Original Article

Co-relation of coagulation profile with glycemic index in patients with type 2 diabetes

Sushil Kumar[1], Soma Dey[1], Abhilasha Bankul[2], Bandana Kumari[1], Bankim Das[3], Goutham Giri[1]

[1]Department of Biochemistry, AIIMS, Patna, Bihar, India, [2]Department of Biochemistry, NMCH, Patna, Bihar, India, [3]Department of Transfusion Medicine, AIIMS, Patna, Bihar, India

Abstract

Background: Diabetes mellitus (DM) has emerged as a significant global concern that accounts for nearly 90% of type 2 DM cases worldwide and characterized by insulin resistance. Hyperglycemia in diabetes leads to increased fibrinogen levels and activates the coagulation cascade, thereby triggering atherothrombotic events. **Aim and Objective:** The study was designed to evaluate the coagulation profile (activated partial thromboplastin time, prothrombin time, and INR) in type 2 diabetes and to analyze the correlation between glycated hemoglobin (A1C) and coagulation profile among the OPD patients coming to AIIMS Patna. **Methods:** A total of 234 patients were included in the study who were divided into 3 categories based on their glycemic status. 85 were non-diabetic, 65 were pre-diabetic, and 84 were diabetic. The demographic profile and clinical details were recorded. Fasting blood glucose, glycated hemoglobin, coagulation parameters such as prothrombin time, INR, and activated partial thromboplastin time along with other biochemical parameters were investigated. **Results:** There was a statistically significant association found between the coagulation profile and the two groups (Diabetics and Non-diabetics). The present study also found significant correlations between age and the diabetic group as compared to the non-diabetic group. A strong statistical significance was found between the gender and coagulation profile PT/INR. A statistically significant difference was found in the pre-diabetic and diabetic groups for coagulation parameters such as the activated partial thromboplastin time and prothrombin time (APTT and PT). **Conclusion:** Clinical tests for prothrombin time, INR, and activated partial thromboplastin time are relatively inexpensive and readily available. The present study shows that a significant association was found between prothrombin time and activated partial thromboplastin time with the glycemic status among the diabetic as compared to non-diabetic or pre-diabetics. These findings can be used as important hemostatic markers in diabetic patients, especially in those at high risk for thrombotic complications.

Keywords: Activated partial thromboplastin time, coagulation profile, diabetes, glycemic status, prothrombin time

Introduction

Diabetes mellitus (DM) stands as a significant global health challenge. Type 2 DM, distinguished by insulin resistance, constitutes roughly 90% of diabetes cases worldwide.[1] Diabetes increases the risk of atherosclerosis, with coronary artery disease emerging as a leading cause of mortality among diabetic patients.[2] It has been found that patients with diabetes mellitus have a high risk of atherothrombotic events. In 80% of diabetic patients, thrombosis is the primary cause of death. Among these cases, 75% are attributed to cardiovascular complications, with the remaining 25% attributed to cerebrovascular events and peripheral vascular complications.[3] It is acknowledged that the vascular endothelium plays a pivotal role in regulating local hemostatic processes. The key defense mechanisms against unwarranted coagulation reside at the surface of endothelial cells. Notably, the endothelium generates both procoagulant

Address for correspondence: Dr. Soma Dey, Department of Biochemistry, AIIMS, Patna, Bihar, India.
E-mail: somadey1983@gmail.com

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factors like von Willebrand factor (vWF) and anticoagulant factors such as heparan sulfate and thrombomodulin. In type 2 diabetes, endothelial dysfunction is a documented occurrence.[4] Coagulation abnormalities, characterized by reduced levels of antithrombin III, protein C, and protein S, have been documented in individuals with diabetes mellitus, alongside elevated levels of clotting factors. Furthermore, there is an increase in plasminogen activator inhibitor type 1, which hampers fibrinolysis, thereby contributing to a hypercoagulable state in diabetes mellitus.[5]

Prothrombin time (PT) and activated partial thromboplastin time (PTT) are standard screening tests that evaluate the overall function of the extrinsic (PT) or intrinsic (PTT) clotting pathways. Measurement of prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT) is routinely carried out in patients with suspected coagulation abnormality. PT and APTT evaluate the extrinsic coagulation pathway, displaying particular sensitivity to deficiencies in factor VII (FVII) and intrinsic coagulation pathway, respectively.[6] The international normalized ratio (INR) was designed to provide a reliable and consistent measure of Vitamin K antagonist (VKA) anticoagulation. The INR aimed to standardize all PT reagents to a World Health Organization (WHO) reference thromboplastin preparation standard. This standardization ensures that a PT measured anywhere globally would yield an INR value comparable to what would be obtained using the WHO reference thromboplastin.[7] Consequently, INRs obtained from different laboratories worldwide would be directly comparable. The INR is calculated from the measured PT using the formula[8]:

$$INR = \{PT\ patient/PT\ mean\}^{ISI}$$

Where PT, patient = measured prothrombin time

PT, mean = geometric mean PT of the reference range

ISI = International Sensitivity Index, specific to each reagent-instrument combination

Recent research has indicated that shortened prothrombin time (PT) and activated partial thromboplastin times (APTTs) may signify procoagulant imbalances characterized by elevated coagulation factors. Consequently, APTT can serve as a means to evaluate the risk of thromboembolic complications in patients with diabetes mellitus.[9] There are many current meta-analyses which have demonstrated a robust correlation between various endocrine disease and an elevated prothrombotic state, whereby diabetes is correlated with elevated levels of tissue plasminogen activator, fibrinogen (FIB), plasminogen activator inhibitor type 1 (PAI-1), and activated partial thromboplastin time (aPTT).[10]

Previously, the American Diabetes Association (ADA) did not advocate for the use of HbA1c assays in diagnosing diabetes, primarily due to the lack of standardization in these assays. However, with significant advancements leading to highly standardized HbA1c assays, an international expert committee has endorsed their use in diabetes diagnosis, setting a threshold of 6.5%. Subsequently, the ADA has aligned with this recommendation.[11]

In the present study, we collected clinical data related to general coagulation function, as well as HbA1c levels from subjects visiting the hospital outpatient in the Department of Medicine. Participants were divided into three groups based on their HbA1c status. The groups based on HbA1c levels were delineated as follows: normal group (HbA1c < 5.6%); high-risk diabetic group (HbA1c 5.7% to 6.4%); and diabetic group (HbA1c, >6.5%). The purpose of the present study was to evaluate the correlation between glycated hemoglobin (A1C) and coagulation profile and to compare the coagulation profile across the glycemic status among the OPD patients coming to AIIMS Patna.

Materials and Methods

The study was designed as hospital-based cross-sectional study, conducted in tertiary care unit at AIIMS Patna between period of 6 months, from August 2022 to February 2023. Consecutive sampling technique was done. Patients were enrolled for the study those who were attending the medicine OPDs of AIIMS Patna within the abovementioned period. A total of 234 patients were included in the study. The inclusion criteria were all adult patients >18 years of age coming to medicine OPD. The exclusion criteria were patients on drugs altering coagulation profile, liver disease, with history of coagulation disorders, malignancy, coronary artery disease, and cerebrovascular accidents patients.

Glycated hemoglobin

Hemoglobin glycation is a non-enzymatic reaction between the intra-erythrocyte glucose and the N-terminal amino group of the hemoglobin ß chains. This reaction takes place during the entire life of the red blood cells. The rate of glycated hemoglobin formation is related to the glycemia insofar as the intra-erythrocyte glucose concentration does not depend on insulin but only on the glycemia. It accumulates in red blood cells during the 120 days of their life.[12]

Principle of the test

The CAPILLARYS Hb A1c kit is designed for separation and quantification of the HbA1c glycated fraction of hemoglobin in human blood, by capillary electrophoresis in alkaline buffer (pH 9.4) with the CAPILLARYS 2 FLEX-PIERCING instrument. Measurement of hemoglobin A1c is effective in monitoring long-term glycemic control in individuals with diabetes mellitus.[13]

Coagulation profile

The principle consists of measuring the variation in amplitude of a steel ball oscillation. At constant viscosity, constant pendular swings of the ball are obtained. A drop in amplitude

corresponds to an increase in the viscosity of the medium, i.e. to the coagulation phenomenon. An electromagnetic field is created alternatively on each side of the cuvette. Fields are created by two activating coils. Motion of the ball is controlled by two curved rail tracks at the bottom of the cuvette. Every 155 ms, the drive coils (left or right) are activated. Pulse width is 25 ms. Initial ball drive is stronger in order to mix the cuvette content (BOOST parameters). Measurement is performed by a transmitting coil and a receiving coil. The transmitting coil emits a high frequency signal. The signal measured in the receive coil is dependent of the ball position. Maximum signal is obtained when the ball is in the center of the cuvette. This generates a sinusoidal signal reflecting the oscillation of the ball. Clot is detected by signal measurement in every 5 ms for the current cycle (to calculate). Algorithm calculates the raw amplitude value for each cycle. Rolling average of the last four cycles is calculated. Average of all cycles is calculated as a reference. Measurement (chronometry) is stopped when: Rolling average of last 4 cycles = 50% Average of all cycles.[14]

This study was approved by the ethics committee of AIIMS Patna. Written informed consent was obtained from each of the participants at the time of enrolment.

Statistical analysis

Data was collected in MS Excel 2011. We used SPSS version 22 software for applying statistics and created various plots by MS Excel. The study included a total of six variables, out of which, five are continuous variables including Age, HbA1c, PT, APTT, INR, and one is categorical variable that is gender. For continuous variables, normality distribution was checked by various plots (Q-Q plot and histogram) and the Shapiro–Wilk test. Mean and standard deviation was presented for normal distribution and median and IQR for the rest. HbA1c was divided into three groups as their glycemic index, non-diabetic patients/control group (HbA1c < 5.6), pre-diabetic patients (HbA1c 5.7-6.4), and diabetic patients (HbA1c ≥ 6.5). For gender variable, we had two values; male and female. Kruskal–Wallis test was used to check for the significant difference between different glycemic index of the patients and their coagulation profiles. *P* value as < 0.05 was chosen as statistical significant.

Results

A total of 234 patients were included in the study. Among 234 patients, 85 were non-diabetic, 65 were pre-diabetic, and 84 were diabetic patients [Table 1]. The median age at presentation was 51 years (range = 20-88 years) with higher prevalence (135, 57.7%) of males. No statistical significant differences in the glycemic index between genders were found. The median value of PT is 14.1 seconds (range = 10.8-36.6), INR is 1.05 (range = 0.78-2.8), and APTT is 27.9 seconds (range = 20.3-68.2) [Table 2].

Association of age among HbA1c groups

The median and IQR of age presented in non-diabetic group are 48 years (40-62), and in diabetic group is 55 years (46-65). Kruskal–Wallis test was used to check if there is difference in age among different HbA1c groups (non-diabetic, pre-diabetic, and diabetic patients). The test showed the *P* value = **0.016***, telling us that the median of each group is significantly different from the others.

Association between age and PT/INR and APTT

Spearman's rank correlation test is used to check for this association. No statistically significant correlation was found between age and PT/INR and APTT.

Association between gender and PT/INR and APTT

Mann–Whitney U test was used to assess the association between PT/INR and gender. The test yielded a *P* value of **0.05* and 0.006*, respectively**, indicating significant result. The median of PT in males (14.6 sec) is higher than in females (13.8 sec) and the median of INR in males (1.09) is higher than in females (1.02). No statistically significant results were found between APTT and gender.

Association between HbA1c groups and PT/INR and APTT

The median and IQR of PT among non-diabetic group were 14.1 (12.9-16.4), pre-diabetic was 13.3 (12.4-15.7), and diabetic was 14.5 seconds (13.6-16.3). The median and IQR of APTT among non-diabetic group were 29 (26.4-30.7), pre-diabetic was 26.9 (25-28.8), and diabetic was 27.6 seconds (24.3-30.2). Kruskal–Wallis test to check if there is difference in PT/INR and APTT among different HbA1c groups (non-diabetic, pre-diabetic, and diabetic patients). A significant difference with respect to PT (*P* value = **0.017***) was found that a pair of pre-diabetic and diabetic group. However, no differences in INR between these specific groups were found. A statistically significant differences in APTT were also found between these specific groups (*P* value = **0.027***).

Discussion

Diabetes mellitus is the most diversified disorder affecting the cellular metabolism in varying ways mostly affecting the coagulation profile.[15] Elevated blood sugar levels in diabetes are associated with increased levels of fibrinogen, which can trigger the coagulation process, leading to higher production of thrombin and breakdown products of fibrinogen. This, in turn, may prompt the liver to produce more fibrinogen. Prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT) are commonly used tests to evaluate the functioning of the coagulation system, and they are also widely utilized to monitor the effectiveness of anticoagulant therapy.[16]

The purpose of this study was to investigate the coagulation abnormalities that lead to hypercoagulability in diabetes.

In the present study, significant differences in age and diabetics and non-diabetics were found which was similar to other

Table 1: Frequency table for glycemic index

Glycemic Index	Frequency (*n*=234)	Percentage (%)
Non-diabetic	85	36.32
Pre-diabetic	65	27.78
Diabetic	84	35.90

Table 2: Median values of coagulation profile among glycemic index of the patients

	Non-diabetic (85)	Pre-diabetic (65)	Diabetic (84)	*P*
PT	14.1 (12.9-16.4)	13.3 (12.4-15.7)	14.5 (13.6-16.3)	0.017*
APTT	29.0 (26.4-30.7)	26.9 (25-28.8)	27.6 (24.3-30.2)	0.027*
INR	1.04 (0.96-1.23)	1.01 (0.92-1.19)	1.06 (0.99-1.18)	0.085

studies.[1,17] The median age presented in non-diabetic group is 48 years and in diabetic group is 55 years. No significant association between PT/INR and APTT and age was found.

In the present study, PT and APTT were significantly lower in type 2 DM patients; however, there was no significant difference in the INR values. The findings are similar to the study done before by Acang and Jalil.[18] However, there are studies where no significant difference was found in diabetic patients and coagulation profile (PT/INR and APTT).[17] There are studies where coagulation parameter PT and APTT are in normal range in the diabetics.[9]

It has been suggested that the natural anticoagulant, antithrombin III, plays a crucial role in inhibiting natural procoagulant activity. In addition factor, Va and VIIIa are inhibited by protein C. Elevated blood sugar levels result in the non-enzymatic glycation of antithrombin III, reducing its biological efficacy, and also directly diminishing the concentration of protein C. Consequently, the impaired functionality of natural anticoagulants leads to the activation of clotting factors, contributing to the development of hypercoagulability in type 2 diabetes mellitus.[19,20]

In this study, there was a significant difference in all of the coagulation parameters between diabetic patients with HbA1c ≤5.6 and those with HbA1c > 6.5 which is in accordance with the studies performed by other researcher.[16,21]

The study has been conducted in a tertiary care center; however, it can be useful for the physicians practicing in primary health care to treat diabetic patients and take necessary preventive steps to avoid abnormal coagulopathy.

Conclusion

Based on the findings of this study, it can be inferred that individuals with diabetes mellitus are at an increased risk of experiencing a hypercoagulable state. Consequently, regular assessments of prothrombin time (PT) and activated partial thromboplastin time (APTT) are crucial for evaluating coagulation abnormalities in diabetes mellitus, aiming to decrease the risk of thromboembolic cardiovascular disease in diabetic patients.

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Conflicts of interest

There are no conflicts of interest.

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