism [19] and intracardiac thrombosis and the rapid normalization of D-dimer values after cardioversion [20] or warfarinization [21] in the patients with arterial fibrillation. This study is supported by Ariel Cohen et al, [22]. The diagnostic value of hemostatic marker in patients presenting to the ED with chest pain syndrome, Shitrit D et al, found that D-dimer levels were significantly higher in patients with acute MI and UAP than in non ischemic patients and significant changes were observed in fasting blood sugar ($p < 0.001$), lipid profile ($p < 0.001$), D-dimer ($p < 0.001$), as compared to control groups [16].

5. Conclusion

D-dimer is the primary degradation product of cross linked fibrin and therefore it can be regarded as a global marker of the turnover of crosslinked 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 contrast to several other marker of hemostasis, D-dimer assays are more suitable and more practical to measure and therefore, may be more suitable from a diagnostic point of view for physicians in emergency department, when patients comes with chest pain.

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Conflicts of interest:

The authors had no conflicts of interest to declare in relation to this article.

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