

# Elevated D-Dimers and C-Reactive Protein Levels as a Risk Factor for Development of Thrombotic Events in Type 2 Diabetes Mellitus

Amjad Ali<sup>1</sup>, Subhan ud Din<sup>2</sup>, Hameed Ullah<sup>1</sup> and Ishtiaq Hussain<sup>1</sup>

## ABSTRACT

**Objective:** To study the levels of C-Reactive Protein and D-dimers in diabetic patients.

**Study Design:** Descriptive study.

**Place and Duration of Study:** This study was conducted at the Departments of Medicine and Pathology at Bacha Khan Medical College and Teaching Hospital Mardan from January to June 2016.

**Materials and Methods:** The study included a total of 150 patients. Out of these 150 patients, d-dimer levels were measured in 50 patients and CRP levels in the other 50. Remaining 50 patients were included in the control group. In control group, which comprised of non diabetic patients, d-dimer and CRP levels were measured in all 50 patients.

**Results:** CRP was elevated in 22 out of 50 patients (44%) and d-dimers were elevated in 32 out of 50 patients (64%). Five out of 50 patients had D-dimers levels in the range of 250-500ng/ml. 15 out of 50 patients had d-dimer levels in the range of 500-1000ng/ml and 10 out of 50 patients had d-dimers levels in the range of 1000-2000ng/ml. The study showed that both CRP and d-dimer levels were elevated in type 2 diabetic patients as compared to control group in which only 3 out of 50 patients had elevated d-dimer and 4 out of 50 had elevated CRP. P-value for CRP was less than 0.0035 and for d-dimer sit was less than 0.0032.

**Conclusion:** The study concluded that diabetic patients are associated with significantly elevated level of CRP and d-dimer level. CRP is an inflammatory marker and d-dimer is hemostatic marker. Elevated levels identify patients who are predisposed to thrombotic events and thus useful to identify at risk patients. Early management in these patients reduce thrombotic complications.

**Key Words:** d-dimers, C-reactive Proteins, Diabetes Mellitus

**Citation of article:** Ali A, Din S, Ullah H, Hussain I. Elevated D-Dimers and C-Reactive Protein Levels as a Risk Factor for Development of Thrombotic Events in Type 2 Diabetes Mellitus. Med Forum 2017;28(7):3-6.

## INTRODUCTION

Diabetes mellitus is a chronic disorder in which absolute or relative deficiency of insulin or its function occurs. The diabetes is associated with a lot of complications including diabetic neuropathy, diabetic nephropathy, diabetic retinopathy and Cardiovascular Diseases. All of these complications arise from common dysfunction of micro or macrovasculature in various parts of the body induced mainly by high concentrations of glucose in DM<sup>2</sup>. Type 2 DM is an inflammatory atherothrombotic condition and inflammation has central role in the pathogenesis of atherosclerosis<sup>3</sup>. This inflammation is reflected by increased plasma levels of several biomarkers of inflammation such as CRP<sup>4</sup>. CRP is a marker of injury and its levels are considerably increased in patients of Type 2 DM.

Without having any signs of injury this increased concentration of CRP might be related to type 2 diabetes mellitus in some way. Elevated levels of CRP and other inflammatory markers are important risk factors for development of insulin resistance<sup>5</sup>. And cardiovascular disease<sup>6</sup>. High CRP levels have been linked to increased risk of thrombotic events<sup>7</sup>. Diabetic patients also presents with hypercoagulable state and have abnormalities in coagulation, hemostasis, platelet dysfunction and reduced activity of fibrinolytic system; these collectively can accelerate atherogenesis in diabetic patients<sup>8</sup>. The prothrombotic state in diabetic patients is characterized by increased fibrinogen levels, increased plasminogen activator inhibitors and different abnormalities in platelet functions. The disordered hemostatic mechanisms in DM play role in the pathogenesis of microvascular and macrovascular complications<sup>9,10</sup>.

d-dimer fragments are the plasmin mediated proteolytic degradation of cross linked fibrin clot and d-dimers assay detects these fragments. High levels of d-dimers have been reported in diabetic patients and its elevated levels predict hypercoagulable and prothrombotic state<sup>11</sup>. The aim of the study is to evaluate the plasma levels of CRP and d-dimers in type 2 DM patients as both hypercoagulable and chronic inflammatory states can

<sup>1</sup>. Department of Medicine, BKMC/MMCTH, Mardan.

<sup>2</sup>. Department of Pathology, GKMC/BKMCTH, Swabi.

Correspondence: Dr. Amjad Ali, Associate Professor, Department of Medicine, BKMC/MMCTH, Mardan.

Contact No: 0333-9418546

Email: dramjadali75@gmail.com

Received: May 10, 2017;

Accepted: June 17, 2017

increase the risk of cardiovascular events ( myocardial infarction), cerebrovascular and peripheral vascular disease. Increased mortality due to cardiovascular disease in diabetics result from atherothrombotic complications, so determination of these two parameters has a predictive value and provides useful information to clinicians in assessing prothrombotic state in these patients.

## MATERIALS AND METHODS

This study was conducted in the Department of Medicine at Mardan Medical Complex Teaching Hospital Mardan and pathology department of Bacha Khan medical college Mardan in Jan 2016 to June 2016. A total of 100 patients of DM were included in the study with blood glucose levels more than 200 mg/dl while 50 normal healthy individuals were placed in the control group. Both the diseased and control healthy individuals were adult males and females.

Patients with history of hypertension, Deep Venous Thrombosis, Pulmonary Embolism, Pneumonia and Septicemia were excluded from the study. 5 ml Blood samples were collected from all these diabetic and healthy individuals in a tube containing sodium citrate 3.2%. The citrated blood was centrifuged to separate plasma for determination of d-dimer levels and for CRP levels blood was taken in an EDTA tube. A sample of 0.5ml of blood was taken in gel tube for blood sugar estimation. Blood glucose levels were determined by a semi- quantifier chemical analyzer (Japan) for both diabetic and healthy individuals and entered in a paper proforma.

For determination of d-dimer levels, spe-d-dimer assays were utilized. Because d-dimer assay is a useful, reliable, quick and accurate method to identify any thromboembolic events in the body.

## RESULTS

The present study included a total of 100 patients of type2 DM and 50 individuals were included as control group. All the patients were adult males and females. In the present study 45% of patients with type 2 DM showed elevated CRP levels, which means value of CRP level was  $5.6 \pm 0.5$  ng/l which were significantly elevated in diabetic patients as compared to control group ( $p < 0.0035$ ). In control group 8% (4 out of 50) had elevated CRP levels.

Similarly d-dimer level was also studied in diabetic patients. 65% of the patients with type 2 DM showed elevated d-dimer levels. Patients had d-dimer levels in the range of 500-1000 ng/ml and 20% of the patients had d-dimer levels in the range of 1000-2000 ng/ml. All these patients had significantly elevated levels of d-dimers compared to control group ( $p < 0.00324$ ). In control group 6% (3 out of 50) of the patients had elevated d-dimers.

The study shows that type 2 diabetes is associated with elevated CRP and d-dimers levels. CRP is an inflammatory marker, more predictive and shows the inflammatory status of the patient as the elevated levels predict the progression and pathogenesis of atherosclerosis. d-dimer is also a useful haemostatic marker and gives useful information to the clinician about the thromboembolic events in the body. So both d-dimers and CRP have predictive role in type 2 DM.

**Table No. 1: Frequency and percentages of CRP and d-dimer levels in type 2 DM**

S.No	Tests	Percentage
1	C Reactive protein	45%
2	d-dimers	65%

**Table No. 2: Percentage of elevated CRP and d-dimers levels in Control group**

S.No	Tests	Percentage
1.	C- Reactive Protein	08%
2.	d-dimers	06%

### Statistical Plan:

**Table No. 3: Ratio of elevated and normal CRP**

	Elevated CRP	Normal CRP	
Type 2 DM	22	28	50
Non-Diabetic (control)	4	46	50
	26	74	100

$$\text{ODDs Ratio(OR)} = 22 \times 46 / 4 \times 28 = 9$$

As the Odds ratio is 9 which means that the patients with Type 2 DM are 9 times more likely to have elevated CRP than Non-Diabetics(Controls).

- In the above 2\*2 Table Type 2 DM is exposure while CRP is outcome.

**Table No. 4. Ratio of elevated and normal d-dimers**

	Elevated d-dimers	Normal d-dimers	
Type 2 DM	32	18	50
Non Diabetic (Control)	3	47	50
	35	65	100

$$\text{ODDs Ratio(OR)} = 32 \times 47 / 18 \times 3 = 28$$

As the Odds ratio is 28 which concludes that the patients with Type 2 DM are 28 times more likely to have elevated d-dimers than Non-Diabetics(Controls).

**Statistical Method:** The statistical method used to analyze the data in our study was Chi square test. The chi square test was run in SPSS & p values were obtained which were statistically significant as given below:

For CRP group the P value was  $p < 0.0035$  while for d-dimers the p value was  $p < 0.00324$ .

The above P values indicates that the difference between Diabetics & control group is statistically

significant & not merely by chance, hence rejecting the null hypothesis.

## DISCUSSION

The present study included a total of 100 patients of DM and 50 as a control healthy individuals. In the present study 55 (40%) of the patients showed elevated CRP levels in diabetic patients, which is similar to the study conducted by Nayak et al which showed 57% elevated CRP levels in DM patients<sup>12</sup>. Various studies have been conducted and reported that DM is associated with elevated CRP levels. Tabak et al reported that CRP levels are higher among Diabetic patients<sup>13</sup>. Kaur et al also reported that DM is associated with high CRP levels<sup>14</sup>. Human CRP is an acute phase reactant involved in acute and chronic inflammation, synthesized by hepatocytes and its production is stimulated in response to infection, tissue injury or inflammation. Its expression is controlled by IL-1, IL-6 and TNF alpha<sup>15</sup>. Chronic low grade inflammation play important role in the pathogenesis of type 2 DM and progression to atherosclerosis<sup>16</sup>. CRP is a potential biomarker for prediction of future risk of cardiovascular disease both in diabetic and non-diabetic individuals and even a small rise in CRP levels leads to cardiovascular events.

Patients with type 2 DM had increased level of CRP and high CRP levels were found to be the predictor of risk for the development of diabetes<sup>17</sup>. IL-6 is a potent stimulant for hepatic CRP production<sup>18,19</sup> which are mainly provided by adiposities. Diabetes mellitus and its various complications involve the role of inflammation in their pathogenesis and link with CRP mediated inflammatory events, elevated levels of CRP causes more severe damage to the endothelial linings<sup>20</sup>. CRP is strongly associated with endothelial dysfunction by damaging endothelial glycocalyx layer, which is a protective barrier for the walls of blood vessels. Elevated CRP levels severely damages the endothelial layers and decreasing their thickness and this endothelial dysfunction is the precursor of many diabetic complications such as diabetic retinopathy and diabetic nephropathy<sup>21</sup>. In the present study 80% of the patients showed elevated d-dimers level, which is similar to the studies conducted by various authors. Mohsin et al conducted study on diabetic patients and reported that d-dimers are significantly elevated in these patients. A similar study has been conducted by Letonja et al on diabetic patients who reported elevated d-dimer levels in these patients<sup>22</sup>.

Various studies have been performed on diabetic patients by various authors who reported elevated d-dimer levels in type 2DM<sup>23,24</sup>. d-dimer is a specific fragment of fibrin clot and formed as a result of plasmin

mediated proteolytic degradation of cross linked fibrin clots. A thrombotic complications are the main cause of mortality in diabetic patients. Premature atherosclerosis increases platelet reactivity and activates coagulation factors with associated hypofibrinolysis all contributing to increased cardiovascular risk in these patients<sup>25</sup>. DM has a hypercoagulable state and is associated with increased risk for thrombosis, and this hypercoagulable status is evidenced by increased fibrinogen level, decreased protein S levels and increased production of von-willibrand factor by endothelium<sup>26</sup>. In addition increased thrombotic tendency is due to platelet hyperactivity, increased activation of prothrombotic coagulation factors coupled with decreased fibrinolysis. All these lead to haemostatic abnormalities in type 2 DM<sup>27</sup>. Due to hypercoagulable state diabetic patients are more prone to micro and macrovascular complications<sup>28</sup>. About 80% of diabetics die from thrombotic events with 75-80% of these deaths resulting from cardiovascular events<sup>29</sup>.

## CONCLUSION

The present study concluded that diabetes mellitus is a chronic inflammatory disorder with hemostatic abnormalities associated with increased coagulation activation markers represented by elevated CRP and D-dimer levels, both these markers have predictive value and their elevated levels identify patients at risk for thrombotic complications, so their elevated levels give valuable information to the clinicians for the appropriate management of these patients and to reduce their chances of further complications and improve their life style.

### Recommendations:

In our community diabetic patients and specifically clinicians should be fully aware of and educated about the importance thromboembolic events and their complications that can occur in patients with elevated d-dimers levels. They should early advise the detection of these inflammatory and hemostatic markers to know at risk patients earlier and reduce complications. More robust methods should be adopted to obtain accurate results for d-dimers.

### Author's Contribution:

Concept & Design of Study:	Dr. Amjad Ali
Drafting:	Dr. Subhan ud Din
Data Analysis:	Dr. Hameed Ullah
Revisiting Critically:	Dr. Ishtiaq Hussain
Final Approval of version:	Dr. Amjad Ali

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

## REFERENCES

- Iyer MU, Desai P. Assessment of CRP and fibrinogen levels in T2DM. *Bio Med Res* 2010;2:218-213.
- Behi T, Goel H, Sudan P, Shams P, Misri WR, et al. Role of CRP in Dm and its associated complication indo. *Am J Pharma Res*
- Mugabo Y, Renier G. The concern between CRP and diabetic vasculopathy. Focus on preclinical findings. *Curr diabetic Rev* 2010;6:27-34
- Ford ES The metabolic syndrome and CRP fibrinogen and leukocyte count findings from 3rd national health and nutrition examination survey, atherosclerosis 2003;168:351-358.
- Numele CE, Prodan AD, Riokar PM. Interrelationship between inflammation, CRP and insulin resistance. *Summer* 2006;3:190-196
- king DE Mainus AG, Buehanan TA. Pearson WS CRP and Glycemic control in adults with diabetes as diabetic. *Care* 2003;6:1535-1539.
- Ridker PM, Stampfer MJ, Rifau. Novel risk factors for systemic atherosclerosis and comparison of CRP, Fibrinogen, homocystein, lipoprotiena and standard cholesterol screening as a predictor of peripheral arterial disease. *JAMA* 2001;285:2481-2485.
- Pradhan AD, Manson JE, Rifal N, Buring JE, Ridker PM. CRP, IL-6 and risk of developing type 2 DM. *JAMA* 2001;226:327-334.
- Vanik A, Erbas T, Park TS, Nolon R, Pitteneger GL, Platelet dysfunction in type 2 DM. *Diabetic Care* 2001;24:1476-1485.
- Muhsin AN, Al-Mudallal SS. Elevation of plasma fibrinogen D-dimers and CRP as a predictive parameter for coronary heart disease in type 2 DM. *Mustansyria Med J* 2014;13:12-17
- Zafar AT. diagnostic value of D-dimers in predicting myocardial infarction among diabetic Makkah pilgrims. *Oxford Res Forum J* 2010;2: 25-35.
- Nayak BS, Brenen B, Narine S, Rampersad A, Dilber A, Singh A et al. Relationship of CRP, uric acid, Lipid profile with type 2 DM in Trinidad. *Int J Res Dev Pharm L Sci* 2015;2:1451-1455.
- Tabak AG, Kivimaki M, Brunner EJ, low GD, Akbarely TN, et al. changes in CRP levels before type 2 DM and cardiovascular death, the whitehell study *Eurp J End* 2010;163:89-95.
- Kaur R, Matharoo K, Sharma R, Bhanwer AS, CRP+1059G>C. Polymorphism in type 2 DM and coronary artery disease. *Patients Meta Gene* 2013;1:82-92.
- Ridker PM, Rifia N, Buring JE, Cook NR. Comparison of CRP and LDL cholesterol levels in the prediction of first cardiovascular events. *N Eng J Med* 2002;347:1557-1565
- Trama L, Sanda GM, Stancu CS, Rogoz D, Sima AV, combined effect of CRP and hyperglycemia on endothelial dysfunction. *Ann RSCB* 2012;1: 29-36.
- Annand SS, Razak F, Yi Q, Jacobs R, Vuksan V, et al. CRP as a screening test for cardiovascularrisk in multi ethnic population. *Arterioscler-thromb-vas* 2004;24:1509-1515.
- Nakanishi S, Yamane K, Kamel N, et al. Elevated CRP as a risk factor for the development of type 2 DM in Japanese Americans. *Diabetic Care* 2003;26:2754-2757.
- Ionica FE, Mota M, Pisoschi C, Popescue F, Gofita E. Statins therapy CRP levels in Type 2 DM. *H Sci J* 2009;35:87-91.
- Stehouwer CD, Gall MA, Twisk J, Knudsen E, Emets JJ, Porwing HH. Increased coronary albumin excretion, endothelial dysfunction and chronic low grade inflammation in type 2 DM. 2002;51:1157-1165.
- Heim TW, Singh J, Vasquez VJ, Devaraj S, Kue L, Jalal. Human CRP induces endothelial dysfunction and uncoupling of eNOS in vivo atherosclerosis 2009;206:61-68
- Letonja SM, Letonja M, Storcevic iv g- petroic C, Ultrasonographic and classical risk factors of cabtidatherosclerosis in patients with Type-2 Diabetic Mellitus. *Acta Med Bio Tech* 2013;6: 33-44.
- Krapniski J, et al, Increase Tissue factor MMP8 and D-dimer expression in Diabetic Patients with unstable advanced carotid atherosclerosis. *Vascular Health and risk management* 2007;11:405-412.
- Erome, Hadhasanoglu A, Celik S, Ovali E, Eroz, Uknic C, et al. Coagulation and fibrinolysis parameters in type2 Diabetic patients with and without diabetic vascular complications. *Med Prime Pract* 2005;14:22-30
- Alzahram SH, Ajjan RA. Coagulation and fibrinolysis in DM and vascular disease. *Res* 2010; 7:260-273.
- Madan R, Gupta B, Saluja S, Kansra US, Gulani BP. Coagulation profile in DM and its association with micro vascular complications. *JAPI* 2010; 58:481-484.
- Grant PJ, Inflammatory atherothrombotic aspects of type 2DM. *Curr Med Res Opin* 2005;1:5-12.
- Bennet PH, Lee ET, Lu M, Keen H, Fuller JH. Increased urinary albumin excretion and its association in the WHO multinational study of vascular diseases in DM. *Diabetologia* 2001;44: 37-45.
- Carr ME, Diabetomellito; a hypercoagulabel state. *J Diabetes Complications* 2001;15:44-45.