

Elevated D-Dimer Levels, a Predictor for Thrombosis in Acute Myocardial Infarction and Unstable Coronary Artery Disease

Mushtaq Ahmed¹, Subhan ud din², Noor ul Hadi¹, Abdur Rahman¹, Tajendar Kumar¹, Jaffar Siddique¹, Khalid Naseem¹

ABSTRACT

Background: Myocardial infarction is prominent cardiovascular event worldwide notorious for increase deaths and about 50% deaths have been reported from the developing countries. Atherosclerosis has an inflammatory activity and results in thrombotic complications of which C-reactive protein is most significant marker.

Objective: To study D-dimer as Coagulation Activation Marker in Acute Myocardial infarction(STEMI) and non-ST elevation ACS(NSTEMI, USA).

Materials & Methods: This study was conducted in the Cardiology Department of MMC Teaching Hospital and Pathology Department Bacha Khan Medical College Mardan from January 2015 to January 2016. The study included 100 patients, 50 acute STEMI, 50 non-ST ACS (NSTEMI, USA) and 50 healthy individuals as a control group. D-dimer levels were performed in all these patients as a Coagulation Activation Marker.

Results: Elevated D-dimer level were found in 40 out of 50 patients of Acute Myocardial infarction. 10 patients had D-dimer level (80%) in the range of 250-500ng/ml; 10 patients D-dimer levels were in the range of 500-1000ng/ml and 20 patients D-dimer levels were in the range of 1000-2000ng/ml. Similarly in non-ST ACS 35 out of 50 patients (70%) had elevated D-dimer levels; 5 patients had D-dimer levels in the range of 250-500 ng/ml and 10 patients had D-dimer level in the range of 500-1000 ng/ml and 20 patients D-dimer level were 1000-2000 ng/ml. D-dimer in both the groups were significantly elevated as compared to the control group (P < 0.0035 for STEMI and P < 0.0034 for NSTEMI and USA respectively).

Conclusion: The study concluded that Acute Myocardial infarction(STEMI, NSTEMI) and Unstable Angina are associated with significant hemostatic abnormality based on t-test with p-value less than 0.05 as significant. D-dimer assay is a useful marker to diagnose these cardiac emergencies.

Keywords: STEMI, NSTEMI, USA, D-Dimer level.

This article may be cited as: Ahmad M, Subhanuddin, Hadi N, Rahman A, Kumar T, Siddique J et.al Elevated D-Dimer Levels, a Predictor for Thrombosis in Acute Myocardial Infarction and Unstable Coronary Artery Disease JSMC 2018.8;2:128-132.

INTRODUCTION

Cardiovascular disease is the leading cause of morbidity and mortality in spite of determination of major risk factors. Myocardial infarction (MI) is prominent cardiovascular event worldwide notorious for increase deaths and about 50% deaths have been reported from the developing countries¹.

Atherosclerosis and activated hemostatic state are important in the pathogenesis of myocardial infarction(MI). MI occurs when there is diminished blood supply to the heart. Significant elevation in fibrin peptide A in myocardial infarction identify patients with a hypercoagulable state and an increased risk of subsequent cardiac death^{2,3}. Atherosclerosis has an inflammatory activity⁴ and results in thrombotic complications of which C-

reactive protein is most significant marker⁵.

Hemostatic and inflammatory responses are major concerns for patients with cardiovascular disease⁶. Several studies suggest that myocardial infarction and acute coronary syndromes have high markers of thrombus formation such as fibrinogen, prothrombin fragments, thrombin antithrombin complex and fibrinopeptides and hypercoagulable state⁷.

Acute coronary syndrome occurs when an unstable plaque ruptures and blocks the coronary artery causing ischemic injury to the heart. In ACS patients, thrombus formation leads to severe reduction in the coronary blood flow⁸. D-dimer is a hemostatic marker for fibrin formation and degradation. Its limit below normal range excludes any thromboembolic phenomenon and elevated levels signify hypercoagulable states and increased risk of venous thromboembolism⁹. It is elevated in patients with acute thrombosis¹⁰. Circulating D-dimer fragments reflects the extent of fibrin turnover and level is elevated in any conditions in which coagulation system is excessively activated¹¹. D-dimer is the end product of cross-linked fibrin breakdown and indicates active thrombus formation and thrombolysis. D-

1. Department of Cardiology MMC/MTI Mardan KP

2. Gajju Khan Medical College, Swabi KP

Correspondence:

Dr. Noor ul Hadi

Senior Registrar Cardiology Department

Mardan Medical Complex/MTI Mardan

Email: hadijandr@gmail.com

Cell: 03339158898

Received: December 09th 2017, Accepted June 08th 2018

dimer testing is a useful aid in the diagnosis of thromboembolic condition¹². The aim of the study was to evaluate D-dimer assay as a hemostatic marker in acute coronary syndrome. As it is a global marker of fibrin turnover, D-dimer assay is a useful marker for determination of D-dimer fragments. It is more suitable and easily performed from a diagnostic point of view and gives immediate information to the clinician. Its negative value excludes thromboembolic phenomena. Elevated levels guide clinicians to proceed further for other supportive investigations to identify thromboembolism. It also provides guidelines for anticoagulation therapy.

MATERIAL AND METHODS:

This study was conducted in the Cardiology Department of MMC Teaching Hospital and Pathology Department of Bacha Khan Medical College Mardan from April 2015 to May 2016.

Cardiac emergencies were divided into two groups. Group A include 50 patients of acute STEMI diagnosed by clinical presentation of typical chest pain, Troponin T and supported by ECG which show ST Segment Elevation MI. Group B included 50 patients of non-ST segment elevation MI and USA. Group C included healthy individuals as a control group. Patients in the two groups included both adult male and female patients. Patients having history of deep venous thrombosis, pulmonary embolism, pneumonia, infection, septicemia were excluded from the study.

Blood samples were collected from the patients of STEMI, NSTEMI and USA. STEMI patients have ST Segment elevation on ECG, While NSTEMI have ST segment depression or normal ECG along with elevated Troponins. USA patients have either normal ECG or ST segment depression with normal Troponins. Blood sample of (5 ml) was collected in a tube containing sodium citrate 3.2%. The citrated blood was centrifuged to separate the plasma and this plasma was then utilized for determination of D-dimer.

Minutex D-dimer is a latex agglutination test for semi quantitative determination of D-dimer fragments. Minutex D-dimer assay contain a monoclonal antibody reacting with fibrin D-dimer fragments. So D-dimer assay increases in any condition with clot formation and its subsequent fibrinolysis occur.

Procedure

It was a semi quantitative method, we took 20 UL of sample, mixed it with 70 UL of D-dimer reagent and observed for agglutination for 180 seconds or 3 minutes. If agglutination came out to be negative its level is less than 250 mg per UL. If agglutination was positive as determined by a level more than 250 ng/uL then serial dilution would be checked. For serial dilution we mixed 100 UL of sample with 100 ul of saline and also put 100 UL saline in other two tubes. We made a serial dilution of 1:2, 1:4 and 1:8 taking 100 UL from the first tube and put in 2nd and 3rd tube.

Again, we performed the same procedure for agglutination by taking 20 UL from reagent and 70 UL from serial dilution.

Normal level of D-dimer less than 250 ng/UL in undiluted sample. When positive in undiluted sample it's level is above 250 to 500 ng/ml. When positive in serial dilution 1:2 it's level is 500 to 1000 ng/ml. If positive agglutination is seen in 1:4 D-dimer level is 1000 - 2000 ng/ml. If agglutination is positive in 1:8 dilution D-dimer level is more than 2,000 ng/ml.

So a raised level characterizes thromboembolic condition in the body and is a useful marker for a cardiologist to know within three minutes about the hemostatic defect of the patient. It's negative value excludes a thromboembolic condition and positive value guides the cardiologist for other supportive investigations.

All the data were subjected to SPSS Version 20. t-test with level of significance was set at $P < 0.05$.

RESULTS

The present study included a total of 100 patients; they were divided into two groups. Group A include 50 patients of Acute STEMI and Group B 50 patients of NSTEMI, USA and 50 individuals were taken as a control group. Patients included adult males and females.

In 50 patients of acute myocardial infarction, 40 patients had elevated D-dimer levels; in 30 patients the D-dimer level was in the range of 500 to 2000 ng/ml; in 10 patients the D-dimer level was 500 to 1000 ng/ml and in 10 patients the level was 250 to 500 ng/ml. While the rest of the patients had a normal value. D-dimer in all these patients were significantly elevated as compared to the control group $P < 0.0036$.

Similarly in 50 patients of non-ST elevation ACS, 35 patients had elevated D-dimer level; in 15 patients the D-dimer level was 250 to 500 ng/ml; and in 20 patients the D-dimer level was in the range of 1000 to 2000 ng/ml while the rest of the patients had normal values. D-dimer level in all these patients were significantly elevated as compared to the control group ($P < 0.0034$). The study shows that elevated D-dimer is a significant finding in both acute STEMI, acute NSTEMI, and USA. D-dimer is the proteolytic degradation of fibrin clot by plasmin and an elevated D-dimer assay show increased fibrin turnover. D-dimer assay was performed by agglutination and semi quantitative method both in undiluted and serial dilution according to standard operation method.

DISCUSSION

The study included a total of 100 patients divided into three groups. Group A included 50 patients of MI. Group B, 50 patients of Non-ST ACS and Group C included 50 healthy individuals as a control group. The sample size was small due to economical constraints involving the high cost of the test.

In the present study in Group A, 40 out of 50 acute STEMI showed elevated D-dimer levels. 30 out of 50 Mean D-dimer level was 1,000 to 2000 ng/ul and 10 out of 50 MI patients had D-dimer level of 500 to 1000 ng/ul.

Similarly, in group B 30 out of 50 non-ST elevated ACS (NSTEMI, USA) had elevated D-dimer levels; mean D-dimer was 1000-2000 in 20 pts; and 500-

1000 ng/ul in 10 pts.

D-dimer is a specific fragment of cross-linked fibrin clot. It is formed as a result of action of plasmin acting on cross-linked fibrin clot and causes their proteolytic degradation leading to formation of fragments known as D-dimer fragments that is the end product of fibrin clot breakdown.

D-dimer fragments increase in any condition where clot formation and their subsequent breakdown occur. D-dimer fragments are the end product of fibrin clot breakdown. Measurement of this fragment by D-dimer assay identify both clot formation and its breakdown. It determines the severity of hypercoagulability and identifies those that are more prone to develop thrombogenesis. So, using a D-dimer assay is a useful marker to detect and identify thromboembolism conditions in any system of the body.

A similar study conducted by Tokita et al showed acute MI patients had increased D-dimer levels¹³. Another study by Wakia et al reported elevated D-dimer level in acute myocardial infarction¹⁴. Various authors conducted studies showing that D-dimer are significantly elevated in acute myocardial infarction and similar to the observations in our study^{15,16}. Similarly in the present study in Group B, 30 out of 50 patients of non-ST elevated ACS D-dimer levels were elevated; mean D-dimer was 1000 to 2000 ng/ul; and in 10 out of 50 patients the mean D-dimer

Frequency and Percentage of D-dimer level in Acute Myocardial infarction and Non-ST elevation ACS.

	Acute Myocardial Infarction STEMI	Acute Coronary Disease NSTEMI
D-dimer level more than 750 ng/ml	40 out of 50 patients 80%	35 out of 50 patients 70%

Value of D-dimer level in Acute Myocardial Infarction and Non-ST elevation ACS.

	Acute Myocardial Infarction, STEMI	Acute Coronary Disease, NSTEMI	Control Group
D-dimer level less than 250 ng/ml	10	15	50
250-500 ng/ml	10	5	
500-1000 ng/ml	10	10	
1000-2000 ng/ml	20	20	
Total	50	50	50

P value for STEMI, $P < .0035$

P value for NSTEMI, USA, $P < .0034$

There are some 18 to 19 different studies that have shown a correlation between D-dimer and ACS patients. Daneshmandi performed a study on 630 patients and reported that the D-dimers were elevated in these patients¹⁷. Similarly, Halaby R et al studies reported an elevated D-dimer in 1057 patients. There was an independent association of high cardiovascular mortality with raised D-dimer levels^{18,19}. In a study reported by Zheng et al there was a significantly higher prevalence of unstable angina in those with raised D-dimer levels and that it was a helpful marker in these patients^{20,21,22}.

It is evident from the above discussion that myocardial infarction and non-ST elevation ACS is associated with significantly elevated level of D-dimer. FDP levels fragment result from plasmin mediated proteolytic degradation of cross-linked fibrin. Increased levels indicate an increased fibrin turnover and the subsequent lysis of the fibrin clot²³. The pathophysiology of elevated D-dimer in ACS patients indicates increased fibrinolytic activity and a hypercoagulable state that might give rise to thrombotic lesions at distant sites of the vascular tree and coronary arteries in particular²⁴.

The mechanism of plaque rupture and extensive atherosclerosis may be associated with increased blood thrombogenicity, but the outcome of this disease varies from patient to patient. Other conditions like diabetes mellitus, hypercholesterolemia, cigarette smoking, inflammation and activation of coagulation factors all contribute to a hypercoagulable state and increased thrombogenicity

Thrombomodulin (TM) is a useful marker of endothelium damage. It also plays a role in thrombogenicity²⁶. Homocysteine is also known factor for arterial thrombosis and atherosclerosis²⁷. Intimal thickening at initial atherosclerosis, defective fibrinolysis play a role in the progression of coronary heart disease events including myocardial infarction and non-ST ACS⁷.

CONCLUSION

The study concluded that STEMI and non-ST ACS (NSTEMI, USA) are associated with significant elevation of D-dimer.

D-dimer assays are easily performed and are a more reliable hemostatic marker to identify thromboembolic condition and it provides useful information to the cardiologist about the

hemostatic status of the patients. We recommend its use in cardiology emergencies to identify Acute Coronary Syndromes like STEMI, NSTEMI and USA.

REFERENCES

- 1 Ali NM, Gameel FE, Elsayid M, Babker AM. Alterations in D-Dimer, Prothrombin Time and Activated Partial Thromboplastin Time as Thrombogenesis Activity Markers in Patients with Acute Myocardial Infarction. *Open Journal of Blood Diseases*. 2016 Jan 11;6(01):1-5.
- 2 Li YH, Teng JK, Tsai WC, Tsai LM, Lin LJ, Guo HR, et al. Prognostic significance of elevated hemostatic markers in patients with acute myocardial infarction. *Journal of the American College of Cardiology*. 1999 May 1;33(6):1543-8.
- 3 Lowe GD. Fibrin D-dimer and cardiovascular risk. In *Seminars in vascular medicine* 2005 Dec (Vol. 5, No. 04, pp. 387-398). Copyright© 2005 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA..
- 4 Oscar M Martins, Vicente F Fonseca, Ivan Borges, Valério Martins, Vera Lucia Portal, Lucia Campos Pellanda Clinics (Sao Paulo), C-Reactive protein predicts acute myocardial infarction during high-risk non-cardiac and vascular surgery, 2011 May; 66(5): 773776.
- 5 Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *New England Journal of Medicine*. 2005 Apr 21;352(16):1685-95.
- 6 Madaram H, Kuranom M, Fukumura K, Fukuda T, Nakajima T, clinical physiolfunet imaging. 2013;33:1-17
- 7 Singh AK, Gupta V, Singh N, Singh SK, Singh N, Raiza A, Singh H. Role of Immunoturbidimetric plasma fibrin D-dimer test in patients with coronary artery disease as well as ischemic heart disease in emergency medicine. *Int J Cur Biomed Phar Res.* 2011 Apr 30;1(2):31-3.
- 8 Shitrit D, Bendayan D, Bar-Gil-Shitrit A, Huerta M, Rudensky B, Fink G, Kramer MR. Significance of a plasma D-dimer test in patients with primary pulmonary hypertension. *Chest*. 2002 Nov 1;122(5):1674-8.
- 9 Adam SS, Key NS, Greenberg CS. D-dimer antigen: current concepts and future prospects. *Blood*, 2009 Mar 26; 113(13):2878-87.
- 10 Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'fallon WM, Melton LJ. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Archives of internal medicine*. 2000 Mar 27;160(6):809-15.
- 11 Lowe GD, Rumley A. Use of fibrinogen and fibrin D-dimer in prediction of arterial thrombotic events. *Thrombosis and haemostasis*. 1999 Aug;82(02):667-72.
- 12 Brown MD, Lau J, Nelson RD, Kline JA, Turbidimetric D-dimer test in the diagnosis of pulmonary embolism: a meta-analysis. *Clinical Chemistry*, 2003 Nov; 49(11):1846-53.
- 13 Tokita Y1, Kusama Y, Kodani E, Tadera T, Nakagomi A, Atarashi H, Mizuno K, Utility of rapid D-dimer measurement for screening of acute cardiovascular disease in the emergency setting. *JCardiol*. 2009 Jun;53(3):334-40.
- 14 Wakai A, Gleeson A, Winter D. Role of fibrin D-dimer testing in emergency medicine. *Emergency Medicine Journal*. 2003 Jul 1;20(4):319-25.

- 15 Correia LC, Noya-Rabelo M. The D-dimer approach for troponin in the diagnosis of myocardial infarction: is it really useful?. *Journal of the American College of Cardiology*. 2012 Apr 24;59(17):1570-1.
- 16 Min L, Shao S, Wu X, Cong L, Liu P, Zhao H, Luo Y. Anti-inflammatory and anti-thrombotic effects of atorvastatin in acute ischemic stroke. *Neural regeneration research*. 2013 Aug 15;8(23):2144.
- 17 Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, Rumley A, Lowe GD. Fibrin D-dimer and coronary heart disease: prospective study and meta-analysis. *Circulation*. 2001 May 15;103(19):2323-7.
- 18 Halaby R, Popma CJ, Cohen A, Chi G, Zacarkim MR, Romero G, Goldhaber SZ, Hull R, Hernandez A, Mentz R, Harrington R. D-Dimer elevation and adverse outcomes. *Journal of thrombosis and thrombolysis*. 2015 Jan 1;39(1):55-9.
- 19 Morange PE, Bickel C, Nicaud V, Schnabel R, Rupprecht HJ, Peetz D, Lackner KJ, Cambien F, Blankenberg S, Tiret L. Haemostatic factors and the risk of cardiovascular death in patients with coronary artery disease: the AtheroGene study. *Arteriosclerosis, thrombosis, and vascular biology*. 2006 Dec 1;26(12):2793-9.
- 20 Zheng Y, Zeng Q, Zhang L, Duan L, He K, Zheng Q. D-dimer is useful in assessing the vulnerable blood in elderly patients with coronary disease. *Journal of Geriatric Cardiology* September. 2008 Sep 28;5(3):131.
- 21 Folsom AR, Aleksic N, Park E, Salomaa V, Juneja H, Wu KK. Prospective study of fibrinolytic factors and incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2001 Apr 1;21(4):611-7.
- 22 Lowe GD, Yarnell JW, Rumley A, Bainton D, Sweetnam PM. C-reactive protein, fibrin D-dimer, and incident ischemic heart disease in the Speedwell study: are inflammation and fibrin turnover linked in pathogenesis?. *Arteriosclerosis, thrombosis, and vascular biology*. 2001 Apr 1;21(4):603-10.
- 23 Von Känel R, Dimsdale JE. Fibrin D-dimer: A marker of psychosocial distress and its implications for research in stress-related coronary artery disease. *Clinical cardiology*. 2003 Apr 1;26(4):164-8.
- 24 Von Känel R, Mills PJ, Fainman C, Dimsdale JE. Effects of psychological stress and psychiatric disorders on blood coagulation and fibrinolysis: a biobehavioral pathway to coronary artery disease?. *Psychosomatic Medicine*. 2001 Jul 1;63(4):531-44.
- 25 Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. *Circulation*. 2003 Oct 14;108(15):1772-8.
- 26 Blann AD, Amiral J, McCollum CN. Prognostic value of increased soluble thrombomodulin and increased soluble E-selectin in ischaemic heart disease. *European journal of haematology*. 1997 Aug 1;59(2):115-20.
- 27 Bostom AG, Silbershatz H, Rosenberg IH, Selhub J, D'Agostino RB, Wolf PA, Jacques PF, Wilson PW. Nonfasting plasma total homocysteine levels and all-cause and cardiovascular disease mortality in elderly Framingham men and women. *Arch Intern Med*. 1999 May 24;159(10):1077-80.