

# Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) in Type 2 Diabetes Mellitus, a Case Control Study

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## ABSTRACT

**Introduction:** Diabetes mellitus (DM) is characterized by hyperglycemia accompanied with the biochemical alterations in carbohydrate, protein and lipid metabolism. Diabetics have been shown to be in procoagulant state due to abnormalities in several plasma proteins in blood coagulation. Measurement of prothrombin time (PT), activated partial thromboplastin time (APTT), bleeding time and clotting factor concentration are usually done in patients with a suspected abnormal coagulation. The present study was planned to assess and compare the coagulation tests in patients with T2DM and healthy individuals.

**Material and methods:** In this prospective case control study 50 diabetic patients and 50 healthy non-diabetic individuals were subjected to Prothrombin time(PT), Activated partial thromboplastin time(APTT) and D-Dimer assay patients in the department of Pathology at Adesh Institute of Medical Sciences and Research, Bathinda from 1st January 2016 to 30<sup>TH</sup> June 2017.

**Results:** A statistically significant increase in Mean Prothrombin time (PT) levels of 17.48 in cases vs 14.52 in controls with a P value was 0.012. The Mean aPTT levels in cases was 48.12 and in controls was 30.56 with a P value was 0.001. However, in case of Mean D-Dimer levels, there was no significant difference between cases and controls with a P value of 1.000.

**Conclusion:** The present study observed a significant association between Type 2 Diabetes mellitus and coagulation parameters. Increased plasma levels of PT and APTT were observed which are consistent with abnormal coagulation mechanisms and may be interpreted as a tendency for bleeding and cardiovascular disorders. It would also be helpful to incorporate coagulation screening as a routine investigations for the better management of diabetic patients.

**Keywords:** Diabetes Mellitus; PT; APTT; D-Dimer; Coagulation; Bleeding

dysfunction are responsible for the generation of hypercoagulable state in Type 2 Diabetes Mellitus individuals. Coagulation tests like prothrombin time (PT) and the activated partial thromboplastin time (APTT) are global tests use to assess the coagulation system in a clinical settings.<sup>5</sup> Coagulation abnormalities with decreased level of antithrombin III, protein C and protein S has been reported in DM with elevated clotting factors VII.<sup>6</sup> Moreover, there is also an increase in plasminogen activator inhibitor type 1 which decreases fibrinolysis. Together they contribute to a hypercoagulable state in DM. Hypercoagulability in diabetes may accelerate atherosclerosis and acts as a risk factor for the development of cardiovascular diseases(CVD)<sup>7</sup>

Measurement of prothrombin time (PT), activated partial thromboplastin time (APTT), bleeding time and clotting factor concentration are usually done in patients with a suspected abnormal coagulation. PT and APTT are the markers for activation of extrinsic and intrinsic pathway respectively.<sup>8</sup> D-Dimer is a direct marker of fibrinolytic activity and a conventional clinical screening marker of preceding coagulation activity. Increased plasma D-dimer levels have been reported in type 2 diabetes mellitus.<sup>9</sup> Since Diabetes mellitus worsens various biological processes like coagulation and fibrinolytic system, the present study was planned to assess and compare the coagulation tests in patients with T2DM and healthy individuals.

## MATERIAL AND METHODS

This prospective case control study was conducted in the department of Pathology, AIMS, Bathinda over a period of one and a half year from 1st January 2016 to 30<sup>TH</sup> June 2017. 50 diabetic patients who were attending out-patient and in-patient departments and 50 healthy non-diabetic individuals were included in the study.

1. Already diagnosed Type 2 Diabetes mellitus individuals of

## INTRODUCTION

Diabetes mellitus (DM) is characterized by hyperglycemia accompanied with the biochemical alterations in carbohydrate, protein and lipid metabolism.<sup>1</sup> Type 2 DM accounts for about 80% of DM<sup>2</sup> In patients with DM, cardiovascular disease (CVD) remains the main cause of morbidity and mortality and approximately 80% of patients die as a result of cardiovascular complications. Apart from the accelerated development of atherosclerosis in patients with diabetes, these patients are also at an increased risk of thrombotic events. These individual have been shown to be in procoagulant state.<sup>3</sup> This procoagulant state is due to abnormalities in several plasma proteins in blood coagulation.<sup>4</sup> The hemostatic abnormality and endothelial

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either sex (male and female) between the age group of 40-65 years were taken as cases in the study.

2. Healthy individuals of either sex (male and female) between the age group of 40-60 years were taken as controls.

#### Exclusion criteria

Patients with the following diseases/conditions were excluded from the study:

- i) Type I Diabetes mellitus
- ii) History of thromboembolism.
- iii) On Anticoagulant therapy and anti-platelet drugs.
- iv) Known inherited coagulation disorder.
- v) Female patients who were pregnant.
- vi) Recently undergone surgery.
- vii) Known liver disease.
- viii) Hemoglobin levels <12 gm/dl (in males) and <11 gm/dl (in females)

Under all aseptic conditions 5 ml blood sample was collected from antecubital fossa veins using 22 G number needles. Blood was drawn gently but quickly after a single and smooth venepuncture. Samples from the patients and controls were collected in a clean tube having 3.2% trisodium citrate. Anticoagulant to blood proportion being 1:9. Immediately the blood was mixed with anticoagulant to avoid foam formation. Coagulation studies were carried out within 2 hours of collection of sample. Hemostatic reagent was taken into a test tube and patient's plasma was added to it. Test tube containing plasma and reagent was incubated for 2-3

minutes.

#### The kit used for PT determination-Diagnos Thrombo 1.0

Diagnos Thrombo reagent is a rabbit brain thromboplastin reagent supplied as liquid thromboplastin reagent with an activator containing calcium, used in the in vitro testing of prothrombin time by photo-optical or mechanical clot detection systems.

#### T kit used for APTT determination-Diagnos APTT.

Diagnos APTT is a ready to use activated cephaloplastin reagent activated with Ellajic acid used for in vitro testing of activated partial thromboplastin time by mechanical clot detection system.

#### D-Dimer Assay- Quantia D- Dimer Kit was used.

D-Dimer is a turbidimetric immunoassay for the determination of D-Dimer and is based on the principle of agglutination reaction results in formation of an insoluble complex resulting in an increase in turbidity which is measured at wavelength 630 nm. The increase in turbidity corresponds to the concentration of D-Dimer in the specimen.

All the cases and controls were subjected to the following blood investigations:

- a) Prothrombin time (PT)
- b) Activated partial thromboplastin time (APTT)
- c) D-Dimer assay.

## RESULTS

The present study was done on 100 patients in the department

Age (Years)	Case Group		Control Group	
	Frequency	Percentage	Frequency	Percentage
36-40	7	14%	10	20%
41-45	4	8%	3	6%
46-50	3	6%	4	8%
51-55	12	24%	9	18%
56-60	19	38%	24	48%
61-65	5	10%	0	0%
Total	50	100%	50	100%
Mean Age	53.98±7.81		52.78±8.07	
Range	40-65		40-60	
t-test	0.755			
p value	0.452			
Sig.	NS			

Table-1: Age wise distribution of cases and controls.

Gender	Case Group		Control Group	
	Frequency	Percentage	Frequency	Percentage
Female	25	50%	25	50%
Male	25	50%	25	25%
Total	50	100%	50	100%
X <sup>2</sup>	1.520			
p value	0.218			

Table-2: Gender-wise distribution of cases and controls

FBG (mg/dl)	N	Mean	SD	Std. Error Mean	t-test	p value	Sig.
Case Group	50	202.20	58.87	8.33	12.269	0.001	HS
Control Group	50	98.62	9.93	1.41			

Table-3: Fasting Blood Glucose (FBG) of cases and controls

FBG (mg/dl)	N	Mean	SD	Std. Error Mean	t-test	p value	Sig.
Case Group	50	202.20	58.87	8.33	12.269	0.001	HS
Control Group	50	98.62	9.93	1.41			

**Table-3:** Fasting Blood Glucose (FBG) of cases and controls

PT (sec)	N	Mean	SD	Std. Error Mean	t-test	p value	Sig.
Case Group	50	17.48	8.13	1.15	2.552	0.012	S
Control Group	50	14.52	1.09	0.16			

**Table-4:** Prothrombin Time (PT) of cases and controls

aPTT (sec)	N	Mean	SD	Std. Error Mean	t-test	p value	Sig.
Case Group	50	48.12	22.32	3.16	5.535	0.001	HS
Control Group	50	30.56	2.22	0.31			

**Table 5:** Mean Activated Partial Thromboplastin Time (APTT) of cases and controls

of Pathology at Adesh Institute of Medical Sciences and Research, Bathinda for a period of one and half year, i.e. from 1st January 2016 to 30<sup>TH</sup> June 2017, 50 cases and 50 controls were included.

Age distribution of cases and controls is shown in table 1. Mean age of the cases was 53.98±7.81 and of controls was 52.78±8.07. P value was 0.452 which is more than 0.005. There was no significant difference between the age of cases and controls.

Table 2 shows gender-wise distribution of cases and controls. Of the total 100 cases studied, equal sex distribution was taken and p value was 0.218 which is more than 0.005. There was no significant difference between the gender wise distribution of cases and controls.

Mean Fasting Blood Glucose (FBG) levels in cases was 202.20 and in controls was 98.62 (Table 3). P value was 0.001 which is < 0.005. A significant difference was seen among cases and controls.

Mean Prothrombin time (PT) levels in cases was 17.48 and in controls was 14.52 (Table 4). P value was 0.012. A significant difference was seen among cases and controls. In our study, PT was seen increased i.e. p value was statistically significant.

The Mean aPTT levels in cases was 48.12 and in controls was 30.56 (Table 5). P value was 0.001. A significant difference was seen among cases and controls. Mean D-Dimer levels show P value of 1.000. There was no significant difference seen among cases and controls.

## DISCUSSION

The present study was conducted in AIMSRS, Bathinda in the department of Pathology for a period of one and half year. A total of 100 cases were analyzed, out of which 50 diabetic cases and 50 healthy individuals who served as controls were taken up for the study. Evaluation of the coagulation profile and few platelet parameters were performed on all the 100 cases included in the study.

Mean age of the cases was 53.98±7.81 and of controls was 52.78±8.07 and p value was 0.452 (>0.05). There was no significant difference between the age of cases and controls. Of the total 100 cases studied, equal sex distribution was done and p value was 0.218 (p value > 0.05) There was no

significant difference between the gender wise distribution of cases and controls.

Mean FBS levels in cases was 202.20 and in controls was 98.62 and p value was 0.001 which was less than 0.05. A significant difference was seen among cases and controls.

Mean prothrombin time levels in cases was 17.48 and in controls was 14.52 and p value was 0.012 (< 0.05). A significant difference was seen among cases and controls. Our study was in concordance with the study conducted by AbdulRahman et al,<sup>10</sup> Alao O et al,<sup>11</sup> Sauls D.L et al<sup>12</sup> and P.Krishna Chaitanya et al.<sup>13</sup> However studies by Madan R et al<sup>4</sup> and Obeague E et al,<sup>14</sup> found that there was no significant change in PT. And studies conducted by Fayeza et al<sup>15</sup> and Sunita Dhule et al<sup>6</sup> concluded that PT was shortened in diabetic patients.

The Mean APTT levels in cases was 48.12 and in controls was 30.56. P value was 0.001 which was less than 0.05. A significant difference was seen among cases and controls.

Alao O et al,<sup>11</sup> Obeagu Emmanuel Ifanyi et al,<sup>14</sup> Hassan et al<sup>16</sup> and Mayasam et al.<sup>17</sup>

also observed that there was significant prolongation of APTT in diabetics when compared with the non-diabetic controls. Madan R et al.<sup>4</sup> Erem et al<sup>18</sup> and Collier et al<sup>19</sup> reported no significant change in APTT. The study conducted by Acang and Jalil<sup>20</sup> decreased APTT which is in discordance with our study.

Dallatu et al<sup>21</sup> and Selvin et al<sup>22</sup> studied the effect of hyperglycemia on haemostasis and revealed that prolonged exposure of the blood cells to high glucose concentration causes glycation of haemoglobin and decrease in synthesis of clotting factors. According to Lippi et al,<sup>23</sup> high glucose level causes incomplete activation of the coagulation cascades of extrinsic and intrinsic pathway. As explained by Laffan et al,<sup>24</sup> the prolongation time of APTT may be due to in-vitro interference of fibrin clot formation by inhibitors. This prolonged APTT may also occur as a result of damage to the liver where most of the coagulation factors are synthesized. Thus, increased levels of PT and APTT are consistent with abnormal coagulation mechanisms and can be interpreted as a tendency for bleeding and cardiovascular disorders (Hassan 2009).<sup>16</sup> The prolongation of these parameters in

the diabetic group may also be due to in-vitro interference of fibrin clot formation by inhibitors such as fibrinogen fragments 1 and 2 and D-Dimer as reported in several studies (Laffan MA,1995).<sup>24</sup>

Mean D-Dimer levels in our study show p value 1.00 which was more than 0.05. There was no significant difference seen among cases and controls in concordance with study by T. Yamada et al.<sup>25</sup> In the study conducted by Kanani D et al<sup>26</sup> diabetic patients with nephropathy had significantly higher plasma D-dimer levels than patients without complications. But according to various studies which contributes to increased levels of D-dimer, it signifies that the D-dimer if employed as an additional test may improve the risk assessment for early coronary artery diseases in DM patients. Therefore it is reasonable to assume that the higher level of D-dimer is primarily the result of increased fibrin clot formation and its breakdown. The increased thrombogenic state may be related to increased susceptibility to vascular disease in these patients. D-dimer can be used as a novel biomarker of diabetic complications and may help to identify diabetics with high risk of vascular complications. Plasma D-dimer test is now routinely employed as a complimentary test in early identification of diabetic complications.

## CONCLUSION

The present study observed a significant association between Type 2 Diabetes mellitus and coagulation parameters. Increased plasma levels of PT and APTT were observed which are consistent with abnormal coagulation mechanisms and may be interpreted as a tendency for bleeding and cardiovascular disorders. Diabetes mellitus is a heterogeneous disorder that affects cellular metabolism in variety of ways and coagulation indices are reported to be adversely affected. As Diabetes mellitus is a complex disorder, its complications should be monitored closely. As it is rightly said that Diabetes is a "double edge sword", which can result in thrombo-embolic or hemorrhagic complications. Thus, coagulation parameters should be closely monitored and should be a part of test requested by the clinicians in diabetes mellitus because of its attendant risk to various complications such as atherosclerosis, stroke, etc. Prothrombin time (PT) and activated partial thromboplastin time (APTT) are haematological indices that give an idea about the coagulation status of patients. These observations made in our study can contribute in better understanding of relationship between Diabetes mellitus, coagulation profile. It would also be helpful to incorporate coagulation screening as a routine investigations for the better management of diabetic patients.

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