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# Assessment of Coagulopathy Risk in Type 2 Diabetes Mellitus: A Retrospective Cross-Sectional Study in Thumbay Hospital, UAE

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## Abstract

***Background*:** Type 2 diabetes mellitus(T2DM) is associated with coagulation abnormalities and a higher risk for blood clots due to changes in the clotting factors and platelet function. This study aimed to assess blood clotting parameters in T2DM patients within a single research center in the UAE.

***Methods and Results*:** This retrospective, cross-sectional study was conducted on 158 patients (112 men and 46 women) diagnosed with T2DM in Thumbay Hospital, Ajman, UAE. Blood samples were properly labeled and used for screening tests. The HbA1c and platelet tests were performed using the Beckman Coulter DxC 700 and DxH 900 analyzers. Coagulation profile tests, including D-dimer, activated partial thromboplastin time (APTT), and prothrombin time (PT), were performed using an ACL TOP 300 CTS analyzer.

All patients were divided into two groups. Group 1 included 68 patients with controlled diabetes (cT2DM), and Group 2 included 90 patients with uncontrolled diabetes (uT2DM). The assessment of the blood clotting parameters showed a lower level of INR in the uT2DM group than in the cT2DM group (1.06±0.10 and 1.53±1.13, respectively, *P*=0.0001). Platelet count, PT, APTT, and D-dimer levels did not differ significantly between the two groups. Men had a higher HbA1c than women (7.30±2.07% and 6.52±2.02%, respectively, *P*=0.0318), indicating poor diabetes control. Higher HbA1c in men was accompanied with a higher D-dimer level (409.1±44.4 ng/mL for men and 388.7±42.1 ng/mL for women, P=0.0086) and a lower level of INR (1.09±0.10 and 1.73±1.13, respectively, *P*=0.0001). Platelet count, PT and APTT levels did not differ significantly between male and female patients. Evaluation of the studied parameters, considering age groups, showed increased HbA1c with age (*P*=0.0018), indicating an increase in poor diabetes control. This was accompanied by a significant increase in the D-dimer levels in the age group above 45 (*P*=0.0000).The levels of other indicators did not differ significantly depending on the age group.

***Conclusion***: Patients with T2DM have a cumulative thrombotic risk. The prothrombotic state in T2DM is primarily mediated by hyperglycemia and insulin resistance. Good glycemic control (HbA1c<7.0%) in T2DM has reduced the risk of developing thrombotic complications.**(International Journal of Biomedicine. 2024;14(4):563-568.)**

**Keywords**: type 2 diabetes mellitus • thrombotic risk • platelet count • diabetes control

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## Abbreviations

**APTT**, activated partial thromboplastin time; **CVD**, cardiovascular disease; **HbA1c**, glycated hemoglobin; **INR**, international normalized ratio; **PLT**, platelet count; **PT**, prothrombin time; **PGI**, prostaglandin; **T2DM**, type 2 diabetes mellitus; **cT2DM**, controlled T2DM; **uT2DM**, uncontrolled T2DM.

## Introduction

The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million people) by 2030 and 10.9% (700 million people) by 2045. Over 90% of diabetes mellitus cases are type 2 diabetes mellitus (T2DM). Type 2 diabetes mellitus is one of the most common chronic metabolic disorders, characterized by elevated blood glucose levels caused by defective insulin secretion by pancreatic β-cells, tissue insulin resistance, and an inadequate compensatory insulin secretory response.[1-6] Many studies have shown the role of insulin resistance in atherosclerosis, endothelial dysfunction, oxidative stress, imbalanced coagulation, hypertension, macrophage accumulation, and inflammation.[7-11]

Patients with T2DM have a 15% higher risk of all-cause mortality compared with individuals without diabetes, with cardiovascular disease being the leading cause of T2DM-related morbidity and mortality.[12-15] Uncontrolled diabetes puts subjects at risk for both ischemic and hemorrhagic strokes.[15-17]

Type 2 diabetes mellitus is associated with coagulation abnormalities and a higher risk for blood clots due to changes in the clotting factors and platelet function. These abnormalities are caused by persistent hyperglycemia, which is a prothrombotic factor.[18] Glycation, the non-enzymatic reaction between proteins and sugars, is a key factor in developing coagulation disorders and other diabetic complications. Coagulation abnormalities, including reduced levels of natural anticoagulants, like antithrombin III, protein S, and protein C, and increased clotting factors, contribute to hypercoagulability in T2DM patients.[19]

Evaluating coagulation markers, such as prothrombin time and activated partial prothrombin time, can identify abnormal coagulation in T2DM patients, indicating a higher risk of premature atherosclerosis and cardiovascular disease.

Hyperglycemia and insulin resistance cause changes in the platelet number and activation and qualitative and/or quantitative changes in coagulation and fibrinolytic factors, leading to the formation of thrombi resistant to fibrinolysis.[18] Among T2DM patients, the mean PLT and mean platelet volume are higher in diabetics with chronic hyperglycemia (HbA1c>8%) than in euglycemia.[20] Hyperglycemia reduces platelet membrane fluidity through the glycation of membrane proteins and leads to increased intracellular calcium influx, directly promoting platelet activation and aggregation.[21] Hyperglycemia causes endothelial dysfunction, thereby suppressing the synthesis and release of $PGI_2$ and NO, further promoting platelet aggregation.[22] In T2DM, hyperglycemia and insulin resistance exert synergistic effects on the extrinsic pathway of blood coagulation. This increases pro-coagulatory activity and FVIIa consumption, leading to thrombus generation.[23] In patients with impaired insulin sensitivity, the increased synthesis of FXII, FXI, and FIX in hepatocytes, the intrinsic coagulation pathway factors, and a shorter activated partial thromboplastin time (APTT) were detected.[24] Both hyperglycemia and hyperinsulinemia stimulate synthesis fibrinogen and prothrombin in the liver of T2DM patients, contributing to the pro-thrombotic state.[18,25] Increased glucose levels inhibit the activity of tissue plasminogen activator, leading to reduced levels of plasmin in the blood, which is responsible for fibrinolysis, and restrains excessive thrombus formation.[26]

Individuals of different ethnic origins may have different specific phenotypes that increase susceptibility to clusters of CVD risk factors, including hypertension, insulin resistance, and dyslipidemia.[27] Unfortunately, there is a deficiency of information about the coagulation profiles of T2DM patients in the UAE population. In the UAE, diabetes prevalence is at 25.1% among adults, and it has one of the highest rates globally at 16.3%.[28,29] UAE is considered one of the most prominent epicenters of the pertinent epidemic of T2DM among Middle Eastern nations.[30] The number of T2DM patients is rapidly increasing, emphasizing the importance of evaluating coagulation profiles to prevent complications. However, various factors hinder coagulation testing, making it crucial to improve screening procedures and raise awareness.[31] This study aimed to assess blood clotting parameters in T2DM patients within a single research center in the UAE.

## Materials and Methods

This retrospective, cross-sectional study was conducted on 158 patients (112 men and 46 women) diagnosed with T2DM in Thumbay Hospital, Ajman, UAE.

Inclusion criteria: T2DM, patients above 18 years, both male and female.

Exclusion criteria: taking anticoagulant medications, hemophilia, renal disease, and liver diseases.

Blood samples were properly labeled and used for screening tests. The samples were collected in purple and blue tubes for different tests. The HbA1c and platelet tests were performed using the Beckman Coulter DxC 700 and DxH 900 analyzers. Coagulation profile tests, including D-dimer, activated partial thromboplastin time (APTT), and prothrombin time (PT), were performed using an ACL TOP 300 CTS analyzer.

Statistical analysis was performed using the statistical software package SPSS version 21.0 (SPSS Inc, Armonk, NY: IBM Corp). Baseline characteristics were summarized as frequencies and percentages for categorical variables and mean±SD for continuous variables. For data with normal distribution, inter-group comparisons were performed using Student's t-test. Multiple comparisons were performed with one-way ANOVA and a post-hoc Tukey HSD test. A *P*-value of $<0.05$ was considered statistically significant.

## Ethical Considerations

The study protocol was reviewed and approved by the Ethics Committee of the Gulf Medical University, Ajman, United Arab Emirates**.** Written informed consent was obtained from all the participants.

## Results

All patients were divided into two groups. Group 1 included 68 patients with controlled diabetes (cT2DM), and Group 2 included 90 patients with uncontrolled diabetes (uT2DM).

Subsequently, all patients were divided into three age groups. In the age groups of 18-30 (n=14, 10 men and 4 women), 31-45 (n=48, 37 men and 11 women), and over 45 (n=96, 65 men and 31 women), cT2DM and uT2DM were identified in 13(92.9%) and 1(7.1%), 27(56.2%) and 21(43.8%), 28(29.2%), and 68(70.8%) cases, respectively. Thus, 90 (57.0%) patients had cT2DM and 68(43.0%) patients had uT2DM, with the incidence of uT2DM increasing with age ($P$=0.000).

The assessment of the blood clotting parameters showed a lower level of INR in the uT2DM group than in the cT2DM group (1.06±0.10 and 1.53±1.13, respectively, $P$=0.0001). PLT, PT, APTT, and D-dimer levels did not differ significantly between the two groups (Table 1).

Evaluating blood clotting parameters, considering the gender of T2DM patients (Table 2), showed that men had a higher HbA1c than women (7.30±2.07% and 6.52±2.02%, respectively, $P$=0.0318), indicating poor diabetes control. Higher HbA1c in men was accompanied with a higher D-dimer level (409.1±44.4 ng/mL for men and 388.7±42.1 ng/mL for women, $P$=0.0086) and a lower level of INR (1.09±0.10 and 1.73±1.13, respectively, $P$=0.0001). PLT, PT, and APTT levels did not differ significantly between male and female patients.

Evaluation of the studied parameters, considering age groups (Table 3), showed increased HbA1c with age ($P$=0.0018), indicating an increase in poor diabetes control. This was accompanied by a significant increase in the D-dimer levels in the age group above 45 ($P$=0.0000). The levels of other indicators did not differ significantly depending on the age group.

***Table 1.***

***Blood clotting parameters in the controlled and uncontrolled T2DM patients***

| Variable | uT2DM (n=90) | cT2DM (n=68) | $P$-value |
|---|---|---|---|
| HbA1c, % | 8.4 ± 1.87 | 4.7 ± 6.1 | <0.0001 |
| PLT, × $10^9$/L | 243.7 ± 95.2 | 226.7 ± 72.8 | 0.222 |
| PT, sec | 12.12 ± 1.19 | 12.69± 3.1 | 0.1123 |
| INR | 1.06 ± 0.10 | 1.53 ± 1.13 | 0.0001 |
| APTT, sec | 32.72 ± 4.49 | 33.2 ± 4.0 | 0.4869 |
| D-dimer, ng/mL | 403.5 ± 55.6 | 391.3 ± 79.1 | 0.2568 |

***Table 2.***

***Blood clotting parameters according to the gender of T2DM patients.***

| Variable | Male (n=112) | Female (n=46) | $P$-value |
|---|---|---|---|
| HbA1c, % | 7.30 ± 2.07 | 6.52 ± 2.02 | 0.0318 |
| PLT, × $10^9$/L | 228.4 ± 91.3 | 255.7 ± 85.7 | 0.0843 |
| PT, sec | 12.28 ± 1.12 | 12.57 ± 2.24 | 0.2807 |
| INR | 1.08 ± 0.10 | 1.73 ± 0.42 | <0.0001 |
| APTT, sec | 32.55 ± 4.79 | 33.04 ± 11.89 | 0.7117 |
| D-dimer, ng/mL | 409.1± 44.4 | 388.7 ± 42.1 | 0.0086 |

Correlations between the HbA1c, PLT, PT, and PTT are presented in Figure 1.

***Table 3.***

***Blood clotting parameters in the different age groups.***

| Age group | HbA1c, % | PLT, × $10^9$/L | PT, sec | APTT, sec | D-dimer, ng/mL |
|---|---|---|---|---|---|
| Young adults (n=14) [1] | 5.54 ± 0.46 | 194.3 ± 57.6 | 12.77± 1.47 | 32.27 ± 6.49 | 311.7 ± 22.5 |
| Middle-aged adults (n=48) [2] | 6.75 ± 2.15 | 237.4 ± 84.3 | 12.16 ± 0.95 | 32.1 ± 4.93 | 240.5 ± 13.7 |
| Old-aged adults (n=96) [3] | 7.47 ± 2.06 | 242.2 ± 96.3 | 12.41 ± 1.76 | 33.05± 8.71 | 489.8 ± 59.8 |
| ANOVA and a post-hoc Tukey HSD test | F=6.5954 $P$=0.0018<br>$P_{1-2}$=0.1189<br>$P_{1-3}$=0.0028<br>$P_{2-3}$=0.1081 | F=1.7303<br>$P$=0.1806 | F=0.9577<br>$P$=0.3860 | F=0.2754<br>$P$=0.7596 | F=459.1538 $P$=0.0000<br>$P_{1-2}$=0.0000<br>$P_{1-3}$=0.0000<br>$P_{2-3}$=0.0000 |

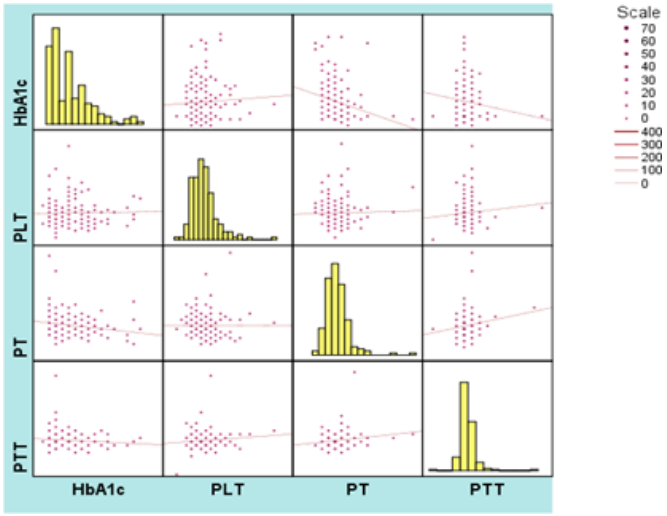


***Fig. 1.*** *The scatter matrix: positive and negative correlations between the HbA1c, PLT, PT, and PTT.*

## Discussion

Type 2 diabetes mellitus is associated with coagulation abnormalities and a higher risk for blood clots due to changes in the clotting factors and platelet function. Our study analyzed blood clotting parameters, such as D-dimer, activated partial thromboplastin time (APTT), platelet count, international normalized ratio (INR), and prothrombin time, in T2DM patients. HbA1c levels, a measure of glycemic control, were found to increase with age, accompanied by a significant increase in the D-dimer levels. This indicates a higher risk of coagulopathy in older individuals with T2DM. Higher D-dimer levels reflect more systemic fibrin formation and a tendency for increased thrombosis.[32] High D-dimer concentrations are associated with cardiovascular events and their prognosis.[33-36]

The prothrombotic state is a recognized component of metabolic syndrome, including T2DM. Previous studies have found shortened activated partial thromboplastin time and prothrombin time in diabetic patients compared to non-diabetic controls.

Lippi et al.[37] showed that diabetic patients had significantly shortened APTT values and suggested that activated partial thromboplastin time might identify diabetic patients at major risk of thrombosis.

In a study by Selleh et al.,[38] T2DM patients had significantly shorter APTT, PT, and INR than controls, but there was no statistically significant difference in APTT, prothrombin time, and international normalized ratio (INR) when T2DM patients were compared based on the quality of glycemic control.

Coagulation activation markers, such as prothrombin activation fragment 1+2 and thrombin-antithrombin complexes, are elevated in diabetes. Plasma levels of many coagulation factors, including fibrinogen, factor VII, factor VIII, factor XII, and von Willebrand factor, are also elevated, as are platelet aggregation and hyperactivity. Taken together, these findings suggest that diabetes is a hypercoagulable state.[19] Poor diabetes control increases the risk of thrombosis.

## Conclusion

Patients with T2DM have a cumulative thrombotic risk that includes platelet hyperreactivity, upregulation of prothrombotic markers, and decreased fibrinolytic potential. The prothrombotic state in T2DM is primarily mediated by hyperglycemia, insulin resistance, endothelial dysfunction, and an increased inflammatory state.[39-41] Evaluating coagulation markers can identify abnormal coagulation in T2DM patients, indicating a higher risk of premature atherosclerosis and cardiovascular disease. Good glycemic control (HbA1c<7.0%) in T2DM has reduced the risk of developing thrombotic complications.

## Competing Interests

The authors declare that they have no competing interests.

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