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Effect of Antidiabetic Drugs on Blood Coagulation in Diabetic Patients

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Diabetes mellitus (DM) is a common endocrine disorder. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are basic haematological indices to screen the coagulation status. Due to persistent hyperglycemia, glycation of proteins involved in clotting mechanism takes place which reduces their availability, thus affecting the clotting capacity. An analytical observational study was conducted on 180 subjects by measuring their PT and aPTT, to observe the effect of antidiabetic drugs on blood coagulation and to compare these indices between treated and untreated diabetics. A significant elevation of PT and aPTT in untreated diabetics when compared to controls was seen (PT ($p<0.001$); aPTT ($p<0.05$)). The effect of antidiabetic drugs showed normal mean values of PT and aPTT in treated group ($p>0.05$). The study revealed that significant elevation of PT and aPTT in untreated DM than non diabetic controls may be interpreted as tendency to bleed while effect of anti diabetic drugs shows normal mean values of PT and aPTT in treated group. This suggests that antidiabetic drugs either in combination or monotherapy may normalize PT and aPTT by reducing glycation of hemoglobin. Therefore, routine examinations of PT and aPTT are important to assess coagulation impairment in diabetes mellitus so as to prevent cardiovascular disease.

Keywords: Antidiabetic Drugs; blood coagulation; Diabetes; HbA1c; PT; aPTT.

Diabetes mellitus (DM) is a common endocrine disorder of multiple aetiology, classified as type 1 DM which is insulin dependent or type 2 DM which is non insulin dependent and can be treated with oral hypoglycaemic drugs like metformin, sulfonylureas[1].

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are basic haematological indices to screen the coagulation status of individuals. Among these PT is a laboratory screening test useful to detect disorders involving extrinsic and common pathways and aPTT is to screen abnormalities of the intrinsic and common clotting pathways and also useful in monitoring anticoagulant effect of circulating heparin[1] .Certain haematological indices are altered in patients with diabetes mellitus[1, 2]. In patient with diabetes mellitus, persistent hyperglycaemia exposes red blood cells (RBCs) to elevated glucose concentration, thus resulting in glycation of

haemoglobin, prothrombin, fibrinogen and other proteins involved in clotting mechanisms[3]. The glycation results in the incomplete activation and function of the clotting cascade[4]. This will decrease the availability of these proteins thereby affecting the clotting capacity[5].

Many studies have shown a variety of Diabetes Mellitus related abnormalities in thrombosis and haemostasis [6, 7]. These reports have shown that the diabetic condition contributes to high risk of atherothrombotic events associated with shortened activated partial thromboplastin time (aPTT) values[8, 9].

But so far the previous study reports have not observed the association of antidiabetic drugs with blood coagulation to the best of our knowledge. Hence the present study had been planned to study the effect of antidiabetic drugs on PT and aPTT levels in diabetics attending a tertiary care teaching Hospital.

MATERIALS AND METHODS

Present study is an analytical - hospital based study and conducted after the institutional ethics committee clearance (Dr. PSIMS & RF, Approval no:UG/25/2018) at a tertiary care teaching hospital. The total sample size included in the current study is n=180, in which healthy subjects were taken as control (n=60) and patients with diabetes (Newly diagnosed diabetic individuals were taken as test (n=60). The current study design was a cross sectional - oservational study hence the newly diagnosed untreated group will undergo respective treatment modules after collecting the sample.

Selection criteria was based on HbA1c (>6.5%) levels as per WHO guidelines and also considering antidiabetic drugs (OHAs/ Insulin). Subjects with age group 18 to 60 years of both the sexes, those who gave informed consent were included in the study. Study subjects were grouped majorly in to three groups with four subgroups in group C based on the class of antidiabetic drug that they were receiving in mono or in combination. Diabetic patients on warfarin or heparin or any other anticoagulation therapy such as aspirin or any other medication which might affect aPTT and PT and also subjects on vitamin k supplementation were excluded from the study.

Study groups

The study subjects were grouped into majorly three groups with four subgroups followed by inclusion and exclusion criteria of present study.

Group A- control (n=60), Group B- untreated (newly diagnosed) diabetics (n=60), Group C- treated diabetics exclusively on antidiabetic drugs (n=60)

Methodology

Venous blood sample (2-3ml) was collected in vacutainer and after collecting the samples they were kept immediately in centrifuge and analysed. Technique of turbidometry was used to analyze PT and aPTT. [10, 11] Reagents used were Thromborel S (SIEMENS) for PT and Pathromtin SL (SIEMENS) for aPTT, which work on the principal that incubation of plasma with the optimal quantity of phospholipids and a surface activator leads to activation of factors of the coagulation system. The addition of calcium ion triggers the coagulation process.[12, 13]. The data obtained was analysed by using ANOVA and Chi square test in Graph pad instat (version 3.1) mean, and 'p' values were calculated and the 'p' value less than 0.05 was considered to denote significant relationship.

RESULTS

On comparison of study results the mean range of prothrombin time (PT) (table 1) and activated partial thromboplastin time (aPTT) in various study groups, we found that for PT, there was a statistically significant difference between control and untreated group ($p<0.001$). The difference between treated and control was not significant ($p>0.05$). For aPTT, a significant difference is found between study groups ($p<0.05$) when compared individually as well as on multiple comparisons.

On seeing association of antidiabetic drugs on blood coagulation in diabetic patients (table 2), we found that no significant differences were seen for PT in subgroups (C1, C2, C3, C4) of treated study group (group C) while for aPTT it reflected increased mean values on comparison of C1 group which included subjects only on insulin with C3 group of subjects on oral hypoglycaemic combination ($p<0.05$). On multiple comparisons

Table 1. Comparison Of Basic Haematological Indices Of Blood Coagulation In Study Groups

S. No	Study Group	Study Subject	PT(in sec)	aPTT(in sec)
1	A(n=60)	Treated	13.351±1.811	31.85±5.458
2	B(n=60)	Untreated	14.795±2.975	32.65±5.916
3	C(n=60)	Control	12.803±1.102	30.181±2.771
		P Value	p=0.0001	p=0.0212

Showing significant difference in PT ($p<0.05$) as well as in aPTT ($p<0.05$) between selected study groups.

Table 2. Association of Anti-Diabetic Drugs with Hematological Indices

S. No	Group	No Of Study Subjects	Drug Used	PT (Mean±SD)	aPTT (Mean±SD)
1	C1	N=15	Insulin Monotherapy	13.92±1.203	33.306±6.488
2	C2	N=15	Insulin+Oral Hypoglycaemics	13.86±1.819	33.913±5.488
3	C3	N=15	Oral Hypoglycaemics Monotherapy	12.95±2.163	31.863±4.607
4	C4	N=15	Oral Hypoglycaemics Combination	12.63±1.755	28.993±4.005

Showing not a significant difference in PT ($p=0.215$) and for aPTT with ($p=0.052$)

there was no significant difference between all the four subgroups.

DISCUSSION

Previous reports suggests that complication of diabetes mellitus (DM) includes coagulation impairment which leads to hypercoagulable state in patient with DM that may accelerate thromboembolic risk for cardiovascular disease (CVD). Those[1, 11, 12,13,14,15] previous available literature showed the association of either diabetes or antidiabetic drugs with changes in haematological indices.

In the present study the low levels of PT & aPTT in treated diabetics and non diabetics than untreated diabetes group (significantly higher mean level of these parameters) may be interpreted as a tendency to bleeding and cardiovascular disorders in diabetics. This shows that insulin and oral antidiabetic drugs, either in combination or as monotherapy may normalize PT &aPTT by maintaining glycated hemoglobin. Therefore, routine examinations of PT & aPTT are important to assess coagulation impairment in diabetes mellitus so as to prevent cardiovascular disease in diabetes.

SUMMARY AND CONCLUSSION

In present study elevated levels of PT & aPTT had been observed in untreated diabetics than treated diabetic patients and control group. Patients those who were already receiving insulin with oral antidiabetic drugs in combination therapy or as monotherapy showed normal range of PT and aPTT.

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Conflict of Interest

There is no conflict of Interest

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