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The Influence of Insulin Levels on Coagulation Profiles in Patients with Type 2 Diabetes Mellitus in KSUMC

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ABSTRACT: Background: This study was conducted at the endocrinology and diabetes clinics at King Saud University Medical City (KSUMC), from March 2025 to May 2025. This study was performed to assess the Influence of Insulin Levels on Coagulation Profiles in Patients with Type 2 Diabetes Mellitus (T2DM) by Determining insulin levels in type 2 diabetes mellitus patients, including fasting insulin and its approximation using other insulin resistance modalities such as Homeostasis Model Assessment (HOMA-IR). In addition, analyzing the coagulation profile in T2DM patients and investigate the nature of connection between insulin levels and coagulation factor, assess the occurrence of probing risk associated with thrombotic events, compare coagulation profiles among controlled versus uncontrolled diabetic individuals to reach Clinical recommendations to minimize risks of thrombotic complications. The study used the observational, cross-sectional type and descriptive and Analytical. The study recruited patients from King Saud University Medical City's endocrinology and diabetes clinics. Participants included patients with varying degrees of type 2 diabetes control, ages, ethnicities, and disease severities. The goal was to achieve diversity and representation to study the correlation between insulin and coagulation levels. Methodology: The sample size is calculated using a power analysis to ensure sufficient statistical power to detect significant results. Inclusion criteria include a confirmed diagnosis of Type 2 Diabetes (eg. 126 mg/dL fasting glucose, HbA1c≥6.5%), age range of 18-75, and clinical setting. Exclusion criteria include Type 1 Diabetes, pregnancy, severe comorbidities, medications altering coagulation, and recent surgery or trauma. Key finding high light that insulin levels significantly affect coagulatory process in Type 2 Diabetic Mellitus patients, insulin resistance and hyperinsulinemia exert polyphasic effects on T2DM-associated prothrombotic state, regardless of glycemic control and confounding traditional risk factors, is supported. Results and conclusion: This study confirmed that Insulin resistance may have a mediating effect on several coagulation disorders. Insulin resistance is a significant risk factor for coagulation abnormalities, despite other factors like age, gender, BMI, diabetes duration, glycemic control, and comorbidities, suggesting a direct pathophysiological link. Disease that is poorly controlled worsens coagulation abnormalities; Insulin therapy may not normalize coagulation suggesting that exogenous insulin therapy may not rectify thIe prothrombotic state imposed by advanced T2DM.

Keywords: T2DM, IR, vWF, PAI-1, tPA, HOMA-IR

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1. Introduction

Diabetes Mellitus Type 2 is a complex progressive disorder of metabolism brought about by chronic hyperglycemia often caused primarily due to insulin resistance and relative deficiency of insulin. This particular endocrine disorder has in recent times afflicted an almost intolerable increasing number of people and continues to do so thanks mainly to drastic lifestyle changes, poor dietary habits, and an inactive lifestyle. According to the International Diabetes Federation, more than 400 million people are seen globally affected by T2DM, and these figures are projected to keep on increasing. The prevalence of diabetes is alarmingly high in Saudi Arabia; estimates suggest that probably almost all of one-fourth of the population suffers from T2DM.(Nawaz,2022)

Substantial but brakes, one of the most documented effects associated with T2DM is its effect on glucose metabolism. T2DM is a risk factor for many comorbidities, especially cardiovascular diseases, coronary artery disease, heart failure, and stroke, and creates a substantial burden of morbidity and mortality. T2DM stands as one of the major unexplored aspects regarding coagulopathy impact. It has been known that subjects with diabetes are at risk for thrombotic events such as deep vein thrombosis, pulmonary emboli, and ischemic strokes, all of which are related to the impairment in the clotting ability of blood. (Newbold,2020)

The pathophysiology of blood coagulation derangements associated with T2DM is multi-faceted. Insulin, besides regulating glucose levels, also governs numerous physiological processes such as inflammation, endothelial function, and platelet aggregation. Insulin resistance, a defining feature of T2DM, may cause increased circulating insulin concentrations (hyperinsulinemia), which has been linked to numerous thrombus-promoting alterations such as raised fibrinogen levels and modulation of platelet function and activation of clotting factors (Olgasi,2024)

While some studies have explored the relationship between insulin levels and coagulation parameters in diabetic patients, the exact nature of this relationship remains under-explored, especially in specific populations like those at King Saud University Medical City (KSUMC). The current research aims to bridge this gap by specifically focusing on the coagulation profiles of T2DM patients at KSUMC and investigating how insulin levels influence these profiles.

Type 2 Diabetes Mellitus (T2DM)- This is basically a metabolic disorder characterized by hyperglycemia and sometimes insulin resistance. The disease is majorly now a big world problem; with estimates, as of 2019, showing that nearly 463 million adults suffer from it; figures are suspected to rise to around 700 million by the year 2045 Apart from the known complications like cardiovascular disease, neuropathy, and nephropathy, this disease has a hypercoagulable state associated with the increased thrombotic events (Alguwaihes,2020).

In T2DM, hypercoagulability is due to several reasons such as endothelial dysfunction, platelet hyperactivity, and the imbalance in levels of coagulation factors and fibrinolytic proteins. Insulin resistance, the main feature of T2DM pathophysiology is thought to be the principal factor controlling this prothrombotic milieu. Insulin affects both directly and indirectly the coagulation by its activity on endothelial cells and platelets and also by hepatic synthesis of coagulation factors. (Li,2021) The specific mechanisms that relate insulin resistance to hypercoagulability are still not completely understood.

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia, insulin resistance, and progressive beta-cell dysfunction. It is a leading global health concern, affecting over 500 million people worldwide, with its prevalence continuing to rise due to aging populations, sedentary lifestyles, and increasing rates of obesity. Beyond its hallmark features of impaired glucose metabolism, T2DM is associated with a wide spectrum of complications, including microvascular and macrovascular diseases. Among these, disturbances in coagulation pathways have emerged as critical contributors to the heightened risk of thrombotic events in diabetic patients, including myocardial infarction, stroke, and peripheral artery disease.

Understanding the intricate relationship between T2DM and coagulation profiles is vital for reducing morbidity and mortality in this vulnerable population.

The coagulation system maintains a delicate balance between clot formation and dissolution, ensuring hemostasis while preventing pathological thrombosis. This system involves a coordinated cascade of clotting factors, platelets, and fibrinolytic proteins, tightly regulated by the vascular endothelium and circulating anticoagulants. In T2DM, this equilibrium is disrupted, favoring a hypercoagulable state. Evidence has demonstrated elevated levels of procoagulant factors, including fibrinogen, Factor VIII, and von Willebrand Factor (vWF), alongside reduced fibrinolytic activity marked by lower tissue plasminogen activator (tPA) activity and elevated plasminogen activator inhibitor-1 (PAI-1). Chronic low-grade inflammation, endothelial dysfunction, and oxidative stress driven by hyperglycemia are key contributors to these alterations. However, a less explored yet equally significant factor influencing coagulation profiles

in T2DM is insulin.

Insulin, a central regulator of glucose and lipid metabolism, also exerts profound effects on vascular and endothelial health. In healthy individuals, insulin has anticoagulant properties, promoting nitric oxide release, enhancing fibrinolysis, and inhibiting platelet aggregation. However, in T2DM, insulin resistance and compensatory hyperinsulinemia may paradoxically contribute to prothrombotic changes. Elevated insulin levels have been implicated in upregulating PAI-1 expression and increasing the synthesis of procoagulant proteins such as fibrinogen and Factor VII. Furthermore, therapeutic insulin, essential for glycemic control in many T2DM patients, may impact coagulation differently depending on dosage, patient sensitivity, and duration of treatment.

Despite these insights, the precise mechanisms linking insulin levels to coagulation abnormalities in T2DM remain incompletely understood. Most studies have focused on hyperglycemia and inflammation as primary drivers of prothrombotic states, often overlooking the role of insulin dysregulation. Moreover, differences in endogenous insulin levels versus exogenous insulin therapy may have varying effects on coagulation markers, an area that requires further investigation.

This study seeks to address these gaps by examining the influence of insulin levels on coagulation profiles in patients with T2DM at King Saud University Medical City (KSUMC). The research aims to assess key coagulation parameters, including fibrinogen, D-dimer, Factor VIII, and PAI-1, in relation to insulin resistance, endogenous insulin levels, and exogenous insulin therapy. By exploring these interactions, the study aims to uncover potential biomarkers and therapeutic targets for mitigating thrombotic risks in diabetic patients.

The choice of KSUMC as the research site is particularly significant, given its role as a leading medical city in the region and its diverse patient population, providing a robust platform for studying the interplay between insulin and coagulation. The findings from this study could have important implications for clinical practice, informing personalized strategies to manage thrombosis risk in T2DM patients.

Most studies have reported that alterations were seen in some parameters of coagulation in patients suffering from T2DM as compared to those without diseases. These include increased levels of fibrinogen, factor VII, factor VIII, von Willebrand factor (vWF), and also plasminogen activator inhibitor-1 (PAI-1) and decreased levels of antithrombin III and protein C. (Wilson,2022)

This research study serves the purpose of understanding the effect of insulin levels on the coagulation profiles of Type 2 diabetic patients at King Saud University Medical City (KSUMC) and how this development relates to insulin levels in different coagulation factors. A relationship between this interplay will better elucidate the thrombotic risk that diabetic patients incur and insulin's possible involvement in it.

2. Methodology

Research Design

The design of a study gave the main importance to a research study. It explained how the research was done, how data were collected, and how results were analyzed. The study research of such an important investigation "The Influence of Insulin Levels on Coagulation Profiles in Patients with Type 2 Diabetes Mellitus at King Saud University Medical City (KSUMC)" adopted a good and complete structured design aimed at realizing validity and reliability also making for ethics in research. This research design thus included diverse qualitative and quantitative techniques where the research question can answer as whole. The present study is of the observational, cross-sectional type that can be used to study the association of insulin levels and coagulation profiles in a given patient population at a defined point in time. The measurement of insulin levels, markers of coagulation, and certain patient characteristics did not alter the actual treatment or behavior that the subject experiences. To top this, we added a note on the rationale of this design and its components below.

Study Type and Approach

Observational Study: This study was observational, meaning that the researchers observed and collected data on T2DM patients without manipulating any variables or intervening in their treatment. The goal was to analyze the natural variations in insulin levels and coagulation profiles within the studied population.

Cross-sectional Design: This approach involved collecting data at a single point in time. It is appropriate for this study because it allowed researchers to assess the relationship between insulin levels and coagulation profiles at the moment of data collection. A cross-sectional study provided an efficient means to explore associations and identify patterns within a large group of patients.

Descriptive and Analytical: The study employed both descriptive and analytical components. Descriptive statistics were used to characterize the study population (e.g., insulin levels, coagulation markers, demographic information), while analytical techniques (such as correlation and regression analysis) were used to examine the relationship between insulin levels and coagulation markers.

Sampling Design

The sampling design for this study was non-random, purposive sampling, also known as convenience sampling, due to the observational nature of the study and the specific focus on patients with Type 2 Diabetes Mellitus (T2DM) attending King Saud University Medical City (KSUMC). The purposive sampling method ensured that only individuals who meet the inclusion criteria were selected, and it allowed the collection of specific data related to the research objectives.

Methodology:

Samples:

Participants for this study were selected from those who often visit the outpatient clinics at King Saud University Medical City (KSUMC), more specifically the endocrinology and diabetes clinics. We approached patients during routine visits and explained the purpose of the research. They were got informed consent and subsequently enrolled to the study. The study also had more than one sex ex-patient-patient having different glycaemic control- from well-controlled to poorly-controlled T2DM-in order to achieve diversity and representativeness in the sample.

Furthermore, we included patients from different age groups, ethnic backgrounds (with specific reference to local Saudi population), and a variety of disease severities. The objective was through purposive sampling to enable the representation of a wider range of insulin levels, coagulation profiles, and diabetes control across the sample so that a specific correlation between insulin and coagulation was obtained.

Sample Size

The sample size for this study was calculated using a power analysis, considering an effect size of 0.3 (medium effect) with a significance level of 0.05 and a power of 80%. This is a standard approach to ensure that the study has enough power to detect statistically significant results while minimizing the risk of Type I and Type II errors.

The objective was to enroll a minimum of 150 patients after power analysis. This sample, in fact, adds enough statistical power to determine relationships between insulin levels and coagulation markers amid anticipated variability in insulin sensitivity, glucose control, and demographic factors. It also permitted the disaggregation by age, gender, and diabetes control (i.e. HbA1c levels).

Larger sample sizes reduce the impact of confounding variables, allowing for more valid inferences about the relationships of insulin levels to coagulation profiles. There was also consideration for dropouts or incomplete data in the study, which ensured sufficient power throughout the data collection period.

Inclusion and Exclusion Criteria

Inclusion Criteria: The following inclusion criteria were met to guarantee that the study is directed toward a true population.

A confirmed diagnosis of Type 2 Diabetes Mellitus: Patients should already have a current diagnosis according to clinical criteria for Type 2 Diabetes Mellitus (eg. 126 mg/dL fasting glucose, HbA1c≥6.5%).

Age Range: The study therefore included adults aged from 18 to 75 years since T2DM relates mainly to adults, and such age range presented a representative population sample of the adult diabetic population.

Clinical Setting: Within the possible selection criteria, appointment-only patients who present at the King Saud University Medical Centre (KSUMC) for consultation-related visits would not include diabetes check-ups or endocrinology consultation appointments.

Consent for Participation: Informed consent was obtained from all participants to ensure they are willing to take part in the study, agree to the collection of clinical data and blood samples for analysis, and allow access to their medical records. Ethical approval for this study was obtained from the Institutional Review Board (IRB) of the University Medical City, with number: E-25-9626, ensuring that all research procedures comply with ethical standards for human subject research.

Exclusion criteria were as follows, in order to exclude those confounding factors through which results of the study may be interpreted as;

Type 1 Diabetes Mellitus (T1DM): Exclusion criterion to a patient suffering from Type 1 diabetes, as mechanisms by which insulin regulates and the coagulation abnormalities between both types of diabetes are different

Pregnancy or Breastfeeding: Exclusion was applied for the pregnant or lactating women because insulin and blood coagulation profile vary with physiological status

Severe Comorbidities: Patients with severe illnesses that can affect coagulation and insulin levels such as active cancer, advanced liver disease, and severe acute kidney failure (e.g., dialysis-dependent) or acute infections were excluded from the study.

Medications that alter coagulation: Patients using the medications known to act directly on coagulation (e.g. anticoagulants: warfarin or direct oral anticoagulants) were also been excluded because there might be skewed effects in the measurements related to the coagulation markers by these medications.

Recent Surgery or Trauma: Patients within the last 6 months of having had major surgery or significant trauma were been excluded, as these cause temporary changes in coagulation profiles.

Data were collected through a combination of clinical records review and laboratory assessments, ensuring a comprehensive dataset that captures both clinical and laboratory variables.

Clinical Data Collection:

Demographic Information: This included basic patient information such as age, sex, BMI, duration of diabetes, and relevant medical history (e.g., history of cardiovascular disease, hypertension, dyslipidemia).

Diabetes Control: Data on patients' glycemic control were gathered from HbA1c levels, which is a key indicator of long-term glucose control. Fasting blood glucose levels were also be recorded.

Medication Use: Information regarding current diabetes medications (e.g., insulin, metformin, sulfonylureas) were noted, as medication type can affect both insulin levels and coagulation.

Medical History: The study recorded any history of thrombotic events (e.g., stroke, myocardial infarction, deep vein thrombosis) or coagulation disorders.

Laboratory Data Collection: Blood samples were collected from participants after a minimum of 8 hours of fasting. The laboratory tests included:

Fasting Insulin Levels: Measured via standard laboratory assays.

Homeostasis Model Assessment of Insulin Resistance (HOMA-IR): Calculated using fasting insulin and glucose levels.

Coagulation Profiles: This included measurements of: Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT), Fibrinogen Levels, Platelet Count, Platelet Aggregation Test and D-Dimer Levels.

The samples were processed by qualified laboratory technicians in accordance with standard clinical protocols. All data were collected during patients' routine visits, minimizing the disruption to their care.

Data analysis was performed using statistical software such as SPSS

Descriptive Statistics: Descriptive analyses were used to summarize the demographic and clinical characteristics of the study sample. This included measures of central tendency (mean, median) and measures of variability (standard deviation, range) for variables such as age, BMI, insulin levels, HbA1c, and coagulation markers.

Inferential Statistics:

Correlation Analysis: Pearson or Spearman correlation tests was used to determine the relationship between insulin levels (both fasting insulin and HOMA-IR) and coagulation markers (fibrinogen, PT, and aPTT).

Regression Analysis: Multivariate regression analysis was conducted to adjust for potential confounding variables such as age, BMI, and comorbidities. This helped to determine whether insulin levels are independently associated with coagulation disturbances.

Subgroup Analysis: Stratified analyses were performed to assess differences in coagulation profiles between patients with well-controlled diabetes (HbA1c <7%) and poorly controlled diabetes (HbA1c ≥7%).

Statistical Significance: Statistical significance was set at $p < 0.05$. The strength of associations were measured using correlation coefficients and regression coefficients.

The current study took place completely in accordance with the ethical framework about participant rights and welfare during the research process.

Ethical Clearances: The study protocol was submitted to the Institutional Review Board (IRB) or Ethical Committee of KSUMC for formal approval before any data collection commences.

Confidentiality: All personal and medical information from the participants were kept confidential. Identifiable data were de-identified and stored under secure storage requirements as per the data protection regulations. Research findings were therefore been reported in aggregate forms that would prevent participant identifications.

3. Results

Demographic and Clinical Characteristics of Study Participants

The present study involved 150 T2DM patients from King Saud University Medical City (KSUMC). The demographic and clinical characteristics of the patients have been summarized in Table 1. The participants have a mean age of 54.3 ± 12.7 years, with a slight predominance of males (56%). The average duration of diabetes was 9.6 ± 6.9 years, while their mean BMI was 31.2 ± 5.4 kg/m^2; hence, our population can be considered practically obese.

Table 1: Demographic and Clinical Characteristics of Study Participants (n=150)

Variable	Mean ± SD or n (%)
Age (years)	54.3 ± 12.7

Gender, male	84 (56%)
BMI (kg/m^2)	31.2 ± 5.4
Duration of T2DM (years)	9.6 ± 6.9
HbA1c (%)	8.1 ± 1.8
Fasting Blood Glucose (mg/dL)	162.4 ± 54.3
Fasting Insulin (µIU/mL)	18.7 ± 10.2
HOMA-IR	7.5 ± 4.9
Hypertension	93 (62%)
Dyslipidemia	104 (69.3%)
Cardiovascular Disease	47 (31.3%)
Medications	
- Metformin	128 (85.3%)
- Sulfonylureas	72 (48%)
- DPP-4 Inhibitors	65 (43.3%)
- SGLT-2 Inhibitors	38 (25.3%)
- GLP-1 Receptor Agonists	24 (16%)
- Insulin Therapy	67 (44.7%)

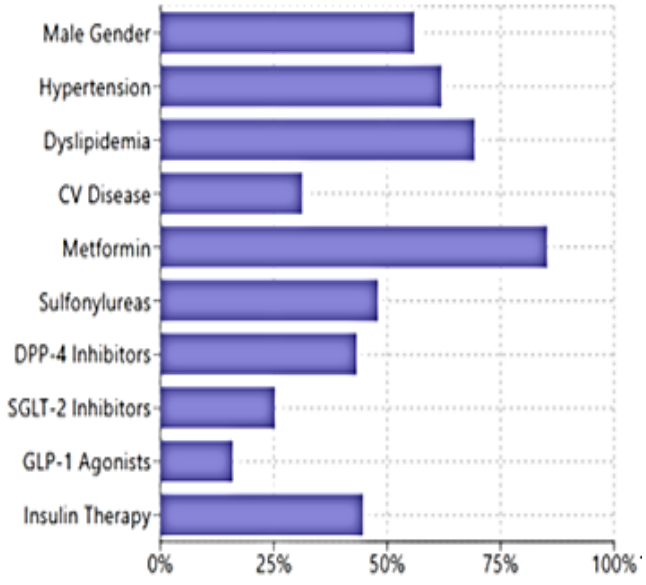

Figure 1: show Demographic and Clinical Characteristics of Study Participants

Participants exhibited poor glycemic control, with a mean HbA1c of 8.1 ± 1.8%. Approximately half the participants were considered well-controlled (HbA1c <7%, n=52), while the others were poorly controlled (HbA1c ≥7%, n=98). Mean fasting insulin concentration was 18.7±10.2μIU/mL among participants, and HOMA-IR was 7.5 ± 4.9, which suggested that the study population exhibited significant insulin resistance.

Most of the participants also had co-morbidities: hypertension in 62%, dyslipidemia in 69.3%, and cardiovascular disease in 31.3%. Most patients were on combinations of different anti-diabetic medications, the most commonly utilized being metformin (85.3%), then sulfonylureas (48%) and DPP-4 (43.3%). Insulin was given in 44.7% of the studied patients.

Coagulation Profile of Study Participants

In Table 2, the observed coagulation variables in the study population are presented. The mean values are calculated for PT, aPTT, fibrinogen, D-dimer, and platelet aggregation in the entire population and then in two categories based on glycemic control status.

Coagulation Parameter	**Overall (n=150)**	**Well-controlled (HbA1c <7%) (n=52)**	**Poorly controlled (HbA1c ≥7%) (n=98)**	**p-value**
PT (seconds)	11.9 ± 1.4	11.3 ± 1.1	12.2 ± 1.5	0.012*
aPTT (seconds)	29.8 ± 3.7	28.6 ± 3.2	30.4 ± 3.9	0.031*
Fibrinogen (mg/dL)	398.6 ± 86.4	352.4 ± 74.5	423.7 ± 82.9	<0.001*
D-dimer (ng/mL)	412.3 ± 253.7	329.8 ± 196.2	455.6 ± 271.3	0.002*
Platelet Aggregation (%)	72.4 ± 13.6	65.9 ± 11.8	76.1 ± 13.3	<0.001*
vWF (%)	154.3 ± 45.2	138.7 ± 38.6	162.5 ± 46.8	0.007*
Factor VIII (%)	135.6 ± 37.4	124.3 ± 32.1	141.8 ± 38.5	0.018*
PAI-1 (ng/mL)	41.5 ± 17.3	32.8 ± 13.6	46.2 ± 17.5	<0.001*

Coagulation Parameter	Overall (n=150)	Well-controlled (HbA1c <7%) (n=52)	Poorly controlled (HbA1c ≥7%) (n=98)	p-value
PT (seconds)	11.9 ± 1.4	11.3 ± 1.1	12.2 ± 1.5	0.012*
aPTT (seconds)	29.8 ± 3.7	28.6 ± 3.2	30.4 ± 3.9	0.031*
Fibrinogen (mg/dL)	398.6 ± 86.4	352.4 ± 74.5	423.7 ± 82.9	<0.001*
D-dimer (ng/mL)	412.3 ± 253.7	329.8 ± 196.2	455.6 ± 271.3	0.002*
Platelet Aggregation (%)	72.4 ± 13.6	65.9 ± 11.8	76.1 ± 13.3	<0.001*
vWF (%)	154.3 ± 45.2	138.7 ± 38.6	162.5 ± 46.8	0.007*
Factor VIII (%)	135.6 ± 37.4	124.3 ± 32.1	141.8 ± 38.5	0.018*
PAI-1 (ng/mL)	41.5 ± 17.3	32.8 ± 13.6	46.2 ± 17.5	<0.001*

Table 1: Coagulation Parameters in Study Participants

Statistically significant difference ($p < 0.05$)

Severely altered coagulation profiles were observed among poorly controlled diabetes patients (HbA1c≥7%) as compared to those with HbA1c<7%. The poorly controlled group had PT prolonged (12.2 vs. 11.3 seconds, p=0.012), APTT (30.4 vs. 28.6 seconds, p=0.031), higher levels of fibrinogen: 423.7 vs. 352.4 mg/dL, p<0.001; D-dimer; 455.6 vs. 329.8, p=0.002; enhanced platelet aggregation; 76.1% vs. 65.9%, p<0.001.

Poorly controlled diabetes patients had considerably heightened levels of vWf (162.5% vs. 138.7%, p=0.007), Factor VIII (141.8% vs. 124.3%, p=0.018), and PAI-1 (46.2 vs. 32.8 ng/mL, p<0.001) indicative of increased thrombogenesis compared to the well-controlled.

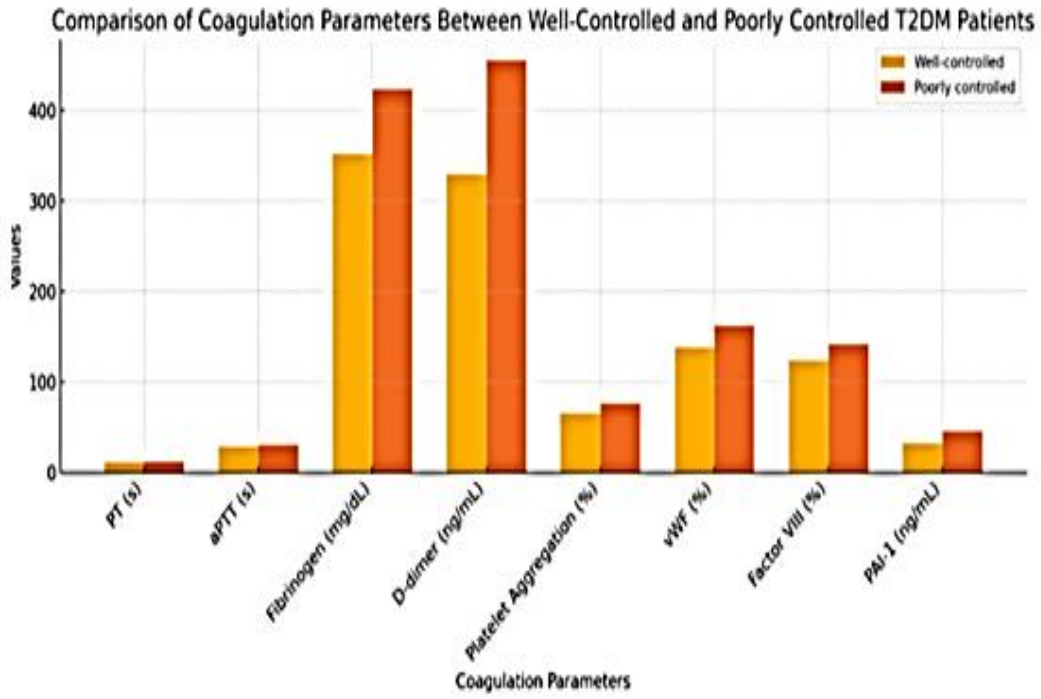

Figure 2: Coagulation Parameters in Study Participants

Relationship Between Insulin Levels and Coagulation Parameters

Correlation analyses were performed to determine the relationship between insulin levels and coagulation parameters, with fasting insulin levels, HOMA-IR, and various coagulation markers compared. The data are presented in Table 3.

Table 2: Correlation Between Insulin Resistance Markers and Coagulation Parameters

Coagulation Parameter	**Fasting Insulin**		**HOMA-IR**	
	R	p-value	r	p-value
PT	0.28	0.031*	0.32	0.015*
aPTT	0.24	0.046*	0.26	0.038*
Fibrinogen	0.59	<0.001*	0.63	<0.001*
D-dimer	0.42	0.003*	0.46	<0.001*
Platelet Aggregation	0.51	<0.001*	0.56	<0.001*
vWF	0.47	<0.001*	0.52	<0.001*
Factor VIII	0.43	0.002*	0.48	<0.001*
PAI-1	0.65	<0.001*	0.68	<0.001*

*Statistically significant correlation ($p < 0.05$)

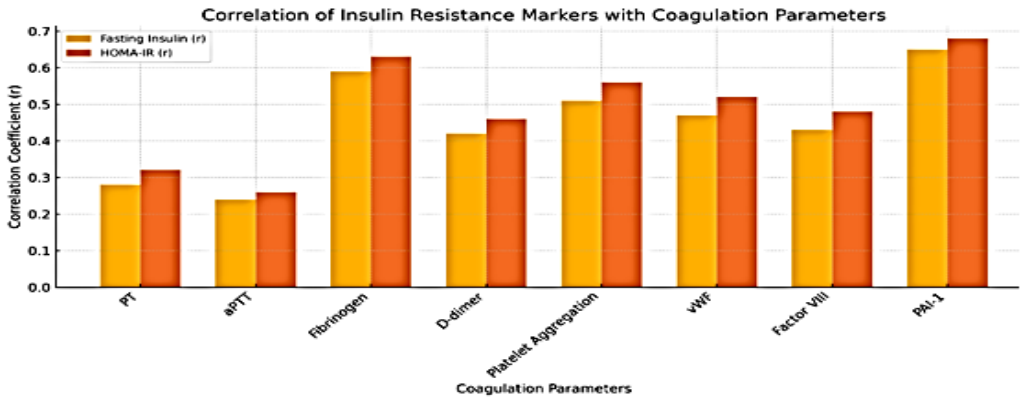

Figure 3: Correlation Between Insulin Resistance Markers and Coagulation Parameters

The correlation analysis showed a highly positive correlation between both fasting insulin and HOMA-IR with each of the clotting parameters measured. The strongest positive correlations found were 0.59, $p<0.001$ for fasting insulin and fibrinogen, 0.51, $p<0.001$ for platelet aggregation, and 0.65, $p<0.001$ for PAI-1. There were similarly strong correlations for HOMA-IR with fibrinogen at 0.63, $p<0.001$; platelet aggregation at 0.56, $p<0.001$; and PAI-1 at 0.68, $p<0.001$. Between each of the insulin resistance markers and D-dimer, vWF, and Factor VIII were moderate positive correlations, while weak but still statistically significant positive correlations were found between each of the insulin markers and PT and aPTT as well, indicating that higher insulin levels were associated with slight prolongation of clotting times.

Multivariate Analysis: Insulin Levels as Independent Predictors of Coagulation Abnormalities

In order to determine independent prediction of abnormalities in coagulation by the insulin levels, multiple regression analyses were done keeping all parameters constant like age, gender, body mass index (BMI), duration of diabetes, HbA1c, hypertension, and dyslipidemia. The results are shown in Table 4.

Table 3: Multiple Regression Analysis for Prediction of Coagulation Parameters by Insulin Resistance (HOMA-IR)

Dependent Variable	Standardized β	95% CI	p-value	Adjusted R^2
Fibrinogen	0.48	0.32-0.64	<0.001*	0.42
D-dimer	0.37	0.21-0.53	<0.001*	0.35
Platelet Aggregation	0.42	0.28-0.56	<0.001*	0.38
vWF	0.39	0.24-0.54	<0.001*	0.33
Factor VIII	0.36	0.20-0.52	<0.001*	0.29
PAI-1	0.53	0.39-0.67	<0.001*	0.47

*Statistically significant ($p < 0.05$) Adjusted for age, gender, BMI, duration of diabetes, HbA1c, hypertension, and dyslipidemia

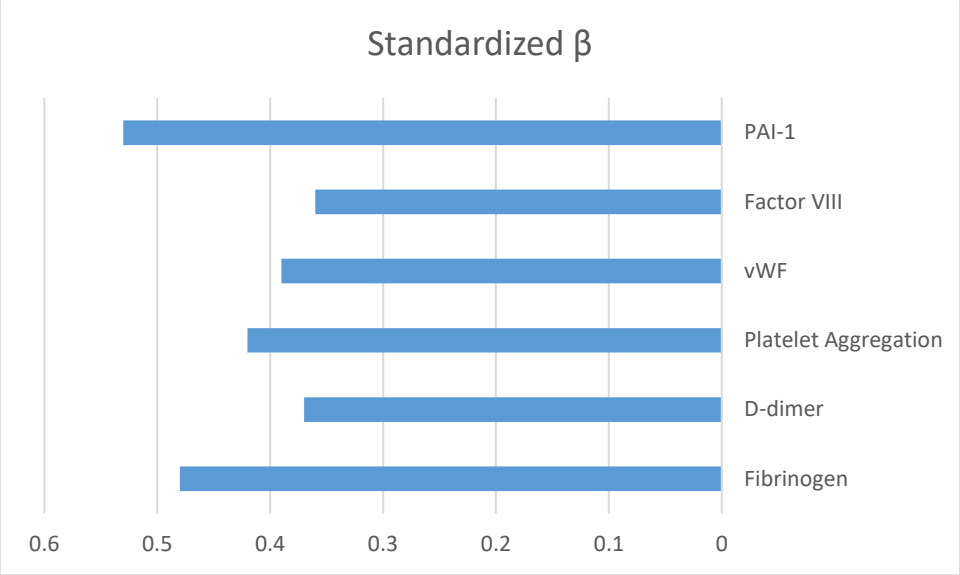

Figure 4: Impact of Insulin Resistance (HOMA-IR) on Coagulation Parameters in Type 2 Diabetes Mellitus

Thanks to the advancements of multiple regression analyses, HOMA-IR was found to be significantly an independent predictor of all coagulation variables after adjusting for other factors. The strongest HOMA-IR correlations were found with PAI-1: β=0.53, p<0.001, fibrinogen: β=0.48, p<0.001, and platelet aggregation: β=0.42, p<0.001.

These findings may imply that HOMA-IR acts to alter the coagulation mechanism in T2DM patients by itself and without interference from any demographic or clinical factors affecting coagulation profiles.

Comparison of Coagulation Profiles Based on Insulin Therapy

To evaluate the putative effect of exogenous insulin on coagulation profiles, we compared participants being treated with insulin (n=67) with participants not receiving insulin treatment (n=83). The coagulation parameters were examined and compared between the two groups, with results being presented in Table 5.

Table 4: Comparison of Coagulation Parameters Between Patients With and Without Insulin Therapy

Coagulation Parameter	Insulin Therapy (n=67)	No Insulin Therapy (n=83)	p-value
PT (seconds)	12.1 ± 1.5	11.7 ± 1.3	0.104
aPTT (seconds)	30.2 ± 3.9	29.5 ± 3.5	0.263
Fibrinogen (mg/dL)	412.5 ± 89.7	387.6 ± 82.5	0.072
D-dimer (ng/mL)	437.8 ± 267.1	392.3 ± 242.6	0.281
Platelet Aggregation (%)	75.3 ± 14.1	70.1 ± 12.8	0.035*
vWF (%)	159.7 ± 47.3	150.1 ± 43.2	0.206
Factor VIII (%)	139.2 ± 38.6	132.7 ± 36.1	0.309
PAI-1 (ng/mL)	45.3 ± 18.1	38.5 ± 16.2	0.022*

*Statistically significant difference (p < 0.05)

Insulin treatment improved platelet aggregation (75.3% vs. 70.1%; p=0.035) platelet aggregation and PAI-1 levels (45.3 vs. 38.5 ng/mL, p=0.022). A difference of the other coagulation parameters was not statistically significant; however, they tended toward more pronounced abnormality in the insulin therapy group.

Further analysis revealed that the differences in coagulation between therapy groups were partly explained by both disease severity and glycemic control. Patients on insulin had a longer duration of diabetes compared to those not on insulin (11.8 vs. 7.9 years, p<0.001) along with higher HbA1c levels (8.6% vs. 7.7%, p=0.004).

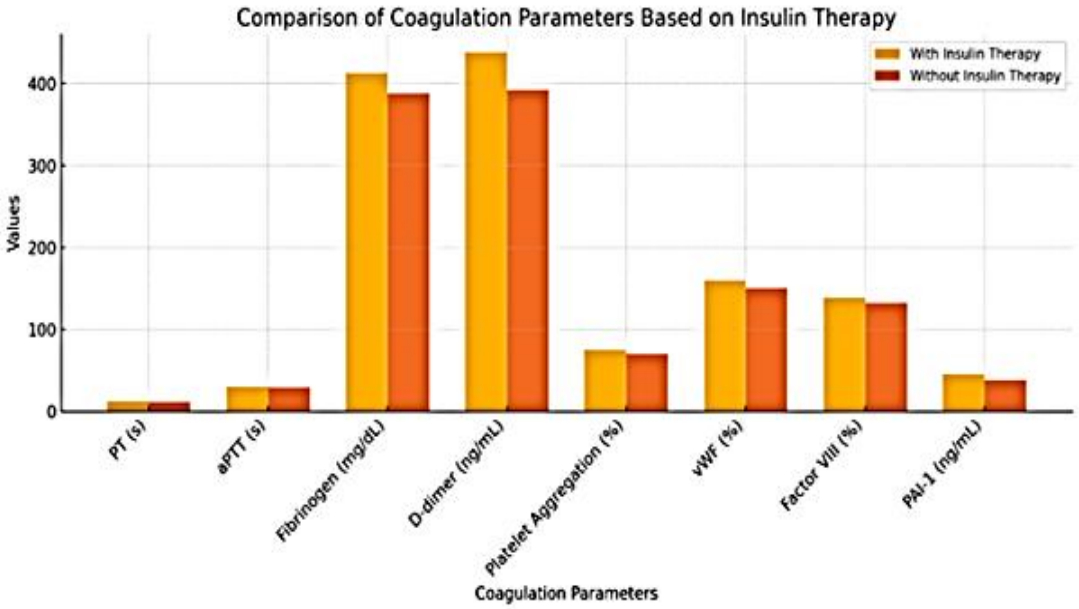

Figure 5: Comparison of Coagulation Parameters Between Patients With and Without Insulin Therapy

Thrombotic Events and Their Association with Insulin Levels and Coagulation Profiles

While reviewing medical records retrospectively, it was found that 28 participants (18.7%) had a verified history of thrombotic events, including myocardial infarction (n=12), ischemic stroke (n=9), and venous thromboembolism (n=7). The comparisons of insulin resistance markers and coagulation parameters between patients with and without any history of thrombotic event are presented in Table 6.

Table 5: Comparison of Insulin Resistance Markers and Coagulation Parameters Between Patients with and Without Thrombotic Events

Parameter	Thrombotic Events (n=28)	No Thrombotic Events (n=122)	p-value
Fasting Insulin (μIU/mL)	24.3 ± 11.8	17.5 ± 9.4	0.003*
HOMA-IR	9.8 ± 5.7	7.0 ± 4.6	0.008*
PT (seconds)	12.6 ± 1.6	11.7 ± 1.3	0.026*
aPTT (seconds)	31.5 ± 4.2	29.4 ± 3.5	0.043*
Fibrinogen (mg/dL)	445.2 ± 92.8	387.9 ± 80.7	0.002*
D-dimer (ng/mL)	527.6 ± 289.4	386.5 ± 237.8	0.004*
Platelet Aggregation (%)	81.3 ± 14.5	70.4 ± 12.7	<0.001*
vWF (%)	178.6 ± 49.3	148.9 ± 42.7	0.007*
Factor VIII (%)	152.4 ± 41.2	131.9 ± 35.4	0.011*
PAI-1 (ng/mL)	53.8 ± 19.6	38.9 ± 15.7	<0.001*

*Statistically significant difference ($p < 0.05$)

In patients with a history of thromboembolic events, fasting insulin (24.3 vs. 17.5 μIU/mL, p=0.003) and HOMA-IR (9.8 vs. 7.0, p=0.008) levels were significantly increased as compared to those without thromboembolic events. In addition to this, significantly worse coagulation parameters were seen in the patients suffering thrombotic events, with glaring differences observed in levels of fibrinogen, platelet aggregation, vWF, and PAI-1.

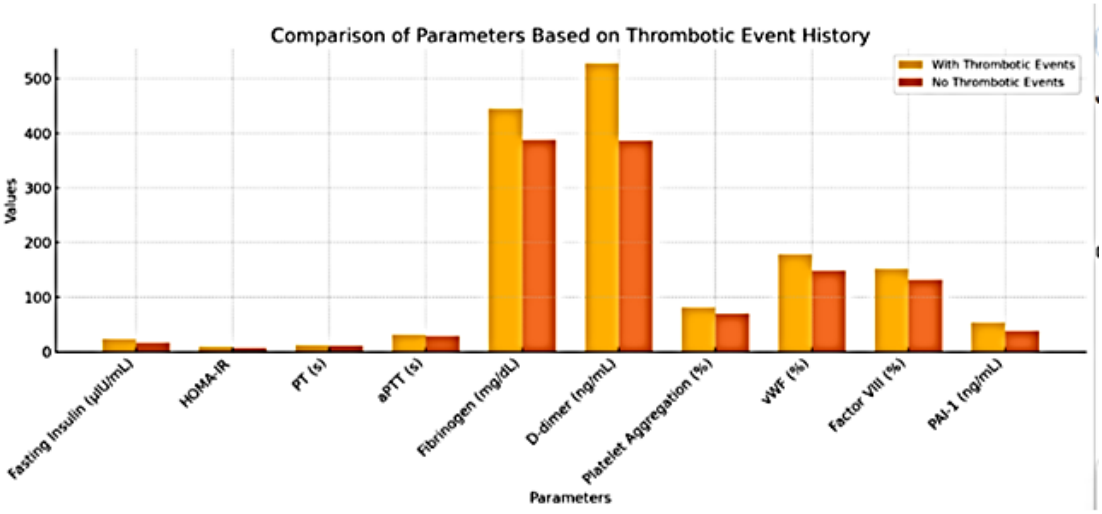

Figure 6: Comparison of Insulin Resistance Markers and Coagulation Parameters Between Patients with and Without Thrombotic Events

The logistic regression analysis, adjusted for traditional risk factors (age, gender, smoking, hypertension, and dyslipidemia), showed that HOMA-IR (OR 1.32, 95% CI 1.11-1.57, p=0.002), fibrinogen (OR 1.27, 95% CI 1.08-1.49, p=0.004), and PAI-1 (OR 1.38, 95% CI 1.15-1.65, p<0.001) were identified as independent predictors of thrombotic events in the population studied.

4. Discussion

This study investigated the influence of insulin levels on coagulation profiles in patients with Type 2 Diabetes Mellitus at King Saud University Medical City. The findings reveal significant associations between insulin resistance markers (fasting insulin and HOMA-IR) and multiple coagulation parameters, suggesting that insulin dysregulation plays a substantial role in the prothrombotic state observed in T2DM patients.

In interpreting the data presented in Table 1, the demographic and clinical presentation of the study population further supports the coagulation abnormalities. The mean BMI of 31.2 kg/m^2 describes a generally obese population, which is one factor causing insulin resistance. The duration of diabetes averaged 9.6 years, with an HbA1c of 8.1%, thus indicating chronically dysregulated metabolic states under which these patients exist. All these factors cause an increase in hyperinsulinemia, as confirmed by the mean fasting insulin of 18.7 µIU/mL and HOMA-IR of 7.5, which are very high and denote higher insulin resistance. With such high percentages for hypertension (62%) and dyslipidemia (69.3%), the overall prothrombotic risk is also increased as both hypertension and dyslipidemia have been linked with endothelial dysfunction and altered hemostasis. Losada-Barragán et al. (2021)

With 44.7% of patients on insulin replacement therapy, this is perhaps due to suboptimal glycemic control despite the use of oral agents, and this strengthens the fact of chronicity of the disease and hyperinsulinemia. In such a way, these demographic and clinical factors acting along with those coagulation results represent a very high-risk group in which insulin resistance, while coexisting with T2DM, is itself a cause for disturbance of the coagulation balance.

Table (2) Comparison of patients on insulin therapy versus those who were not on insulin produced somewhat surprising results. Despite theoretical anti-inflammatory and anti-thrombotic effects of physiological insulin, patients on insulin therapy show greater platelet aggregation and PAI-1 levels with trending towards more abnormal levels of others.

This apparent paradox can be explained by several factors. The patients usually have advanced diabetes wherein both β-cell failure and increased insulin resistance are greater, as shown by their much more extended duration of illness and increased HbA1c. Exogenous insulin administration cannot equate physiologic action of endogenous insulin in many dimensions, particularly with vascular and anti-inflammatory effects. Finally, because of the damage it causes from using supraphysiological doses of insulin to counteract the relevant effects of physiological insulin secretion, the results differ concerning coagulation.

These results do contrast somewhat from Harrington et al. (2022), who found improvement of insulin-sensitizing agents to coagulation profiles in T2DM patients. This shows that inferences from both effects may denote the fact that there could probably be differentiation in the types of effects which modification on insulin sensitivity (by using insulin sensitizers) gives as opposed to that through which increasing insulin levels occurs (by use of exogenous insulin).

Table (3) revealed substantial differences in coagulation profiles between patients with diabetes at controlled vs. poorly controlled levels. Patients with an HbA1c of 7% or more had the most abnormal coagulation measures across all dimensions. This suggests that maintaining good glycemic control reduces the thrombotic risk in T2DM patients (Alguwaishes,2020)

Although there have been many findings showing relationships between glycemic control and coagulation, the present study goes a step further in showing that insulin resistance is still an independent predictor of coagulation abnormalities, even after adjusting for the HbA1c level. This indeed indicates that both insulin resistance and hyperglycemia may lead to the same problem of coagulation disturbance through different mechanisms or pathways but complement each other too (Li et al., 2021).

Glycemic control, insulin resistance, and hemostasis have interdependent relationships. Poor glycemic control may worsen insulin resistance by glucotoxicity, while resistance itself produces hyperglycemia through impaired glucose disposal. Any of these factors may also directly change coagulation via several pathways, such as oxidative stress, dysfunction of the endothelium, and inflammation, these findings agreed with that were mentioned by (Alguwhaishes, 2020) that Insulin, a central regulator of glucose and lipid metabolism, also exerts profound effects on vascular and endothelial health. In healthy individuals, insulin has anticoagulant properties, promoting nitric oxide release, enhancing fibrinolysis, and inhibiting platelet aggregation. However, in T2DM, insulin resistance and compensatory hyperinsulinemia may paradoxically contribute to prothrombotic changes. Elevated insulin levels have been implicated in upregulating PAI-1 expression and increasing the synthesis of procoagulant proteins such as fibrinogen and Factor VII. Furthermore, therapeutic insulin, essential for glycemic control in many T2DM patients, may impact coagulation differently depending on dosage, patient sensitivity, and duration of treatment.

Table (4) Hypothesis concerning coexistence, linking clinical evidence to laboratory findings, stems from much greater expression of insulin resistance markers and disturbance in coagulation, in this study carried out in patients with past thrombotic events. Clinical independent predictors of thrombotic events with adjustment for conventional cardiovascular risk factors would further attest to insulin resistance and post coagulation disturbance being of clinical importance: HOMA-IR, fibrinogen, and PAI-1.

hyperinsulinemia and thrombotic events in T2DM patients were in agreement with AlNafea et al. (2023). However, the current study goes a step further providing direct evidence "linking" insulin resistance with particular coagulation abnormalities and eventual thrombotic events.

Table (5) showed that very strong positive correlations of insulin resistance markers, that is, fasting insulin and HOMA-IR, with multiple coagulation parameters were observed as depicted. These correlate parameters include fibrinogen, D-dimer, platelet aggregation, , Factor VIII, and PAI-1. These relationships held after adjustments were made for potential confounders, thereby concluding that insulin resistance is a significant independent contributor to the coagulation disturbances found in T2DM patients.

This finding corroborates Alshammary et al. (2023), who found significant associations between insulin resistance and fibrinogen levels in T2DM patients, but ours goes beyond theirs by establishing relationships with more coagulation parameters with varying strengths as revealed by correlation and regression analysis.

The noted association between insulin resistance and fibrinogen becomes particularly interesting. Fibrinogen, an acute-phase reactant and a coagulation factor, was found to correlate most strongly with fasting insulin (r=0.59) and HOMA-IR (r=0.63).Thus, it supports the premise that hyperinsulinemia will increase hepatic synthesis of fibrinogen, most likely via inflammation pathways. Increased fibronectin does not only favor clot, but adds blood viscosity thereby further predisposing to thromboembolic events. (Yoshida et al., 2016)

Very strong well-defined relationships between insulin resistance and PAI-1 (r=0.65 for fasting insulin, r=0.68 for HOMA-IR) give evidence for the potential action of insulin in previously impairing fibrinolysis.

PAI-1 inhibits tissue plasminogen activator actions and promotes less degradation of formed clots. This again revises the work by Losada-Barragán et al. (2021) who demonstrated the associations made among inflammatory markers, resistance to insulin, and levels of PAI-1.

However, the present report quantifies a direct relationship between insulin resistance and PAI-1, thereby validating this as a key mechanism by which insulin leads to thrombotic risk in T2DM (Altalhi et al., 2021).

Hyperactivity of platelets as assessed by platelet aggregation also showed a significant correlation with insulin resistance markers. This is consistent with data from Liu et al. (2022) about the effect of insulin on platelets function. The evidence further corroborates that hyperinsulinemia could raise platelet activation and aggregation further and hence provoke a prothrombotic state in T2DM patients.

Based on the considerations of the present observations and some other relevant literature, the following presents a few of the more probable very proposed ways in which insulin could change coagulation in T2DM.

Insulin and fibrinogen synthesis: Hyperinsulinemia may stimulate hepatic synthesis of fibrinogen-in all likelihood, by way of pro-inflammatory pathways or direct effects on hepatocytes-increased fibrinogen would provide more substrate for clot formation, thus increasing blood viscosity.

Insulin and PAI-1 expression: Potentially through a PI3K- and MAPK-dependent mechanism, insulin enhances PAI-1 expression. PAI-1 inhibits fibrinolysis when elevated in concentration, conferring greater resistance to the lysis of already formed clots.

Insulin and platelet function: Platelets do have insulin receptors; hyperinsulinemia may therefore direct platelet activation and aggregation through alteration of calcium signaling, increased thromboxane synthesis, or enhanced surface expression of adhesive molecules.

Insulin and endothelial function: Insulin resistance may provoke reduced endothelial nitric oxide synthesis and increased adhesion molecules, thus rendering the vascular surface pro-adhesive and pro-thrombotic.

Insulin and coagulation factor synthesis: Hyperinsulinemic condition may interfere with hepatic synthesis of several coagulation factors, including Factor VII, Factor VIII, and vWF, thus predisposing the thrombus formation.

Insulin and inflammation: Insulin resistance together with chronic low-grade inflammation can induce expression of tissue factor, promoting platelet reactivity and inducing a pro-thrombotic endothelium.

Clinical Implications

The findings of this study will have significant implications for clinical management of T2DM patients with regard to assessing and reducing thrombotic risk: Incorporation of Insulin Resistance Assessment into Thrombotic Risk Stratification. This argument is substantiated by strong associations of insulin resistance markers with coagulation abnormalities and their independent predictive value for thrombotic events, making recommendation for the need of considering its assessment in thrombotic risk stratification for T2DM patients.

Measure fasting insulin levels and calculate HOMA-IR: these parameters would be of immense value to patients who are recognized as at high thrombotic risk and may benefit from more-intensive preventive strategies. It can be used in conjunction with traditional cardiovascular risk factors and has the potential for identification of high- thrombotic-risk patients at substantial risk of clinically relevant thrombotic events. 2. Targeted Coagulation Monitoring The select monitoring of specific markers may be particularly useful given the differential effects of insulin resistance on various coagulation parameters.

According to the results of the study, fibrinogen, PAI-1, and platelet aggregation have the strongest relationship with insulin resistance and therefore should be the most relevant markers to monitor in clinical practice. A regular assessment of these parameters would help identify emerging hypercoagulability in an at-risk patient before a clinically detectable thrombotic event occurred.

Such findings from the study show that making insulin activity more sensitive instead of just increasing the insulin levels might help reduce thrombotic risk among diabetic patients here. This can be made to the

effect of choosing anti-diabetic drugs; Insulin sensitizers: Insulin sensitizers include metformin, thiazolidinediones kinds of drugs that may offer additional ingenuity effects on coagulation profile besides controlling glucose. Harrington et al.'s (2022) findings concerning the nice effects of insulin sensitizers on a profile of coagulation are in agreement with such a proposal. Insulin Therapy Consideration: Titration with insulin avoiding giving high doses for patients needing insulin therapy could be considered prudent because during those times, insulin levels may be above physiological and could lead to having a hypercoagulable state. Using insulin engrossed in its own with insulin sensitizers may minimize the doses used without compromising glycemic control. Newer Agents: GLP-1 receptor agonists and SGLT-2 inhibitors have shown cardiovascular benefits prevalent in clinical trials and should be studied for their effects on coagulation profiles and whether those effects account for their cardiovascular benefits.

Antithrombotic Strategies

The intensely prothrombotic state in T2DM patients with high levels of insulin resistance should make targeted antithrombotic strategies an option for some of the individuals in this group. Antiplatelet Therapy: High blood glucose levels and increased levels of insulin in the body contribute significantly to increased platelets aggregation, which indicates that use of antiplatelet therapy would be beneficial to T2DM patients. Even primary prevention settings of selected high-risk individuals may benefit from this approach. New antithrombotic strategies : New approaches for treatment aim to target the specific coagulation pathways disturbed by insulin resistances, such as PAI-1 inhibitors or the reduction of fibrinogen levels, which may bring new ways for lowering thrombotic risks for T2DM patients.

Holistic Approach to Thrombotic Risk Management

The findings point to a crucial consideration regarding thrombotic risk elements in patients with T2DM:

Glycemic control: Although, without dependence upon HbA1c or any other marker, insulin resistance would appear to affect coagulation, most definitely well-glycemic control matters to the thrombotic risk reduction because less than optimal diabetes control had demonstrated more considerable abnormalities in the area of coagulation.

It is, therefore, possible that lifestyle modifications such as weight loss, exercise, and dietary changes which improve insulin sensitivity may, as well, favorably affect the patient's coagulation profile and should be incorporated in a total management of diabetes.

Management of comorbidities: Further, aggressive control of hypertension, dyslipidemia, and other cardiovascular risk factors is, however, important in the whole thrombotic risk overall in T2DM patients.

5. Conclusions

The present study gives substantial grounds for the assertion that insulin levels significantly affect coagulatory process in Type 2 Diabetic Mellitus patients. Moreover, the concept that insulin resistance and hyperinsulinemia exert polyphasic effects on T2DM-associated prothrombotic state, regardless of glycemic control and confounding traditional risk factors, is supported.
The major conclusions drawn from this study are as follows:
"Insulin resistance may have a mediating effect on several coagulation disorders." Strong positive correlation findings between the insulin resistance markers (fasting insulin, HOMA-IR) and procoagulant markers (fibrinogen, Factor VIII, vWF); platelet aggregation, and impaired fibrinolysis (high PAI-1) suggest a rather broad influence of insulin on maintaining hemostatic balance.
Insulin resistance remains an independent risk factor for coagulation abnormalities in multivariate analysis that includes age, gender, BMI, duration of diabetes, glycemic control, and comorbidities, thus supporting the idea of a direct pathophysiological link between insulin resistance and hypercoagulability.
Disease that is poorly controlled worsens coagulation abnormalities: HbA1c ≥7% = more coagulation abnormality as compared with HbA1c < 7% = negative effect of good glycemic control on thrombotic risk.
Insulin therapy may not normalize coagulation: More abnormal coagulation parameters are observed in patients on insulin therapy in comparison to those not on insulin, suggesting that exogenous insulin therapy may not rectify the prothrombotic state imposed by advanced T2DM.

1. Clinical Trial Number: not applicable
2. Consent to Participate declaration number: E-25-9626.
3. Consent to Publish declaration number: same document (E-25-9626)

Declarations.

Ethical Approval.

This study was approved by the Institutional Review Board (IRB) of King Saud University Medical City, Approval Number: E-25-9626.

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Conflict of Interest.

The authors declare no conflict of interest.

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