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Correlation of glycated hemoglobin with coagulation profile and hematological parameters in type II diabetes mellitus

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Original Article

Abstract

BACKGROUND: Patients with diabetes mellitus (DM) have a high risk of atherothrombotic events, with 80% of patients with DM dying a thrombotic death and 75% of these deaths being due to cardiovascular complications. This study aims to evaluate glycated hemoglobin [hemoglobin A1c (HbA1c)] with other parameters [prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, and complete blood count (CBC) indices] and compare various hematological parameters between people with DM and people without complications.

METHODS: This cross-sectional study was conducted at Mahatma Gandhi Institute of Medical Sciences, Sevagram, Maharashtra, India, over period of 2016 to 2018 on those diagnosed as a case of type II DM (T2DM) with or without complication. Blood samples from all 108 cases were collected. Statistical analysis was performed by Student's unpaired t-test, Bonferroni multiple comparison test, one-way analysis of variance (ANOVA) test, and chi-square test.

RESULTS: In T2DM cases, mean PT was 12.25 ± 1.22 seconds and APTT in total T2DM cases was 30.12 ± 3.05 seconds ($P \leq 0.005$). Hemoglobin (Hb) and hematological parameters like mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were decreased significantly in DM cases compared to the control group, while red cell distribution width (RDW) and total white blood cell (WBC) counts were found to be significantly increased in DM group ($P = 0.021$, $t = 3.37$; $P = 0.001$, $t = 3.51$, respectively). The correlation of HbA1c with PT, APTT, international normalized ratio (INR), and fibrinogen was statistically significant ($P = 0.005$, $P = 0.0001$, $P = 0.005$, and $P = 0.0001$, respectively). The mean fibrinogen level was 422.22 ± 119.77 mg/dl and was statistically significant ($P = 0.0001$).

CONCLUSION: There was a shortening of PT and APTT, indicating a hypercoagulable state in T2DM. Glycemic control affects the PT, APTT, INR, and fibrinogen levels.

KEYWORDS: Glycosylated Hemoglobin; Coagulation; Diabetes Mellitus

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Introduction

Diabetes mellitus (DM) is a metabolic disorder that affects glucose, protein, and lipid metabolism. It is caused by insulin insufficiency (absolute or relative) and tissue sensitivity to its activities. Insulin deficiency and sensitivity to its activities cause diverse clinical phenotypes with varying degrees of disrupted metabolism, most easily tracked by the degree of hyperglycemia. Absolute insulin insufficiency (type 1 DM) is caused by the autoimmune destruction of insulin-secreting cells (type 1A DM) as well as other congenital (genetic abnormalities in the creation or function of the endocrine pancreas) and acquired (relapsing pancreatitis and

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pancreatectomy) disorders. In the total lack of insulin receptors, absolute insufficiency of insulin activity can also occur.

Genetic or acquired abnormalities cause relative insulin deficiency in insulin synthesis or secretion that is insufficient to overcome resistance to insulin action caused by fewer working insulin receptors, or resistance to insulin action caused by stress, medications, and most commonly, obesity (type 2 DM). Acute clinical signs include polyuria, increased thirst, dehydration, electrolyte abnormalities, weight loss, and metabolic decompensation, recognized as diabetic ketoacidosis and non-ketotic hyperosmolar coma in extreme cases. Macrovascular [coronary artery disease (CAD), cardiovascular disease (CVD), amputations] and microvascular (retinopathy, nephropathy, neuropathy) diseases are chronic consequences. The degree of metabolic control obtained has an inverse relationship with acute and chronic problems.[1] Globally at present, diabetes is one of the most common non-communicable diseases. In most high-income countries, it is the fourth or fifth leading cause of death, and there is evidence that it is an epidemic in many low- and middle-income countries.[2]

Patients with DM have a high risk of atherothrombotic events, with 80% of these patients dying a thrombotic death and 75% of these deaths being due to cardiovascular complications.[3] The basic mechanisms for elevated risk for thrombosis in type II DM (T2DM) are complicated and involve multiple pathways. Patients with diabetes have premature atherosclerosis and more extensive vascular disease, leading to plaque rupture and thrombus formation.[4] Furthermore, these patients have a higher thrombotic potential due to platelet hyperreactivity and enhanced activation of prothrombotic coagulation factors combined with reduced fibrinolysis.[5] Many studies have shown that diabetes is a hypercoagulable state.[3,6,7] DM worsens various biological processes like coagulation and the fibrinolytic system; the present study was planned to assess and compare the coagulation tests in patients with T2DM and healthy individuals.

Agarwal et al. studied 60 (30 without complication and 30 with microvascular complication) cases with T2DMversus 30 controls. Prothrombin time (PT) and activated partial thromboplastin time (APTT) in DM cases without complication and patients with complications were 10.8 seconds and 10.5 seconds, 27.5 seconds and 24.1 seconds, respectively. They were significantly reduced, and fibrinogen was found to increase significantly compared to the control.[8]

Ambelu et al. studied 40 treated and 40 untreated patients with T2DM with 40 control subjects. Mean APTT in untreated DM, treated DM and nondiabetic cases was 25.42 ± 8.46 seconds, 34.4 ± 5.3 s and 32.8 ± 4.12 s respectively, showing significant shortening of APTT in DM cases. At the same time, PT is also reduced significantly in untreated (13.54 ± 3.44 seconds) cases. They hypothesized that shortened APTT could be considered a risk marker for venous thromboembolism (VTE), and concluded that APTT was a better predictor of a hypercoagulable state than PT in patients with T2DM.[9]

Ephraim et al. studied 60 T2DM cases and 40 control subjects. PT and APTT were significantly reduced in DM cases compared to control (11.03 ± 2.06 vs. 14.46 ± 1.86, P = 0.0001 and 20.88 ± 5.19 vs. 31.23 ± 5.41, P = 0.0001, respectively). No significant difference was found in platelet count between controls and DM cases (168.55 ± 35.77 × 10^3/mm^3 vs. 179.85 ± 66.15 × 10^3/mm^3, P = 0.326).[10]

Pan et al. measured hematologic and coagulation parameters before treatment in 297 cases. In this study, PT in DM cases without complication was 11.40 ± 2.12 while in DM with complication was 12.20 ± 4.62 and APTT noted in DM cases without complication was 25.10 ± 3.70 while in cases with

complication was 24.70 ± 4.80. The study demonstrated reduced APTT and platelet counts in patients with T2DM without complications compared with controls.[11]

Bhutto et al. selected 119 patients in their study. They demonstrated that red cell distribution width (RDW) had a significant correlation with hemoglobin A1c (HbA1c). The correlation of HbA1c with RDW was statistically significant (P = 0.035), while other hematological parameters like hemoglobin (Hb), platelets, and mean corpuscular volume (MCV) showed no significant correlation.[12]

Buch et al. recruited 300 patients with T2DM and 200 as controls. The study suggested that mean platelet volume (MPV) was significantly increased in DM cases with complications than in DM cases without complications in the non-diabetic group (P < 0.0001). Platelet count was significantly decreased in DM cases (P = 0.005).[13] In patients with DM, metabolic disorders disturb these physiological mechanisms, leading to a prothrombotic state characterized by platelet hypersensitivity, coagulation factor disorders, and hypofibrinolysis. Studies on altered coagulation in DM suggest that hyperglycemia, insulin resistance, and other comorbidities contribute to the hypercoagulable state.

Our study may fill the gap and explain the coagulation profile in DM. Besides, it arouses the usefulness and need of these tests in early diabetes to avoid the deadly complication. The current study focuses on evaluating glycated Hb and its correlation with PT, APTT, fibrinogen, and complete blood count (CBC) parameters in patients with T2DM to assess the impairment of the coagulation status in them.

Methods

This prospective observational cross-sectional study was conducted at a rural tertiary care institute from 2016 to 2018 at the Department of Pathology, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Wardha, Maharashtra, India. It is a rural tertiary care hospital in Central India. All people in the age group of 30-80 years who were diagnosed with T2DM with or without complications related to T2DM were included in this study. Patients with type I DM, those with hypertension (HTN), smokers, and pregnant women were excluded from the study. A total of 108 cases were included in this study, of which 39 patients were without complications, and 69 cases had different microvascular complications. 100 age- and sex-matched participants from a community with negative history of diabetes and fulfilling the exclusion criteria of patients were included in the control group. Inclusion criteria included all patients with T2DM between 30 to 80 years old with or without complication. Cases of pregnancy, type I DM, patients with HTN and/or smoking, and patients from whom informed consent could not be obtained were excluded from the study.

Sample collection methods and instruments: Venous blood samples of all the participants (patients and controls) were collected in ethylenediaminetetraacetic acid (EDTA) and citrate bulb and were subjected to Hb, red blood cell (RBC) indices, platelet count, fibrinogen level, HbA1c, PT, and APTT. HbA1c assay was done by particle-enhanced immunoturbidimetric methodology.

The PT and APTT were determined within 2 hours using the Behnk electronic coagulometer (Model no. 3424). All the blood samples were analyzed on the same day to avoid systemic variability at the same laboratory of our tertiary care teaching hospital.

Ethical considerations: The Institutional Ethics Committee of Mahatma Gandhi Institute of Medical Sciences approved this study (MGIMS/IEC/PATH/82/2014, 14/11/2014). Informed consent was also taken from every patient in their language regarding their willingness to participate in the study.

Statistical analysis: The data thus obtained were tabulated, and statistical analysis was performed by the Student's unpaired t-test, Bonferroni multiple comparison test, one-way analysis of variance (ANOVA) test, and chi-square test. Statistical significance was considered at $P < 0.05$, and thus the data would be analyzed statistically. All statistical analysis was done using SPSS software (version 27, IBM Corporation, Armonk, NY, USA).

Results

Among the 108 patients studied, 64 (59.3%) were men, and 44 (40.7%) were women, whereas in 100 cases of the control group studied, 55 (55%) were men, and 45 (45%) were women. The majority of the patients were in the age group of 51-60 years (30.56%,) followed by 61-70 years (29.63%) and 41-50 years (26.85%). The youngest was 35 years old, and the oldest was 80 years old. Of 108 patients, 39 cases were T2DM without complication, and 6 cases were with different DM complications. The mean age of patients with uncomplicated T2DM was 53.58 ± 11.10 years; for patients with complicated DM, it was 57.85 ± 11.33 years, and for the control group, mean age was 54.33 ± 12.13 years. Maximum patients of T2DM with complications were found in the age group of 61-70 years (33.33%) followed by 51-60 years (30.43%).

Analysis of clinical data and biochemical parameters using the t-test showed a significant correlation between age, duration of diabetes with HbA1c, and fibrinogen levels in patients with T2DM with and without complications. All T2DM cases had a mean PT of 12.25 ± 1.22 seconds, whereas controls had a mean PT of 13.20 ± 0.81 seconds. In all T2DM cases, the mean APTT was 30.12 ± 3.05 seconds, whereas the mean APTT in controls was 31.39 ± 1.42 seconds. PT and APTT were found to be decreased in cases compared to that in control, and it was found to be statistically significant. The mean platelet count was found to be reduced in total DM cases. Statistically significant difference was not found in the MPV between the total diabetic group and the control group.

Both PT and APTT was found to be decreased in cases as compared to control. Using the Student's unpaired t-test, a statistically significant and insignificant difference was found in PT and APTT, respectively, as shown in table 1. By using the Pearson coefficient test, a negative correlation was found between the duration of DM in years and mean PT. It was found to be statistically significant ($r = -0.390$, $P = 0.001$), whereas it was not found to be statistically significant between the duration of DM in years and mean APTT shown in table 2 ($r = -0.141$, $P = 0.40$). Mean HbA1c in total T2DM cases was found to be 8.02 ± 1.88 mg/dl with a range of 5.50-14.50.

Discussion

The main purpose of this study was to evaluate glycated Hb correlation with PT, APTT, fibrinogen, and CBC parameters to assess the impairment of the coagulation cascade.

Patients with T2DM are at increased risk for the development of bleeding disorders and thrombosis. PT and APTT are tests that give an insight into the coagulation status of patients. Approximately 80% of patients die due to cardiovascular complications, and the incidence due to thrombosis is 2-4 folds greater than the general population.[14]

All T2DM cases had a mean PT of 12.25 ± 1.22 seconds, whereas controls had a mean PT of 13.20 ± 0.81 seconds.

PT was found to be decreased in total cases compared to that in control, and it was found to be statistically significant. Among the subgroup of patients, no statistically significant difference was found between uncomplicated DM cases versus the complicated DM groups (Table 3). These findings are concurrent with a few other studies.[15,16]

Table 1. Comparison of the mean value of parameters in different study groups and control group

Group	Uncomplicated type II DM (n = 69)	Complicated type II DM (n = 39)	Type II DM (n = 108)	Control (n = 100)	Uncomplicated vs. complicated type II DM	Type II DM vs. control
PT	12.48 ± 1.04	12.12 ± 1.31	12.25 ± 1.22	13.20 ± 0.81	t = 1.48, P = 0.1400	t = 6.51, P = 0.0001*
APTT	31.99 ± 2.94	29.06 ± 2.59	30.12 ± 3.05	31.39 ± 1.42	t = 1.33, P = 0.0001*	t = 3.79, P = 0.0001*
INR	0.94 ± 0.11	0.93 ± 0.07	0.93 ± 0.10	1.01 ± 0.06	t = 0.51, P = 0.6100	t = 6.48, P = 0.0001*
Fibrinogen	372.30 ± 123.78	450.43 ± 108.51	422.22 ± 119.77	323.60 ± 73.16	P = 0.0001*	t = 7.09, P = 0.0001*
Platelets	244.76 ± 84.95	235.13 ± 93.61	238.61 ± 90.29	278.76 ± 88.20	t = 0.43, P > 0.9999	t = 3.24, P = 0.0010*
MPV	9.36 ± 1.50	9.66 ± 1.10	9.55 ± 1.36	9.43 ± 1.22	t = 0.56, P = 0.2770	t = 0.70, P = 0.4800
WBC	10.61 ± 4.10	9.76 ± 2.58	10.30 ± 3.64	8.57 ± 3.47	t = 1.16, P = 0.2400	t = 3.51, P = 0.0010*
Hb	11.65 ± 2.05	11.77 ± 2.00	11.70 ± 2.02	12.62 ± 1.77	t = 0.29, P = 0.7600	t = 3.48, P = 0.0010*
MCV	80.98 ± 8.69	81.14 ± 8.69	80.98 ± 8.69	85.20 ± 6.60	t = 0.09, P = 0.9200	t = 4.04, P = 0.0010*
MCH	26.90 ± 4.10	27.06 ± 2.94	26.96 ± 3.71	28.49 ± 2.72	t = 0.21, P = 0.8300	t = 3.37, P = 0.0010*
RDW	15.10 ± 2.05	15.25 ± 2.12	15.16 ± 2.06	14.22 ± 3.59	t = 0.37, P = 0.7100	t = 2.32, P = 0.0210*
BMI	26.86 ± 2.42	27.08 ± 2.11	26.94 ± 2.31	25.48 ± 2.11	t = 0.47, P = 0.6300	t = 4.75, P = 0.0001*

Data are presented as mean ± standard deviation (SD)

*Statistically significant

DM: Diabetes mellitus; PT = Prothrombin time; APTT: Activated partial thromboplastin time; INR: International normalized ratio; MPV: Mean platelet volume; WBC: White blood cells; Hb: Hemoglobin; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; RDW: Red cell distribution width; BMI: Body mass index

Table 2. Correlation of duration of disease with prothrombin time (PT) and activated partial thromboplastin time (APTT)

Duration (year)	N	Mean ± SD		SE		F-value		P		Correlation 'r'	
		PT	APTT	PT	APTT	PT	APTT	PT	APTT	PT	APTT
< 1	15	12.56 ± 1.12	30.37 ± 2.76	0.29	0.71	4.95	1	0.001*	0.400	-0.390	-0.141
1 to 5	39	12.77 ± 1.11	30.64 ± 2.99	0.17	0.47						
6 to 10	29	11.96 ± 1.27	29.44 ± 2.89	0.23	0.53						
11 to 15	15	11.76 ± 1.06	30.52 ± 4.14	0.27	1.07						
> 15	10	11.35 ± 1.03	29.10 ± 2.01	0.32	0.63						

Statistically significant

PT: Prothrombin time; APTT: Activated partial thromboplastin time; SD: Standard deviation; SE: Standard error

Table 3. Correlation of hemoglobin A1c (HbA1c) with different parameters

Parameters	Mean ± SD	Correlation 'r'	P
HbA1c	8.02 ± 1.88	-	-
Hb	11.70 ± 2.02	0.070	0.4600
MCV	81.04 ± 8.08	-0.063	0.5200
MCH	26.96 ± 3.71	-0.520	0.5900
MCHC	33.19 ± 1.97	-0.008	0.9600
RDW	15.16 ± 2.06	-0.086	0.3700
WBCs	10.30 ± 3.64	-0.070	0.4700
Platelet	238.60 ± 90.29	0.050	0.5800
MPV	9.55 ± 1.26	0.030	0.6900
PT	12.25 ± 1.22	-0.267	0.0050*
APTT	30.12 ± 3.05	-0.365	0.0001*
INR	0.93 ± 0.10	-0.268	0.0050*
Fibrinogen	422.22 ± 119.77	0.782	0.0001*

*Statistically significant

PT: Prothrombin time; APTT: Activated partial thromboplastin time; INR: International normalized ratio; MPV: Mean platelet volume; WBC: White blood cells; Hb: Hemoglobin; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; RDW: Red cell distribution width; MCHC: Mean corpuscular hemoglobin concentration; HbA1c: Hemoglobin A1c; SD: Standard deviation

Probable reasons for the decrease in PT levels in patients with DM are protein C, which inactivates factors Va and VIIIa. Hyperglycemia causes non-enzymatic glycation of antithrombin III, depresses its biological activity, and directly decreases the concentration of protein C. Hence, decreased function of natural anticoagulants initiates clotting factors and leads to the emergence of hypercoagulability in diabetes.

In all T2DM cases, the mean APTT was 30.12 ± 3.05 seconds, whereas the mean APTT in controls was 31.39 ± 1.42 seconds.

APTT was found to be shortened in cases compared to that in control and was found to be statistically significant. A statistically significant difference was found among the subgroup of subjects between uncomplicated DM cases versus complicated DM cases (Table 3). Shortening of APTT in patients with T2DM is a high risk for the hypercoagulable state as reported in other studies.[9,11,16-18] This may happen due to the glycation of intrinsic clotting factors caused by persistent hyperglycemia in patients with untreated DM. Persistent hyperglycemia may result in the glycation of intracellular and extracellular proteins, which will change the normal functioning of these proteins and affect their clotting capacity.[19] Thus, glycation of clotting factors may result in the activation of inactive intrinsic factors, resulting in the shortening of APTT.[20]

Mean HbA1c in total T2DM cases was found to be 8.02 ± 1.88 mg/dl with a range of 5.50-14.50.

In total cases of T2DM, mean fibrinogen level was 422.22 ± 119.77 mg/dl, whereas, in the control group, it was found to be 323.60 ± 73.16 mg/dl. Among the patients with 10 to 15 years duration, the mean fibrinogen level was found to be maximum compared with another group and it was 502.00 ± 142.68 mg/dl [P = 0.002, r = 0.295 (+ve correlation)].[21] The correlation of HbA1c with PT, APTT, international normalized ratio (INR), and fibrinogen turned out to be statistically significant (P = 0.005, P = 0.0001, P = 0.005, and P = 0.0001, respectively), while other parameters such as Hb and hematological parameters like MCV, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RDW, white blood cells (WBC), and platelets revealed no significant correlation (Table 3).

Hb and hematological parameters like MCV and MCH were decreased significantly in DM cases compared to the control group. In contrast, RDW and total WBC counts were found to be significantly increased in patients with DM (P = 0.021, t = 3.37 and P = 0.001, t = 3.51, respectively) (Table 1). RDW is one of the variables of RBCs and reported as a simple routine laboratory investigation of the CBC without any extra cost and is an index of heterogeneity in the size of circulating erythrocytes.[22] In patients with DM, a high RDW number is attributed to anisocytosis, caused by inadequate erythropoiesis or destruction. Hyperglycemia causes a decrease in RBC deformability, changes in mechanical properties, and several hemodynamic effects.[23]

Platelet count in patients with T2DM was 238.61 ± 90.29, while in control was 278.76 ± 88.20.

Platelet count was found to decrease with the severity of the disease, but this decrease in mean platelet count was statistically significant (Table 1). Similar results have been observed by Hekimsoy et al.[24] Because it directly affects platelets and promotes glycosylation of platelet proteins, hyperglycemia contributes to an increase in their reactivity.[24,25] As a result, an increase in MPV reflects large circulating platelets, and its elevation is considered an independent risk factor for thromboembolism, stroke, and acute myocardial infarction (MI). MPV in patients with T2DM was 9.55 ± 1.36 while in control, it was 9.43 ± 1.22.

MPV was found to be increased in the DM group, and it was not significant, which is similar to other studies.[24,25] As the duration of DM increased over the years, PT and APTT values were found to be decreased (Table 2). Because the levels of glycosylated proteins such as fibrinogen, anticoagulant proteins such as antithrombin III, protein C, and protein S increase with the duration of diabetes. As a result, glycosylation reduces biological activity. It decreases the quantity of protein C. Consequently, impaired natural anticoagulant function activates clotting factors, contributing to a reduction in PT and APTT as diabetes duration increases.[16] Contrary to the findings of the present study, many studies show an increase in mean PT with an increasing duration of DM.[26,27] The inflammatory process associated with atherosclerosis is known to involve leukocytes. They generate foam cells in the atheromatous plaque after being recruited at the site of endothelial damage. Endothelial dysfunction is caused by the production of interleukins and tumor necrosis factor-alpha (TNFα) by activated leukocytes. The number of WBCs in the blood is associated with a higher risk of cardiovascular mortality, primarily from coronary heart disease (CHD).[28]

Limitations: This is one of the rare studies in this area; data collection for this study is going on, and a limited number is taken due to the financial constraints of a small study. And it is suggested that more cases with complications should be included, and more emphasis needs to be given to them.

Conclusion

Diabetes is a hypercoagulable status; therefore, monitoring the PT and APTT hematological indices in patients with newly diagnosed DM is essential and gives an idea about the coagulation status of patients. It would also be helpful to incorporate coagulation screening as a routine investigation to better manage patients with DM. RDW is uprising as a new marker associated with higher mortality in health and disease. Glycemic control affects the PT, APTT, INR, and fibrinogen levels in individuals with DM.

Conflict of Interests

Authors have no conflict of interests.

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