DOI: https://doi.org/10.53350/pjmhs2023175228

ORIGINAL ARTICLE

Coagulopathies among Patients of Diabetes Mellitus in Gujrat, Pakistan

NOOR FATIMA[1], HANNANA MARYAM[2], ABID ALI[3], MAHNOOR FATIMA[4]
[1]Student, Doctor of Medical Laboratory Sciences. [2,4]Lecturers, [3]Associate Professor, University of Cheenab, Gujrat
Correspondence to: Noor Fatima, Email: 70059689@student.uol.edu.pk, Cell: 0310-0603647

ABSTRACT

Objective: To evaluate the behavior of coagulation-related tests like prothrombin time (PT) and activated partial thromboplastin time (APTT) in chronic diabetic patients.

Study Design: Cross-sectional study

Place and Duration of Study: Department of Hematology, Aziz Bhatti Hospital, Gujrat, Pakistan from 1st July 2022 to 31stDecember 2022.

Methodology: One hundred and seventy nine patients were enrolled. Prothrombin time and activated partial Thromboplastin time were performed from the patient's samples.

Results: Forty four patients were with good glycemic control and 135 were with poor glycemic control. It was revealed that patients with type 2 diabetes with poor glycemic control had lower levels of PT concentration 10.95±1.67 and prothrombin time was 11.50±1.331 in good glycemic control patients (P=0.04).APTT result was insignificant with 33.40±2.889 in poor glycemic control patients and while in good glycemic control APTT 34.08±1.348 (p=0.389).

Conclusion: Prothrombin time was low if diabetes is uncontrolled. Early detection of lower PT may indicate that micro or macrovascular coagulopathies are in progress. APTT analysis shows insignificant results in diabetic patients and did not find a special role in coagulopathies disorders.

Keywords: Coagulopathies, Prothrombin time, Activated partial thromboplastin time, Chronic diabetic patients

INTRODUCTION

Diabetes term was used by Araetus of Cappadocia .Mellitus term was added by Thomas Willis in 1675, which means (Honey sweet).Patient blood and urine sample sweetness was discovered by ancient Indians. Latter in 1776 Dobson first time confirmed that blood and urine has sweetness due high glucose level. In modern medicine scientists stated that liver play major role in glycogenesis. In 1889 Minkowski describes the role of pancreas in diabetes pathogenesis, due to this discovery latter isolation of insulin was found in Canada in 1921 by Banting.[1] Diabetes has a long history back into ancient times during that period people have a poor knowledge of medical science like, anatomy, and pathophysiology.[2]

At that time diagnostic tools was not advance so disease remained extremely perplexing to physicians. However physicians in ancient time observed the features of diabetes and proposed many therapeutic approaches. At the time of 1500BC, people who suffer in diabetes presented with excessive thirst, copious urination and treated by plant's extraction.[3] There are two types of diabetes mellitus type 1 diabetes and type 2 diabetes. Type 1 diabetes is genetic disorder and develops in early life. Type 1 diabetes caused by autoimmune disorder in which body consider its own cells to as invader, due to this autoimmunity immune system attack and destroy the insulin producing beta cells.[4] Patients who are suffered with type 2 diabetes have resistance against insulin, body produce insulin but does not use properly.[5]Risk factors for type 2diabetes: have prediabetes, obesity, age, physically less active, have gestational diabetes.[6]

Diabetes mellitus (DM) is chronic disorder that occurs when proper insulin is not produced by pancreas or insulin does not work accurately. Diabetes mellitus is endocrine disorder with multiple aetiology. Diabetes mellitus is characterized by hyperglycemia with subsequent carbohydrates, fat, and protein metabolism disturbance. Low level of insulin to achieve accurate response or insulin resistance to target tissues like adipose tissue, skeletal muscles.[7] At the level of insulin receptors, signal transduction some enzymes or genes are responsible for this metabolic abnormalities.[8]

Hyperglycemia is a condition in which blood glucose raised and cross the thresh hold.[9]As we already discuss that diabetes is a chronic disorder and metabolic disorder which characterized by elevated level of blood glucose which can leads to serious complications for heart, blood vessels, eyes, kidneys, and nerves.[10] Coagulopathy is bleeding disorder in which patient blood coagulation factors did not work properly. In diabetes mellitus complication of coagulation impairment are reported.[11] Clotting factors turns the blood in semisolid state, clots are made of fibrin fibers and these fibrin fibers come from an inactive precursor call "Fibrinogen" also called Factor I, fibrinogen plays a major role in blood viscosity.[12] A study was done by the students by taking 40 healthy and 40 subjects were already diagnosed with diabetes and they find that factor FII was the main cause of hyper coagulation state they directly induced FX and FVII in normal individual and FX, FXI, FV and VWF cofactors in diabetic patients.[13]

Diabetes mellitus causes both micro and macro vascular problems, which are linked to increased platelet activation, aberrant vascular endothelium function, and altered coagulation systems. The abnormalities related to the condition of the coagulation and fibrinolysis system are diagnosed by laboratory parameters which are PT and APTT. Conflicting results of PT and APTT test have been observed in patients with diabetes mellitus. Shorter PT and APTT indicate the presence of activated coagulation factors in vivo. Conversely, normal PT in patients with type 2 diabetes mellitus has also been observed.[14] The thrombin activation expresses the coagulation activation and more information than a study of individual factors which are actively investigated in diabetology. Among all the clotting factors the most interesting factor is fibrinogen.[15]

MATERIALS AND METHODS

This was cross sectional study conducted in the Department of Hematology laboratory of Aziz Bhatti Hospital, Grujrat. The study was ethically approved by the institutional review committee of university of Lahore, Gujrat campus, Pakistan. For this study patients having a demographic data, medical history was included.PT and APTT test was performed from patient's samples. Performa was used to collect data in order to collect the information from the individuals. The demographic data of individuals like name, age, gender, clinical features and study variables were noted.3ml venous blood sample was taken in Sodium citrate vials from each individual. Separated the plasma and performed PT and APTT on state of the art instrument Sysmex CA-101 (Coagulation analyzer)

Sysmex CA-101 instrument was used for test run and analyzed the control before performing subject sample for verification of instrument. Sample was taken in Sodium Citrated vial from selected population by using sterile techniques. Sample was centrifuged to separate plasma for test requirement.100 microliter thrombin reagent was taken in cuvettes. Cuvettes were incubated in instrument and after 1 min of incubation 50 microliter sample added and then note the result in seconds. Normal PT value: 11-14 seconds.

Sysmex CA-101 instrument was used for test run and analyzed the control before performing subject sample for verification of instrument. Sample was taken in sodium citrate vial from selected population by using sterile techniques. Sample was centrifuged to separate plasma for test requirement.100 microliter APTT reagent was taken in cuvettes. Add 100 microliter sample in cuvettes. Cuvettes were incubated in instrument and after 3 min of incubation 100 microliter calcium chloride were added and note the results in seconds. Normal APTT value was 33-48 seconds. The data was entered and analyzed through SPSS-25.The independent student's t-test was used and P<0.05 was considered significant.

RESULTS

The mean age of the cases was 55.65±14.01 years in poor glycemic patients while it was 51.12±7.68 in good glycemic control cases. There were more females in both groups of diabetic patients. The BMI of poor glycemic control cases was insignificantly higher than that of good control diabetic patients (Table 1).

The present study results verified that the platelets count of poor glycemic control patients was higher than that of good glycemic control. However, the prothrombin levels were lowered in uncontrolled cases of diabetes with a significant p value (<0.0001). The APTT also had an unchanged mean value with no specific variance between the poor glycemic control cases vs controlled diabetic patients (Table 2).

The patients with type 2 diabetes with poor glycemic control had lower levels of PT concentration (p=0.04) with 10.95±1.670. Prothrombin time mean was in good glycemic control 11.50±1.331 while APTT results was insignificant (p=0.389) with these findings mean was 33.40±2.889 in poor glycemic control patients and while in good glycemic control APTT mean was 34.08±1.348 (Fig 1).

The association of the factors related with the reduction in coagulation abnormality in cases of diabetes was analyzed in the present study through regression analysis. It was observed that female gender as well as elderly age had a strong association present. Obesity was also related with the disturbances in coagulation factors (Table 3).

Table 1: Demographic detail comparison between poor and good glycemic control cases

Variable	Poor glycemic control (n=135)	Good control (n=44)	p-value
Age (years)	55.65±14.01	51.12±7.68	<0.0001
Gender			
Male	54 (40%)	18 (41%)	0.813
Female	81 (60%)	26 (59%)	
SBP (mmHg)	147.28±31.92	118.76±14.01	<0.0001
DBP (mmHg)	80.29±20.37	76.51±9.23	0.275
FBG (mmol/L)	11.85±6.30	5.56±0.42	<0.0001
WHR (cm)	0.95±0.11	0.84±0.11	<0.0001
BMI (Kg/m^2)	21.47±4.42	20.68±4.61	0.382

Table 2: Comparison of PT, APTT and other hematological and mineral analytes in poor and good glycemic control patients

Coagulation profile	Poor glycemic control (n=135)	Good control (n=44)	p-value
PLT×10^3/mm^3	179.91±66.20	171.55±35.87	0.326
APTT	33.40±2.889	34.08.23±1.348	0.389
PT	10.46±1.85	11.03±2.06	<0.0001
INR	0.83±0.19	1.13±0.12	<0.0001
Albumin, g/L	34.96±3.90	34.73±2.87	< 0.0001
Magnesium mmol/L	0.80±0.12	0.74±0.15	< 0.0001
Calcium-total mmol/L	2.51±0.28	2.49±0.21	0.110
Calcium-ionized mmol/L	1.37±0.22	1.35±0.12	0.024

Table 3: Association of factors with reduction in coagulation abnormality through Regression analyses

Parameter	Platelets		APTT		PT	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Gender						
Male	1		1		1	
Female	1.92 (0.62–5.99)	0.265	1.72 (0.52–5.71)	0.387	3.51 (0.88–14.12)	0.079
Age group						
< 30	1		1			
30–39	-	-	0.51 (0.02–11.08)	0.661	0.2 (-)	-
40–49	0.08 (0.00–2.5)	0.130			1.51 (0.09–25.40)	0.781
50–59	0.20 (0.01–2.32)	0.191	1.43 (0.11–18.60)	0.791	0.43 (0.03–5.90)	0.520
60–69	0.51 (0.05–7.11)	0.610	2.51 (0.15–42.80)	0.527	2.00 (0.14–28.43)	0.610
≥ 70	0.43 (0.035-6.05)	0.523	1.34 (0.09–20.71)	0.837	2.00 (0.01–4.73)	0.317
Body mass index						
Underweight	1.23 (0.36–4.09)	0.761	0.53 (0.14–1.97)	0.338	0.62 (0.15–2.84)	0.550
Normal	1		1		1	
Overweight	0.64 (0.14–2.88)	0.555	1.30 (0.22–7.61)	0.768	2.26 (0.55–9.38)	0.270
Obese	0.18 (0.000)	-	2.84	-	0.03 (0.000)	-

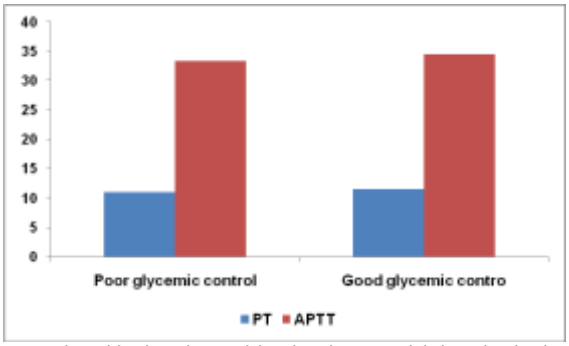

Fig. 1: Prothrombin time (seconds)and activate partial thromboplastin time (seconds) findings in type 2 diabetes patients with poor and good glycemic control

DISCUSSION

With the recent literature available the prothrombotic state is recognized as more component for causing the metabolic syndrome. Those people who are suffering from metabolic syndromes like diabetes have a specific pattern of coagulation factors which facilitates thrombosis as well as causes anomalies in the thrombolysis.[16] The current study was designed to analyses the clotting profile andmeasure the platelet counts in cases of diabetes. The results of this study showed that a reduction in prothrombin was associated with uncontrolled diabetes cases. The findings of the current study demonstrate an augmented predisposition to thrombotic measures in diabetic cases in comparison to controls with no type 2 diabetes formation. The findings presented in this study are in consistency with the previously reported researches where reduction in APTT and PT in type 2 diabetic patients have been elaborated.[17-21]

A study conducted through an epidemiological survey it was clearly documented that the blood plasma levels of glucose was associated with the APTT in diabetic patients. Lippi et al.[22] Reported reduced APTT in diabetic cases than controls. Madan et al[23] also elaborated variance in the demographic details of glycemic uncontrolled cases with glycemic controlled as well as normal control cases. There research also highlighted shortened INR and PT levels in the diabetic patients. The present study has also identified a shorter value of INR in the poor glycemic control cases than those having a good glycemic control among diabetic patients.

The APTT found in the current research had no significant association with the diabetes cases. Zhao et al [24] established the similar fact in their research findings wherein they conducted a case control study in China and reported no significance of APTT with diabetes. There are studies reporting abnormal calcium levels in diabetic patients[25,26], however insignificant contribution of calcium were observed in the present study in addition to other important minerals.

Platelet functionality in conditions of hemostasis are reported to be affected through the quality as well as quantity of platelets. Viniketel[25] stated that functional anomalies in platelets in diabetic patients which suggests an impact of diabetes ion the levels of platelets more like qualitative than quantitative. However, the present study strongly found an association of platelets with the diabetes in quantity as well.

CONCLUSION

Diabetes Mellitus is a disease in which effected individual needs to more care, management, treatment and proactive. Diabetes mellitus if remains uncontrolled it leads to serious complication which will be surely life threatening if these complications related to coagulopathies may lead to amputation. Statistical analysis of this study indicated that PT will low if diabetes is uncontrolled. Physician and patient must be aware for PT tests interpretation in diabetes. Early detection of lower PT may indicate that micro or macro vascular is in progress. APTT analysis shows the insignificant results in diabetic patients and did not find the special role in coagulopathies in diabetic patients.

REFERENCES

1. Ahmed AM. History of diabetes mellitus. Saudi Med J 2002; 23(4): 373-8.
2. Hess K. The vulnerable blood Coagulation and clot structure in diabetes mellitus. Hamostaseologie 2014; 35.
3. Karamanou M, et al. Milestones in the history of diabetes mellitus: The main contributors. World J Diabetes 2016; 7(1): 1-7.
4. Ford I, et al. Activation of coagulation in diabetes mellitus in relation to the presence of vascular complications. Diabetic Med 1991; 8: 322-9.
5. Ephraim RK, et al. High risk of coagulopathy among Type-2 Diabetes Mellitus clients at a municipal hospital in Ghana. Ghana Med J 2017; 51(3): 101-7.
6. Ndisang JF, Vannacci A, Rastogi S. Insulin resistance, type 1 and type 2 diabetes, and related complications 2017. J Diabetes Res2017; 2017: 1478294.
7. Lim HY, et al. Global coagulation assays in patients with diabetes mellitus. Res Practice Thrombosis Haemostasis 2021; 5.
8. Ambelu YA, et al. Prothrombin time, activated partial thromboplastin time and platelet counts of type II diabetes mellitus: a comparative study. J Diabetes MetabDisord 2018; 17(2): 117-21.
9. Gentile N, Vaidyula V, Rao AK. Diabetes mellitus and hyperglycemia promote blood coagulation after acute ischemic stroke.AcadEmerg Med 2007; 14.
10. Nogami K, et al.Risk of disseminated intravascular coagulation in patients with type 2 diabetes mellitus: Retrospective cohort study. BMJ Open 2017; 7: e013894.
11. Agarwal C, et al. Association of coagulation profile with microvascular complications and glycemic control in type 2 diabetes mellitus – a study at a tertiary care center in Delhi.Hematol Transfusion Cell Therapy 2018; 41.
12. Abdulrahaman, Y. and M. Dallatu, Evaluation of Prothrombin Time and Activated Partial Thromboplastin in Patients with Diabetes Mellitus. Nigerian Journal of Basic and Applied Science., 2012. 20: p. 60-63.
13. Dayer, M.R., et al., Causality relationships between coagulation factors in type 2 diabetes mellitus: path analysis approach. Med J Islam Repub Iran, 2014. 28: p. 59.
14. Thukral, S., et al., Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) in Type 2 Diabetes Mellitus, a Case Control Study. 2018.
15. Waheed, U. and M. Saboor, Coagulation abnormalities in diabetes mellitus. Journal of Public Health and Biological Sciences, 2013. 2
16. Lippi G, et al. Epidemiological association between fasting plasma glucose and shortened APTT.ClinBiochem2009;42(1–2):118–20.
17. Madan R, et al. Coagulation profile in diabetes and its association with diabetic microvascular complications.J Assoc Physicians India 2010;58:481–4.
18. Zhao Y, Zhang J, Wu J. Diabetes mellitus is associated with shortened activated partial thromboplastin time and increased fibrinogen values. PLoS One. 6(1):e16470.
19. Sun G, et al. Altered calcium homeostasis is correlated with abnormalities of fasting serum glucose, insulin resistance, and beta-cell function in the Newfoundland population.Diabetes2005;54(11):3336–9.
20. Yamaguchi T, et al. Serum calcium is positively correlated with fasting plasma glucose and insulin resistance, independent of parathyroid hormone, in male patients with type 2 diabetes mellitus.Metabolism2011;60(9):1334–9.
21. Sorva A, Tilvis RS. Low serum ionized to total calcium ratio: association with geriatric diabetes mellitus and with other cardiovascular risk factors?Gerontology1990;36(4):212–6.
22. Levy J, et al. Effects of food restriction and insulin treatment on (Ca2+ + Mg2+)-ATPase response to insulin in kidney basolateral membranes of noninsulin-dependent diabetic rats.Metabolism1990;39(1):25–33.
23. Vinik AI, et al. Platelet dysfunction in type 2 diabetes. Diabetes Care 2001;24(8):1476–85.
24. Walti MK, et al. Measurement of magnesium absorption and retention in type 2 diabetic patients with the use of stable isotopes. Am J Clin Nutr 2003;78(3):448–53.
25. Nadler JL, et al. Intracellular free magnesium deficiency plays a key role in increased platelet reactivity in type II diabetes mellitus.Diabetes Care1992;15(7):835–41.
26. Ferreira-Junior M, et al. Rational use of blood calcium determinations. Sao Paulo Med J 2014;132(4):243–8.