

Detection of Hemostasis Abnormalities in Type 2 Diabetes Mellitus Using Thromboelastography

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Abstract

Introduction. Type 2 DM (T2DM) is associated with inflammation and vascular dysfunction which impact hemostasis. Thromboelastography (TEG) as a hemostasis assessment method, is not routinely applied in T2DM. We aimed to detect hemostasis abnormalities by using the TEG method in association with glycemic levels and type of therapy among T2DM patients.

Methodology. A cross-sectional study was conducted among T2DM patients attending the Endocrinology Clinic of Saiful Anwar Hospital, Indonesia. Glycemic profiles were determined using fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2hPPG), and glycosylated hemoglobin (HbA1c). Therapy for T2DM was classified into insulin and non-insulin regimens. The primary and secondary hemostasis profile were examined using TEG and was classified as hypo-hyper- and normo-coagulable states.

Result. A total of 57 T2DM patients were included. Kruskal-Wallis test did not reveal a significant association between glycemic profiles and groups of hemostasis. However, the median HbA1c was higher in the hypercoagulable group of primary hemostasis and fibrinolysis. The median FPG and 2hPPG were higher in the normo-coagulable group of secondary hemostasis. Logistic regression did not indicate a significant association between type of therapy for diabetes and hemostasis profile.

Conclusion. This study did not find significant associations between glycemic levels and type of DM therapy with hemostasis profiles using the TEG method in patients with T2DM.

Key words: diabetes mellitus, thromboelastography, hemostasis

INTRODUCTION

Type 2 DM (T2DM) is characterized by inflammation, vascular dysfunction, and thrombosis, all of which could impact hemostasis. The mechanisms leading to hemostasis dysfunction in T2DM include endothelial dysfunction, activation of coagulation factors and platelet hyperreactivity. These are hypothesized to be related to hyperglycemia and insulin resistance.^{1,2} The latter also increases fibrinolytic inhibitor, plasminogen activator inhibitor-1 (PAI-1) activity and levels of fibrinogen and coagulation factors.¹

The prothrombotic condition in T2DM can be classified as abnormalities in platelet and fibrinolytic activity, and coagulation factor levels. In vitro thrombin formation from platelet-rich plasma was found to be higher in patients with T2DM than in normal individuals. Furthermore, T2DM with poor metabolic control have significantly higher

thrombin levels than those who have good metabolic control.³ While complications of DM are determined by disease duration and the average level of chronic hyperglycemia,⁴ studies show that glycemic control was the only significant predictor for decreasing blood thrombogenicity in T2DM, irrespective of the type of therapy.^{5,6}

Thromboelastography (TEG) is one of the hemostasis assessment methods which was first developed in 1948.⁷ TEG is used for optimizing coagulation management because it can holistically identify the hemostasis process and results are faster than the standard coagulation tests namely, prothrombin time and activated partial thromboplastin time.⁸ TEG principally measures the viscoelasticity of blood during the hemostasis process.⁹ It provides an examination of the entire process of hemostasis from the initial fibrin formation, platelet aggregation, amplification and propagation of the coagulation process

to fibrinolysis.¹⁰ TEG presents a comprehensive insight into the entire cell-based coagulation process. On the other hand, standard coagulation tests only measure initial fibrin strand formation and does not always reflect minor hypercoagulable states.¹¹

With faster and more comprehensive results, TEG may be considered as a point-of-care test.¹² Clinical studies using TEG were mostly performed in the setting of acute conditions such as organ transplantations, perioperative setting of coronary artery bypass grafting, liver surgery and management of trauma, obstetric procedures and massive transfusion.^{10,13,14} It has also been studied as an early predictor of disseminated intravascular coagulopathy in patients with septic shock.¹⁵ However, TEG has not been routinely applied to patients with T2DM. Several studies of TEG in T2DM compared the diabetes group with a healthy control group and only a few studies analyzed the correlation between hemostasis and glycemic profile and the type of therapy for diabetes.^{7,12,16}

Therefore, the current study aimed to detect hemostasis abnormalities in association with glycemic levels and type of therapy among patients with T2DM by using TEG.

METHODOLOGY

In this cross-sectional study, we recruited all T2DM patients with ages between 40-80 years in the Endocrinology Out-patient Clinic of Saiful Anwar General Hospital Indonesia, from January until March 2021, using a consecutive sampling method. The sample size was calculated using the cross-sectional sample formula using G power software version 9 (G Power, Dusseldorf, Germany). A total of 54 patients was required as the minimum sample with 95% power based on the prevalence of T2DM at 6%¹⁷ and the prevalence of coagulation abnormality in these patients at 58%.¹⁸ The exclusion criteria were use of the antiplatelets, anti-thrombin, and anti-coagulants 10 days before sampling; acute infections; chronic kidney disease; acute and chronic liver failure; congenital hemostasis abnormalities; active malignancy; and pregnancy. All subjects were informed about the study and written consent was obtained. The study was approved by the Ethical Committee of the Medical Faculty, Universitas Brawijaya. Data regarding disease progression and therapy were obtained through history taking and review of medical records.

Glycemic control assessment

Glycemic profile was determined using fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2hPPG), and glycosylated hemoglobin (HbA1c). Plasma glucose examination was carried out with auto-analyzer Cobas c6000 using the hexokinase enzymatic method. HbA1c measurement was performed appropriately according to National Glycohemoglobin Standardization Program using HPLC (high-performance liquid chromatography) method (Biorad D10).

Hemostasis profile assessment

Assessment of hemostasis profile utilized whole blood sample in a citrated tube (about 4 mL for each procedure). A comprehensive analysis was performed by using Thromboelastography Analyzer 5000 (Haemonetics Corp, USA). TEG simulates venous blood flow using a rotational cup. About 360- μ L citrated whole blood sample is placed inside the cup and mixed with kaolin. A pin on a torsion wire is then put inside the blood which is connected to an electromagnetic transducer. The cup is rotated alternately (rotation angle 4°45', 10 seconds for each cycle). The rotation process will induce fibrin clot formation between cup and pin. A fibrin clot creates a torque on the pin and the torque force will be read by an electromagnetic transducer from the platelet aggregation and initial fibrin formation until maximum clot strength is reached. The reading curve will reach the maximum until it decreases as fibrinolysis begins.⁸ TEG examination was performed according to the manufacturer's instructions.

There were several thromboelastogram parameters analyzed in this study. The maximum amplitude (MA) represents primary hemostasis, the maximum strength of clot which is determined 80% by platelet level and function and 20% by fibrinogen activities. The normal range of MA is between 50-70% and a value below this is considered hypo-coagulable for primary hemostasis and vice versa. The second parameter, R-value, represents initial fibrin formation and correlates with enzymatic coagulation with a normal range between 5'-10'. The third parameter was the α -angle which depicts dynamic clot strengthening through amplification and propagation processes which are determined by the activities of thrombin that catalyze fibrin formation from fibrinogen. The normal range is between 53-72°. Both R-value and α -angle represent secondary hemostasis. R-value below the normal range and α -angle above the normal range reflect hypercoagulability for secondary hemostasis. Finally, LY30 reflects percentages of lysed thrombin in 30 minutes after MA which was determined by activities of fibrinolysis. The normal range is between 0-8% and a value below the normal range represents hypercoagulability for fibrinolysis and vice versa. All subjects were then classified into hypocoagulable, normocoagulable, and hypercoagulable for each of the hemostasis groups.

Statistical analysis

Data analysis was performed using Statistical Package for Social Sciences (IBM Corp, USA) version 26.0 software. The normality of continuous variables was measured using the Kolmogorov-Smirnov test, while the homogeneity of variances was determined using the Levene test. Continuous variables were presented in median and interquartile range (IQR) because of skewed distribution, whereas categorical variables were presented in numbers (%). Kruskal Wallis test was performed to compare the median HbA1c, FPG, and 2hPPG in each group of hemostasis profiles. The

association between the type of therapy and hemostasis categories were analyzed using logistic regression. Data results were presented as a descriptive table and odds ratio. A *p*-value <0.05 was considered significant.

RESULTS

A total of 80 patients were enrolled in this study, but due to the pandemic restrictions of movement, only 57 patients

were able to fulfill all study requirements. Table 1 shows the baseline characteristic of the study subjects. Most participants were female (63.2%; *n* = 36) and the median age was 55 (51–62.5) years. The median duration of T2DM was 3 (0.83 – 10) years with more patients receiving insulin therapy (59.6%).

All subjects were classified into hypocoagulable, normocoagulable, and hypercoagulable for each group of hemostasis (Table 1). Most subjects were normocoagulable for primary hemostasis (69.5%, *n*=41), secondary hemostasis (84.7%, *n*=50), and fibrinolysis (93.2%, *n*=55). The median value and IQR of laboratory parameters were presented in Table 1.

Primary Hemostasis

Overall, there were no significant differences between glycemic levels in each group of primary hemostasis as presented in Table 2. The median level of HbA1c was higher in the hypercoagulable group but the median levels of FPG and 2hPPG were higher in the hypocoagulable group.

Secondary Hemostasis

Analysis of secondary hemostasis only yielded hypocoagulable and normo-coagulable groups and there were no significant differences between the glycemic levels in these 2 groups. FBS and 2hPPG were higher in the normocoagulable group but HbA1c was higher in hypocoagulable group (Table 2).

Fibrinolysis

Analysis of fibrinolysis only yielded hypocoagulable and normocoagulable groups (Table 2). The median level of HbA1c was higher in normocoagulable groups but the median level of FPG and 2hPPG were higher in the hypocoagulable group. However, these differences were not statistically significant.

Therapy of DM

Logistic regression analysis showed no significant association between the type of therapy for T2DM and hemostasis profile (primary, secondary, and fibrinolysis) as shown in Table 3.

Table 1. Baseline Characteristics of Participants

Variables	N (%)
Sex	
Male	21 (36.8%)
Female	36 (63.2%)
Type of Therapy	
Insulin	34 (59.6%)
Non-Insulin	23 (40.4%)
History of CVD	
Yes	8 (14%)
No	49 (86%)
Hypertension	
Yes	29 (50.9%)
No	28 (49.1%)
History of PAD	
Yes	19 (33.3%)
No	38 (66.7%)
Hemostasis profiles	N (%)
Primary hemostasis	
Hypocoagulable	12 (20.3%)
Normocoagulable	41 (69.5%)
Hypercoagulable	4 (6.8%)
Secondary hemostasis	
Hypocoagulable	7 (11.9%)
Normocoagulable	50 (84.7%)
Fibrinolysis	
Hypocoagulable	2 (3.4%)
Normocoagulable	55 (93.2%)
	Median (IQR)
Age (years)	55 (51 – 62.5)
BMI	24 (22 – 28)
DM duration (years)	3 (0.83 – 10)
Laboratory Parameters	
Platelet count (/L)	302.000 (256.500 – 368.000)
PT (second)	10.3 (10.0 – 10.6)
aPTT (second)	26.8 (24.4 – 28.5)
INR	0.99 (0.96 – 1.02)
HbA1c (%)	8.40 (7.70 – 10.15)
FPG (mg/dL)	161 (116 – 197)
2hPPG (mg/dL)	204 (173.5 – 281)

Continuous data were presented as median (IQR); categorical data were presented as number (%); BMI: body mass index; PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: international normalized ratio; CVD: cardiovascular disease; PAD: peripheral artery disease.

Table 2. Median comparisons between glycemic parameters in each group of hemostasis profiles

Variables	Primary Hemostasis			<i>p</i>	Secondary Hemostasis		<i>p</i>	Fibrinolysis		<i>p</i>
	Hypo-coagulable	Normo-coagulable	Hyper-coagulable		Hypo-coagulable	Normo-coagulable		Hypo-coagulable	Normo-coagulable	
HbA1c	8.65 (7.28 – 11.25)	8.3 (7.70 – 9.55)	10.9 (7.90 – 13.48)	0.368	8.60 (7.80 – 9.10)	8.35 (7.58 – 10.33)	0.990	7.85 (5.60 – 7.85)	8.4 (7.70 – 10.2)	0.573
FPG	205 (128.8 – 268.3)	150 (116 – 180.5)	192 (126 – 206.3)	0.082	126 (102 – 166)	169 (118.3 – 200.3)	0.193	171.5 (101 – 171.5)	161 (116 – 196.0)	0.931
2hPPG	257.5 (183 – 381.5)	199 (163.5 – 252)	224 (155 – 281.8)	0.162	161 (99 – 207)	204.5 (180 – 288.5)	0.126	266 (245 – 266)	203 (171 – 275)	0.269

Continuous data were presented as median (IQR); *p* was significant if <0.05. HbA1c: hemoglobin A1c; FPG: fasting plasma glucose. 2hPPG: 2-hour postprandial plasma glucose.

Table 3. Analysis between type of therapy and hemostasis profile

Variables	Insulin	Non-Insulin	OR (95% CI)	p
Primary hemostasis				
Hypocoagulable	7 (12.3)	5 (8.8)	0.933 (0.256 – 3.402)	0.917
Normocoagulable	25 (43.9)	16 (28.0)	0.823 (0.255 – 2.652)	0.744
Hypercoagulable	2 (3.5)	2 (3.5)	1.524 (0.199 – 11.670)	0.685
Secondary hemostasis				
Hypocoagulable	5 (8.8)	2 (3.5)	0.552 (0.098 – 3.126)	0.502
Normocoagulable	29 (50.9)	21 (36.8)	1.810 (0.320 – 10.246)	0.502
Fibrinolysis				
Hypocoagulable	0 (0.0)	2 (3.5)	NA	0.999
Normocoagulable	34 (59.6)	21 (36.8)	NA	0.999

Categorical data were presented as number (%); p significant if <0.05.

To our knowledge, this is the first study to examine hemostasis disorders using TEG among T2DM from the outpatient clinic without any acute or critical disorders. Our study showed a non-significant difference in median and IQR of glycemic profiles among categories of primary hemostasis. HbA1c was higher in the hypercoagulable group than in the other two groups. This result is consistent with previous study which showed that poor glycemic control increased prothrombotic conditions.¹ Primary hemostasis implicates complex interaction between thrombocyte, vascular wall and adhesion protein to form a platelet plug.¹⁹ Hyperglycemia increases oxidative stress to endothelial dysfunction, formation of advanced glycosylation end products (AGEP). The latter inhibits nitric oxide expression and increases the expression of adhesion molecules, tissue factors, proinflammatory cytokines and monocyte chemoattractant protein-1.⁵ Insulin resistance leads to platelet over-activation due to the reduction of receptors and insulin sensitivity on the platelet surface. Hyperinsulinemia also induces the formation of tissue factors and thrombus generation.²⁰⁻²²

The current study revealed a higher median value of FPG and 2hPPG in the hypocoagulable group of primary hemostasis than in the other two groups. This is in contrast to other studies where prothrombotic conditions such as myocardial infarction, stroke, and venous thromboembolism in the setting of acute hyperglycemia were observed.³ Several studies have shown that acute hyperglycemia is characterized by increased formation of thrombin-antithrombin (TAT) complexes, soluble tissue factors, induced platelet hyperreactivity and acute oxidative stress.^{5,23-25} Hyperglycemia also disrupts the glycocalyx of the vascular endothelial layer which eventually increases adhesion between platelet and endothelial cells.²⁶

In a study by Lam et al.,²⁷ the specificity of TEG for platelet abnormalities was low. Thus, the TEG result had to be confirmed by other platelet function tests. Assessment of primary hemostasis abnormalities due to poor glycemic control cannot simply be concluded by the MA as a parameter of primary hemostasis in TEG. A study by Maatman et al.,²⁰ did not reveal any significant difference in MA value between patients with and without diabetes. Higher glycemic levels in the hypocoagulable group might

also be related to the paradoxical effect of insulin therapy, especially in patients with long duration of T2DM.²⁸ Insulin therapy potentially increases platelet reactivity in the condition of insulin resistance.²⁹ Hence, patients with long-standing T2DM on insulin therapy often show a hypercoagulable state even with lower glycemic levels.

Our study also observed a statistically non-significant difference in the median value of glycemic profile among groups of secondary hemostasis. Previous studies showed that glycemic control was a significant predictor for improvement in blood thrombogenicity.⁵ Poor glycemic control is associated with increased activation of tissue factor and coagulation factors.^{3,24} These factors such as fibrinogen, FVII, FVIII, FXI, FXII, kallikrein, and von Willebrand are increased in patients with diabetes compared to healthy individuals.⁷ Hyperglycemia also leads to protein glycation which eventually causes dysfunction of proteins in the coagulation cascade.³⁰

Our analysis indicated contradictory results between HbA1c and FPG and 2hPPG in secondary hemostasis. HbA1c was higher in the hypocoagulable group, whereas FPG and 2hPPG were higher in the normocoagulable group. Chronic hyperglycemia as evidenced by high HbA1c is related to hypocoagulability of secondary hemostasis. On the other hand, acute hyperglycemia as manifested by high FPG or 2hPPG, is associated with hypercoagulability. Several studies showed that acute hyperglycemia could induce coagulation disorder and eventually lead to thrombosis.³¹⁻³³ A study by Xie et al.,³⁴ revealed a decrease in R-value among patients with gestational diabetes mellitus which was not observed in normal pregnancy. Wang et al.,¹⁶ also obtained a lower R-value in acute stress after surgery among patients with DM compared to non-DM. Hyperglycemic condition combined with hyperinsulinemia may activate the coagulation system by increasing the activation of TF, FVII, FVIII, and platelet.³⁵ Furthermore, acute hyperglycemia may decrease the protective effect of endothelial glycocalyx which results in faster clot formation.³⁶ Several studies correlated acute hyperglycemia with thrombotic events such as myocardial infarction, stroke and venous thromboembolism.^{3,26} These conditions, in addition to acute hyperglycemia, are risk factors for secondary hemostasis hypercoagulability in TEG.

Chronic hyperglycemia may increase fibrinogen and other coagulation factors such as FVII, FVIII, FIX, FXII, and vWF.^{7,25} Higher coagulation factors may render stronger, denser and structurally different clot in patients with chronic hyperglycemia compared to healthy control requiring a longer time for fibrinolysis.³⁵ However, our study showed higher HbA1c in the hypocoagulable group.

Our study showed higher HbA1c in the normocoagulable group of fibrinolysis. By considering that fibrinolysis only yielded hypo and normo-coagulable groups, this result is consistent with several previous studies which revealed that uncontrolled DM leads to a hypercoagulable condition due to the increase in the levels of fibrinogen, t-PA, PAI-1, and D-dimer.³⁷ In vitro study using endothelial cells also pointed to an increase in PAI-1 secretion in the setting of high glucose levels.³⁸ Bryk et al.,³⁹ showed that intensive glycemic control would improve the fibrinolysis system as measured by PAI-1. Other studies about fibrinolysis compared T2DM patients with healthy control and found that those who have diabetes tended to have hypofibrinolytic conditions.^{3,40}

The hypocoagulable group of fibrinolysis, in this study, had a higher FPG and 2hPPG. Several previous studies, on the other hand, showed contradictory results regarding acute hyperglycemia and fibrinolysis. Acute hyperglycemia may inhibit fibrinolysis due to decrease in tissue plasminogen activator and increase in PAI-1 level.^{26,41} Hyperglycemia also disrupts fibrin clot lysis due to increase in beta-thromboglobulin.⁴ On the contrary, another study by Wang et al.,¹⁶ in DM patients undergoing CABG, showed no significant difference in LY30 between DM and non-DM patients.

Analysis between the therapy for DM and hemostasis profile also revealed a non-significant association in all three hemostasis groups (primary, secondary, and fibrinolysis). In this study, more than 50% of subjects were on insulin therapy. Insulin has prothrombotic activities and insulin resistance condition in T2DM may induce increase in PAI-1 and fibrinogen.⁴² In contrast, oral hypoglycemic agents such as metformin, sulfonylurea and thiazolidinediones could ameliorate coagulation dysfunction in diabetes by decreasing the level of FVII, PAI-1, fibrinogen concentration, and in vivo FXIII activity. Newer therapy such as gliptins and GLP-1 agonists exhibited in vitro anti-inflammatory activities by decreasing TNF- α and PAI-1.⁴³⁻⁴⁵ Nevertheless, overall glycemic control rather than type of therapy is the significant predictor for improvement in blood thrombogenicity.^{5,6}

Several factors may explain the contradicting results of our study with previous studies on TEG in T2DM. Our study subjects were different from previous studies since we included T2DM subjects without acute illness or critical comorbidities. Published data on TEG revealed the sensitivity and specificity of TEG in hemostasis

monitoring of acute conditions.^{11,16-19} Therefore, TEG might be less sensitive and less specific in detecting hemostasis abnormalities in subjects without acute critical comorbidities. Although several studies indicated significant associations between acute and chronic hyperglycemia with hemostasis abnormalities, those associations were not consistently found in all parameters of hemostasis and all subsets of T2DM patients.^{16,20,27,34}

The TEG method has several shortcomings. It is less specific in detecting platelet abnormalities.²⁷ Primary hemostasis is represented in TEG as MA value, where MA value is influenced by both platelet function and fibrinogen activities. TEG also does not measure several factors in hemostasis such as endothelial function, tissue factor and microparticles. Therefore, the TEG method may be less reliable in detecting hemostasis abnormalities in association with glycemic profile and type of therapy, especially in T2DM patients without any acute and critical comorbidities.

There were some limitations in the current study. Assessment of FPG and 2hPPG were only done once, thus, our study did not reflect glycemic variability. Our study also did not perform multivariate analysis to observe the association between the therapy for T2DM and glycemic profile towards hemostasis profile. Because of the pandemic restrictions, our study could only recruit the aforementioned sample size. A future study might be needed to confirm the results of the current study. The current study only included T2DM patients without any acute diseases, thus our study results might not be applicable to acute clinical settings.

CONCLUSION

This study did not find a significant association between glycemic levels and hemostasis profiles using the TEG method in patients with T2DM. Chronic hyperglycemia was poorly associated with hypercoagulability of primary hemostasis and fibrinolysis. Acute hyperglycemia was associated with hypercoagulability in secondary hemostasis, although the association was not significant. The type of DM therapy was also not significantly associated with the hemostasis profile. Further research is still needed to evaluate the role of TEG in analyzing the hemostasis profile of T2DM patients to stratify the risk and consider anticoagulation therapy. Further research might also require healthy control and T2DM patients with acute conditions to evaluate the effect of acute glycemic fluctuations on hemostasis profile using the TEG method.

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Statement of Authorship

All the authors certified fulfillment of ICMJE authorship criteria.

Author Contribution Statement

PMA, NKF, SF, AKW, ADN conceived the study; conducted the research; provided the study materials; prepared the original draft; reviewed and edited the manuscript and managed the research activity planning. PMA, NKF, SF designed the methodology; verified the research outputs and supervised the research activity. NKF, SF, AKW, ADN programmed the software. NKF, AKW, ADN synthesized and curated the study data and prepared the data presentation. PMA and NKF acquired financial support.

Author Disclosure

The authors declared no conflict of interest.

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