

Use of Kaolin Thromboelastography (Teg®) In the Management of Diabetic Foot

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Abstract

Background

This observational study aims to compare the potential application of thromboelastography (TEG) in diagnosing Normality (NP/C), Diabetic Foot (DF), Diabetic Foot Ulcer (DFU), and Ulcer without Diabetic Foot (WDFU). Research suggests that fibrinogen (Fib) concentrations are used to assess the onset and severity of diabetic foot (DF) and to monitor its progression in patients. However, the correlation between TEG and Fib has not been reported in these patients. In this study, DF, DFU, NP, and WDFU are correlated with α angle, k (clot formation time) and Maximum Amplitude (MA) on Thromboelastography which reflect Fib functional and blood Fibrinogen.

Methods

According to relevant clinical criteria, patients were divided into 5 groups, and their blood samples underwent TEG. Subsequently, R, k, α angle e MA. Spearman's correlation analysis was used to analyze the correlation between non-parametric data sets. Continuous variables were analyzed using the Kruskal-Wallis's test and the χ^2 test. Ordinal categorical variables were compared using ordinal logistic regression analysis, estimating the Odds Ratio of risk factors and the Relative Risk. A Receiver Operating Characteristic (ROC) curve was constructed to detect the diagnostic ability of TEG parameters, and areas under the curve (AUROC) were compared using DeLong's test. The primary and secondary hemostatic profiles were examined using TEG and plasma fibrinogen and were classified into hypocoagulable, hypercoagulable, and normocoagulable states.

Results

The presence of an ulcer had a positive effect on the correlation between Fib and the TEG MA parameter both before ($p = 0.65$, $p = 0.36$) and after surgery ($p = 0.64$, $p = 0.32$), in both diabetic and non-diabetic patients; median k e di Fib levels increased markedly in subjects with DF compared to those without, particularly in those with ulcers. α angle levels (median) decreased significantly in subjects with DF and ulcers compared to those without ($p < 0.01$). Spearman's correlation analysis (ρ) showed that α angle and Fib were poorly negatively correlated in the DF group ($\rho = -0.27$, $p = 0.12$) before surgery and positively correlated ($\rho = 0.25$, $p = 0.16$) after surgery, k value was positively correlated in DF ($\rho = 0.40$, $p < 0.05$) preoperatively and negatively correlated in DF ($\rho = -0.2$, $p = 0.26$) after surgery.

Abstract

ROC curve analysis showed that in patients with preoperative fibrinogenemia between 401 and 600 mg/dL, the optimal cut-off point for distinguishing patients with DF from those without was 53.5° for α angle, with a sensitivity and specificity of 63.6%. In the same patients, the optimal cut-off point for the k value was 3.8 min, with a sensitivity of 87.5% and a specificity of 50%. The optimal cut-off point for preoperative fibrinogen was 3.98 g/L, with 100% sensitivity and specificity. For postoperative fibrinogen, the cut-off was >4.18 g/L with 50% sensitivity and 0% specificity. In patients with preoperative fibrinogenemia >600 mg/dL, the optimal cut-off points for evaluating the risk of diabetic foot progression was >665 mg/dL, with 100% sensitivity and specificity. The optimal cut-off point for the k value was 2.40 min, with 100% sensitivity and specificity. In control group C, the optimal cut-off point for preoperative fibrinogen was 2.78 g/L, with a sensitivity of 66.7% and a specificity of 100%.

Conclusion

Pre-operative α angle, k value and Fib hold clinical significance regarding the risk of onset and development of diabetic foot and its evolution into an ulcerative form, and can contribute to early diagnosis and early clinical intervention in Diabetic Foot.

Key words

Diabetic Foot Ulcer (DFU); Type 2 Diabetes Mellitus (T2DM); Diabetic Complications; Inflammatory Biomarkers; Systems Biology; Thromboelastography; Fibrinogen

Introduction

Given endothelial vascular damage and platelet dysfunction, patients with diabetes mellitus are 17 times more likely to develop gangrene, and five out of six major limb amputations occur in this population. Globally, the age-adjusted prevalence of diabetes is projected to increase from 9.3% to 10.9% by 2045. People with Type 2 Diabetes Mellitus (T2DM) evaluated last year in Italian diabetes centers are increasingly elderly, with the proportion over 75 years of age rising from 34.8% to nearly 36%. Obesity among them decreased by one percentage point, dropping from 36% to 35%, confirming an improving trend in weight management in these patients. The group maintaining HbA1c under control remained stable at 56%, over 44% have cholesterol levels within target (compared to 40.2% in the previous survey), but only 26.5% achieve adequate blood pressure values. Metformin usage remains stable, prescribed to approximately 70% of the sample, as does insulin (32%), while lipid-lowering and antihypertensive drugs are taken by two-thirds of patients. Renal disease and cardiovascular disease are confirmed as the prevailing chronic complications in T2DM, found in 50% and 15% of patients, respectively, followed by diabetic retinopathy (12%). The global prevalence of diabetic foot is 6.3%.

Superficial or closed lesions that do not penetrate the dermis (e.g., hyperkeratosis, blisters, localized warmth, or erythema) are considered pre-ulcerative lesions and carry a high risk of progression to ulceration. Over the years, there has been an increased prevalence of the ischemic component, as highlighted in a recent study of a cohort of 1,198 diabetic patients, of whom 33.2% presented with neuropathic ulcers and 67.8% with neuro-ischemic/ischemic ulcers [1,2]. Research suggests that fibrinogen (Fib) concentrations are used to assess the onset and severity

of diabetic foot and to monitor its progression. However, its correlation with Fib parameters on TEG has not been reported in these patients. Furthermore, elevated plasma fibrinogen levels have been correlated with an increased thromboembolic risk. This study correlates Normality (NP)(C), Diabetic Foot (DF), Diabetic Foot Ulcer (DFU), and Ulcer without Diabetic Foot (WDFU) with Thromboelastography α angle and k (clot formation time) values, reflectin Fib function, as well as baseline and post-surgical blood fibrinogen levels, TEG's MA values and blood levels of CRP, ESR and Plt.

Viscoelastic tests are crucial in targeted, modern coagulation management for evaluating patient coagulation status. Therefore, in the current absence of uniform quantitative standards regarding biomarkers that can serve as benchmarks for the risk of diabetic foot onset and progression, and considering that an increased α angle and a decreased k value may represent important indicators for the development of vascular lesions, we hypothesize whether they can achieve standing as novel Diabetic Foot biomarkers. Type 2 diabetes mellitus (T2DM) is a common metabolic disorder that can also cause anticoagulant dysfunction, in addition to vascular endothelial damage and platelet dysfunction. Thromboelastography (TEG®) is one of the most important methods for monitoring coagulation function in clinical practice. TEG® monitors the process of blood clotting and clot dissolution based on the levels and functions of fibrin and platelets. Currently, it is widely utilized to guide clinical blood transfusion and the administration of drugs affecting platelet function, for real-time coagulation monitoring across various conditions, and to predict the risk of venous thrombosis. Indeed, numerous studies demonstrate that preoperative TEG is the most appropriate modality for predicting postoperative thromboembolic events [3].

Comprehensively evaluating coagulation status remains challenging because the coagulation cascade is dynamic and depends on the interplay of several factors, including primary hemostasis, platelet plug formation, secondary hemostasis, thrombin generation, and fibrinolysis. Viscoelastic coagulation tests (TEG®) are designed for rapid, global hemostatic assessment that closely mimics *in vivo* hemostasis by continuously monitoring the clotting process through initiation, amplification, propagation, and conclusion via fibrinolysis. It also serves to guide the use of related pharmacological agents such as Warfarin, NoVo Seven, Bivalirudin, tPA, tranexamic acid, etc.

The prothrombotic state of T2DM can be classified as an abnormality in platelet and fibrinolytic activity as well as coagulation factor levels. TEG can be considered a point-of-care test (POCT) performed in approximately 20 minutes. Clinical studies using TEG have largely been conducted in acute settings such as organ transplantation, perioperative coronary artery bypass grafting, hepatic surgery, trauma management, obstetric procedures, and massive transfusions. It has also been investigated as an early predictor of disseminated intravascular coagulation in septic shock patients. However, as noted, it has not been routinely applied to T2DM patients. Therefore, this study aims to detect hemostatic abnormalities in association with glycemic levels and diabetic foot subtypes (ulcerated vs. non-ulcerated) among T2DM patients using kaolin-activated TEG, even in the presence of anticoagulants such as acetylsalicylic acid and/or enoxaparin.

Numerous studies have linked acute hyperglycemia with thrombotic events such as myocardial infarction, stroke, and

venous thromboembolism. These conditions, alongside acute hyperglycemia, are risk factors for the secondary hemostatic hypercoagulability detected by TEG. Chronic hyperglycemia can increase blood levels of fibrinogen and other clotting factors such as FVII, FVIII, FIX, FXII, and vWF. Upregulated coagulation factors can result in a stronger, denser, and structurally altered clot in patients with chronic hyperglycemia compared to healthy controls, requiring longer fibrinolysis times. The TEG method has several limitations. It is less specific in detecting isolated platelet abnormalities. Primary hemostasis is represented in TEG® by the MA value, which is influenced by both platelet function and fibrinogen activity (Arsana et al., 2022) [4]. The advantage of TEG lies in its capacity to evaluate interactions among all components of the coagulation process including platelets, fibrin, clotting factors, and thrombin, while providing information regarding clot quality. With this methodology, it is also possible to distinguish whether bleeding is due to failed surgical hemostasis, platelet dysfunction, abnormalities in coagulation proteases or their inhibitors, or excessive early fibrinolysis. The TEG method is performed on whole blood samples and provides an accurate, comprehensive overview of the patient's coagulation status. The trace is based on measuring the physical characteristics of clot formation up to clot completion. Once coagulation begins, TEG comprehensively records the entire clotting process observed in whole blood samples, reflecting the complete coagulation profile and recording nearly 20 parameter values visualized as curved tracing lines (Figure 1). The primary TEG parameters are reaction time (R), clot formation time (k) α angle, maximum amplitude (MA), and lysis at 30 minutes (Ly30) (Volod et al., 2022) [5].

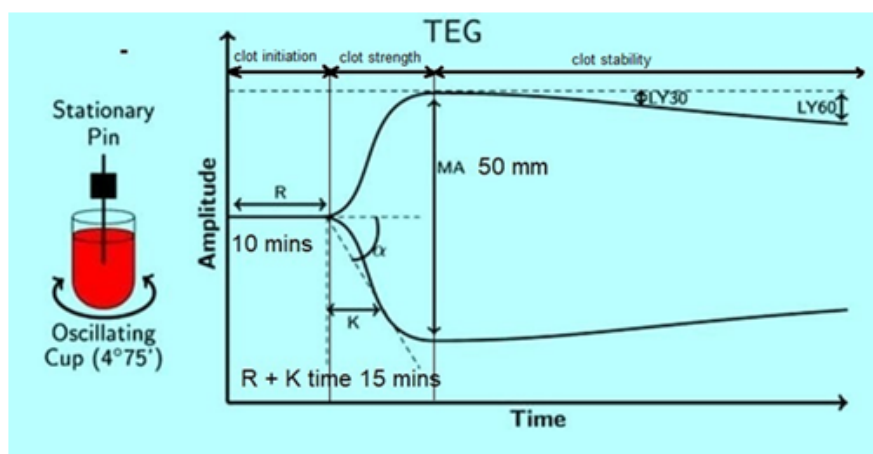


Figure 1: Schematic diagram of the TEG trace. TEG parameters illustrate the functional activity of clot initiation, kinetics, maximum strength, and clot stability.

In addition to TEG profiling and fibrinogen levels, we performed routine platelet counts, CRP (C-Reactive Protein), PCT (Procalcitonin), and ESR (Erythrocyte Sedimentation Rate) assays on the study cohort. This allowed us to investigate the correlation between TEG parameters and inflammatory/infectious markers, as

well as their diagnostic and predictive value.

k time and α are considered reliable surrogates for fibrinogen levels because they are measured during the propagation phase of coagulation; moreover, MA represents another fibrinogen

surrogate because its measurement reflects a combination of fibrin polymerization and thrombin-mediated platelet activation [6].

We hypothesized that kaolin-TEG parameters, such as kinetic time(*k*), α angle and/or maximum amplitude (MA), could accurately diagnose both moderate (Fib >400 mg/dL) and severe hyperfibrinogenemia (Fib >600 mg/dL) (reference range:200-400 mg/dL). We examined whether Receiver Operating Characteristic (ROC) curve analysis of *k* time, α angle and MA could diagnose moderate or severe hyperfibrinogenemia. The area under the ROC curve (AUROC) was calculated for each TEG parameter with a 99% bootstrap confidence interval (CI). In addition, ROC analysis was used to estimate optimal cut-offs for diagnosing moderate and severe hyperfibrinogenemia by maximizing sensitivity and specificity. Multiple investigations have shown that plasma fibrinogen levels <1.5 g/L correlate strongly with an increased risk of bleeding (Figure 1) [7,8]. Conversely, there is no clear association between free-flap thrombosis rates and elevated plasma fibrinogen levels [3,9]. Coagulation factor deficiency frequently results from anticoagulant administration. In some studies, prothrombin time (PT) and kaolin-activated TEG R-time values were within the normal range in nearly half of cases. Other TEG parameters (*k*-time, α -angle, MA) remained almost entirely within normal ranges [9].

Materials and Methods

In this study, we investigated the clinical value of each thromboelastography (TEG) index on the prognosis of infected and non-infected diabetic patients. TEG was performed using the CFMS LEPU-8800 Thromboelastography Analyzer (Lepu Medical Technology Company, Beijing, China) available in our facility, Analysis Laboratory, using blood collected in 3.2% sodium citrate tubes (BD Vacutainer, 4.5 mL; BD, Franklin Lakes, NJ). For study purposes, we collected the following TEG parameters: reaction time (R-time, minutes), *k* time (minutes), α angles (degrees), MA (mm) and lysis at 30 minutes (%). TEG assays not performed within 15 minutes of standard coagulation tests were excluded from analysis. Furthermore, sample analysis was adjusted for patient core temperature, as temperature variations significantly influence coagulation kinetics. This clinical study enrolled 165 patients as a representative sample of 288 patients (5% margin of error, 95% CI, confidence level 4.99, SD 50%) treated at our center for stage II-IV Chronic Obstructive Arteriopathy in 2022.

This prospective clinical study was approved prior to enrollment by the Institutional Review Board. Formal Local Ethics Committee authorization was not required because no investigational drugs or chemical agents were administered; the study relied solely on the analysis of routine admission hematological data. Informed consent for research participation was obtained from all patients. Between January and December 2024, 121 patients with Type 2 Diabetes Mellitus (T2DM) were enrolled: 72 patients without diabetic foot ulcers (DF) (mean age: 70.61±10.57 aa), 49 patients

with diabetic foot ulcers (DFU) (mean age: 67.64±9.74 aa), and 44 non-diabetic patients comprising 30 unrelated non-diabetic controls without ulcers operated on for other conditions (NP) (mean age: 61.9±20.68 aa) and 14 non-diabetic patients with ulcers (WDFU) (mean age: 64.64±15.41 aa). Twenty apparently healthy, non-operated subjects were included as a control group (C), consisting of 10 males (mean age: 44.5±14.37 aa) and 10 females (mean age: 43.4±8.75 aa) (Mean values: Blood Glucose: 93.20±8.51 mg/dL; HbA1C: 38±0.46 mmol/mol; CPR: 2.5±1.46 mg/L; ESR: 17.9±10.44 mm/h). Patients received no antifibrinolytics or other procoagulant drugs. Blood samples were collected via venipuncture into a 3.2% buffered sodium citrate PET tube with a 1:9 citrate-to-blood ratio (BD Vacutainer, 4.5 mL). Additional tubes were drawn for routine tests, yielding a total of 20 mL of blood per patient. Citrate tubes were gently inverted several times to ensure thorough mixing. Clotted specimens, indicative of overfilling or improper handling, were discarded. For TEG processing, unclotted samples were considered stable and usable for up to 2 hours at room temperature. Patients met the 2012 American Diabetes Association (ADA) diagnostic criteria for T2DM and the Wagner classification criteria for DF (Crisci, 2025) [10]; patients with Wagner grade ≤were defined as mild DF (DF), whereas Wagner grade >1 was designated as severe DF (DFU). Patients on acetylsalicylic acid discontinued treatment on the morning of admission, without subcutaneous low-molecular-weight heparin substitution unless severe predictable complications arose. Exclusion criteria comprised: type 1 diabetes, gestational diabetes, secondary diabetes, acute diabetic complications (e.g., diabetic ketoacidosis, hyperosmolar hyperglycemic state), concurrent acute/chronic infections, trauma, combined cardiac, hepatic, or renal failure, arterial/ venous embolism, cerebrovascular events, autoimmune rheumatic diseases, hematological disorders, malignancies, and use of medications directly impacting coagulation (e.g., exogenous fibrinogen, systemic steroids/hormones, antiplatelet agents, anticoagulants). All tests were blinded and performed in our clinical facility's biochemistry laboratory. Antiplatelet, antithrombotic, and anticoagulant therapies were maintained up to the day before admission due to thrombotic risk, as low doses of acetylsalicylic acid or enoxaparin do not significantly alter standard TEG parameters [11]. Indeed, previous studies showed that thromboelastogram analysis failed to demonstrate significant differences between baseline and 1-week parameters at a significance level of $p=0.05$ (Mayne 2007) [11]. Only a non-significant decrease in Maximum Amplitude was consistently observed between pre- and post-aspirin samples ($p=0.09$). Hence, no significant baseline distortion occurs in these patients on TEG [12].

Paracetamol (Paracetamol, B. Braun Melsungen AG, Germany) 1.0 g four times daily combined with non-steroidal anti-inflammatory drugs twice daily was administered for multimodal postoperative analgesia (Vanags et al., 2020) [9]. Per hospital guidelines, postoperative thromboprophylaxis consisted of enoxaparin 40 mg (Clexane®, Sanofi-Aventis SA, Spain) once daily

starting on postoperative day 1 for all enrolled patients. Blood samples were collected for TEG evaluation preoperatively and 48 hours postoperatively.

R. reaction time (minutes): An elevated or prolonged R value (>8 minutes) indicates clotting factor deficiency, hemodilution, heparin presence (anticoagulant effect), or severe hypofibrinogenemia. A shortened R time (<4 minutes) reflects hypercoagulability requiring anticoagulation.

K. (clot formation time): Reflects clot kinetics and is closely linked to platelet function, plasma factors, and fibrinogen. An increased k value indicates delayed clot formation, whereas a reduced value indicates hypercoagulability (normal range: 1-3 min). k value is primarily governed by fibrinogen levels.

Alpha angle: α angle increases with enhanced platelet and fibrinogen activity and decreases with anticoagulants or platelet inhibitors. The reference range is 47 to 74° (deg). Fibrinogen levels are the primary determinant of this angle.

MA. Maximum Amplitude (mm): Measures maximum clot strength, fundamentally dependent on platelet-fibrin interactions. The reference range is 55 to 73 mm. It reflects platelet function (80%) and fibrinogen contribution (20%). MA is considered the most sensitive thromboelastography parameter for evaluating platelet function. A low MA value indicates diminished clot strength resulting from hypofibrinogenemia, thrombocytopenia, or platelet dysfunction [11-13].

Critical aspects of TEG®

Recognized sources of error on TEG traces include: 1) a false k=0 in severe hypocoagulable states mimicking hypercoagulability; 2) artifact spikes caused by mechanical vibrations in the testing environment; 3) improper cup placement yielding a "beak-shaped" artifact; 4) falsely elevated MA due to sample evaporation during runtime; 5) failed auto-calibration prior to running a sample resulting in apparent hypercoagulability; and 6) delayed clot initiation resulting from reconstituted calcium chloride older than 24 hours [14].

In summary "*the lower the R and k values and the higher the α angle, the greater is the blood coagulability*" [14].

Analytical procedures of TEG®

Hemostatic profiling was performed on whole blood collected in sodium citrate tubes (approximately 4 mL, 109 mmol/L citrate mixed 1:9 with whole blood). Tubes must be polypropylene (PET). Complete analyses were conducted using the CFMS LEPU-8800 Thromboelastography Analyzer (Lepu Medical Technology Company, Beijing, China), strictly following the manufacturer instructions.

TEG simulates venous shear blood flow using an oscillating cup. Approximately 340 μ L of citrated whole blood is placed into the cup and mixed with kaolin. A pin suspended by a torsion wire

is immersed into the blood and coupled to an electromagnetic transducer. The cup oscillates alternately (rotation angle 4.75°, 10 seconds per cycle). Clotting generates fibrin strands linking the cup and pin, transmitting torque to the pin. This torque is transduced from initial platelet aggregation and fibrin polymerization up to maximum clot strength. The tracing peaks at maximal elasticity and subsequently narrows as fibrinolysis occurs. Clotting completes in approximately 30 minutes, while fibrinolytic assessment should extend for 1 hour. All subjects were classified as normocoagulable or hypercoagulable across study groups (NP, DF, DFU, WDFU, C) based on preoperative and postoperative fibrinogen levels (<400, 401~600, >600 mg/dL). When all indices fall within reference limits, TEG indicates normal coagulation and fibrinolysis. Tests were marked complete once all numerical values registered on the TEG software. In samples failing to form a clot where no values were generated, the run was terminated at 60 minutes and discarded. TEG parameters can predict both coagulopathy and thrombotic complications. The use of TEG-MA, TEG R-time, TEG-k and TEG α -angle in patients suffering from cardiac diseases is predictive of coagulopathy and thromboembolic events [15-17].

Few studies have examined the utility of TEG in diabetic patients undergoing general surgery; however, TEG/ROTEM implementation in diabetics enhanced coagulopathy detection and enabled early sepsis prediction [15]. To date, no study has evaluated TEG parameters in relation to moderate or severe hyperfibrinogenemia in Diabetic Foot disease. In summary, the initial flat line represents the initiation phase of coagulation with thrombin generation (Figure 1). As thrombin cleaves fibrinogen into fibrin and the clot develops, trace amplitude increases progressively. The thromboelastogram thus tracks thrombin generation, fibrin polymerization, whole-blood clot consolidation, and subsequent fibrinolysis.

Data Analysis and Intergroup Correlation

TEG parameters, fibrinogen, Plt, ESR, and CRP values were analyzed statistically. Patients were stratified by hyperfibrinogenemia status (Fib >400 mg/dL) upon admission and sub-classified by admission diagnosis (NP, C, DF, DFU, WDFU). Data distribution normality was assessed using the Shapiro-Wilk W test. Normally distributed data are presented as mean $\pm$ standard deviation, whereas non-parametric continuous variables are reported as median and interquartile range (IQR at 25%).

Given non-normal distributions, non-parametric statistical tests were applied. Scatter plots of fibrinogen levels and TEG parameters were generated to evaluate bivariate relationships [Spearman's rank correlation coefficient ρ (*rho*)] calculating a ρ for each model. AUROC analysis evaluated predetermined TEG parameters; k-time, α angle and MA for hyperfibrinogenemia diagnostic accuracy across patients groups [4]. For each parameter, AUROC was computed with a 99% bootstrap confidence interval (CI) (1 o <1). Having traced the ROC curves, the point on each curve minimizing the distance from the upper left corner of the graph (sensitivity=1,1; specificity=0) was used to determine the optimal

hematic fibrinogen levels, for each examined group. p values less than 0.05 were considered statistically significant.

Correlation strength was classified as perfect (± 0.59), poor ($\pm 0.29 \sim \pm 0.1$) or absent ($\leq \pm 0.1$) (Schober et al, 2018) [18]. Correlation strength was calculated, using also absolute p values, as such: $0 \sim 0.19$ was defined as very weak, $0.20 \sim 0.39$ as weak, $0.40 \sim 0.59$ as moderate, $0.6 \sim 0.79$ as strong and $0.8 \sim 1$ as very strong correlation (Aklogu, 2018) [18].

Key study questions included:

1. Does TEG-MA predict platelet counts in diabetic patients? It can be evaluated by correlating TEG-MA with platelet count (Plt).
2. Can TEG-MA, TEG-k and TEG- α angle predict the onset of

Diabetic Foot and/or Diabetic Foot Ulceration? It can be evaluated by correlating these indices with preoperative and postoperative fibrinogenemia across the four pathological cohorts.

Version 6.0 of the Santon-Glantz 2007 Statistics for Biomedical Disciplines was used for general statistical calculations; GraphPad Prism 5 was used for plotting graphs. MedCalc® Statistical Software version 23.2.7 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2025) was used to analyze and compare ROC curves of TEG parameters within groups. Cut-off sensitivity and specificity were compared using McNemar exact test.

Sample screening processes, data collection and analysis are shown in Table 1, 2 and 3 and Figure 2-5.

Table 1: Median and IQR for non-parametric values in the groups under study. [Normal (NP/C), Diabetic Foot (DF), Diabetic Foot with Ulcer (DFU), Ulcer without Diabetic Foot (WDFU)].

WDFU										
	Age aa	Fibr.Pre.	Fibr.Post.	R	k	Angle α	MA	PCR	VES	PLT
Median	64.6	424.00	389.50	5.05	2.6	49.0	67.70	6.9	42.5	280.0
Q ₁	55.5	327.5	305.50	3.05	2.03	46.68	62.65	4.43	18.5	198.5
DFU										
Median	68.0	537.00	479.00	6.8	2.6	53.6	71.40	9.0	50.0	234.0
Q ₁	59.0	406.00	388.00	4.7	2.00	46.10	65.10	6.0	28.0	200.0
DF										
Median	72.5	426.00	380.00	6.5	2.40	54.70	67.30	6.0	33.5	229.0
Q ₁	62.0	352.00	330.70	3.6	1.90	48.80	61.20	5.35	20.0	186.2
C.										
Median	41.0	337.50	---	4.45	2.60	53.30	72.40	2.3	14.5	232.5
Q ₁	36.5	283.00	---	2.0	1.50	50.25	69.17	1.5	10.0	213.5
N.P.										
Median	64.0	371.00	361.00	3.9	2.15	57.20	70.40	6.0	28.0	224.0
Q ₁	50.0	296.00	281.00	2.73	1.60	51.23	63.48	2.35	22.0	194.7

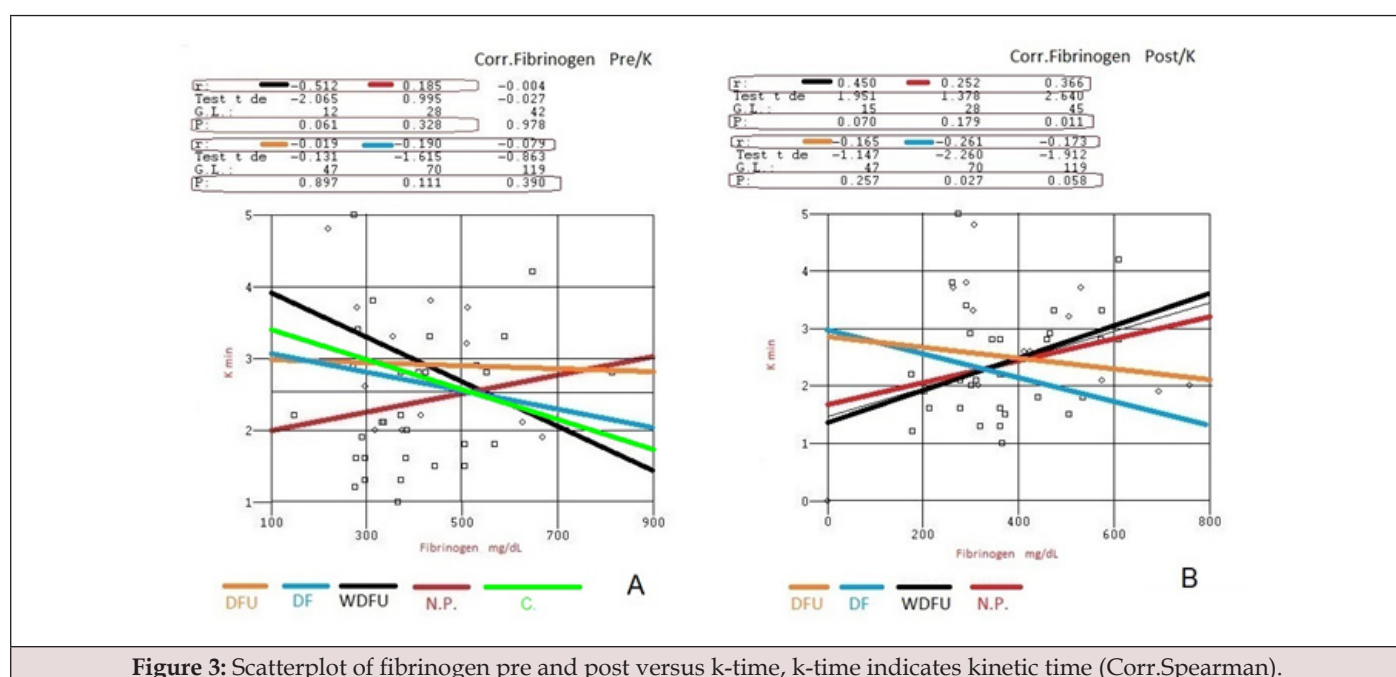
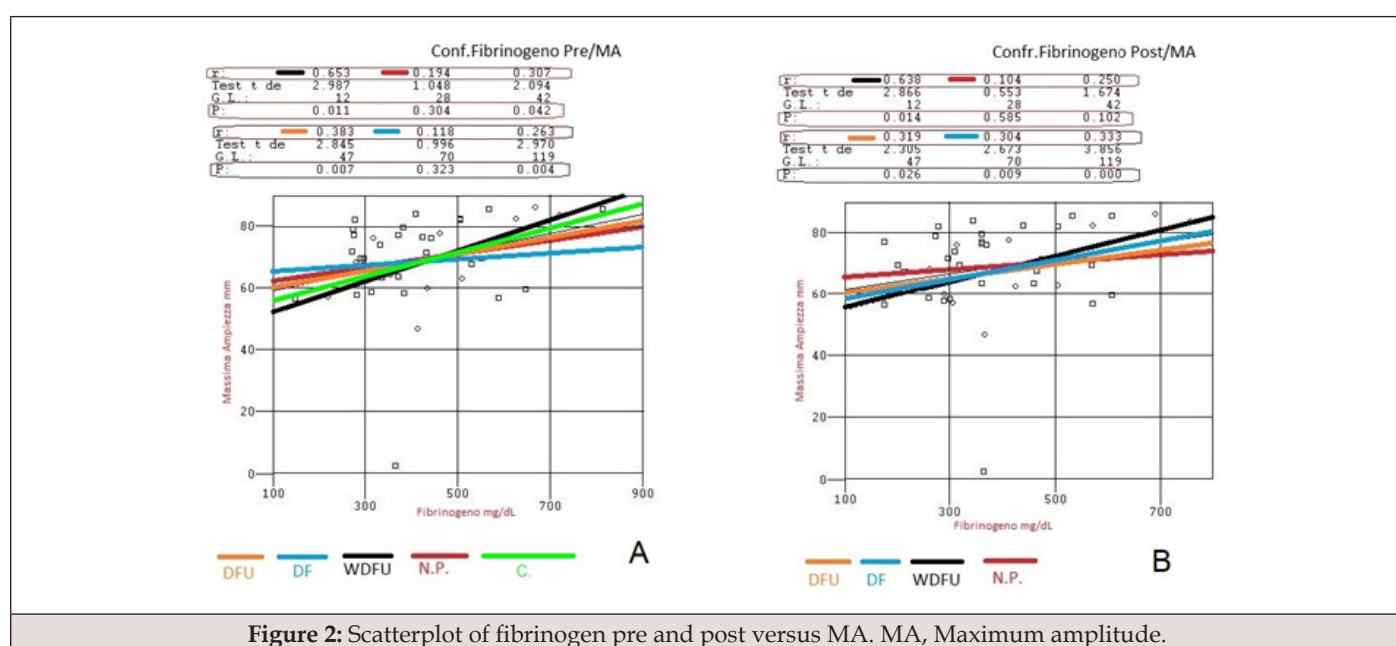
Table 2: Correlation of TEG parameters (ρ) with baseline and post-intervention fibrinogenemia of each experimental group after excluding the effect of age.

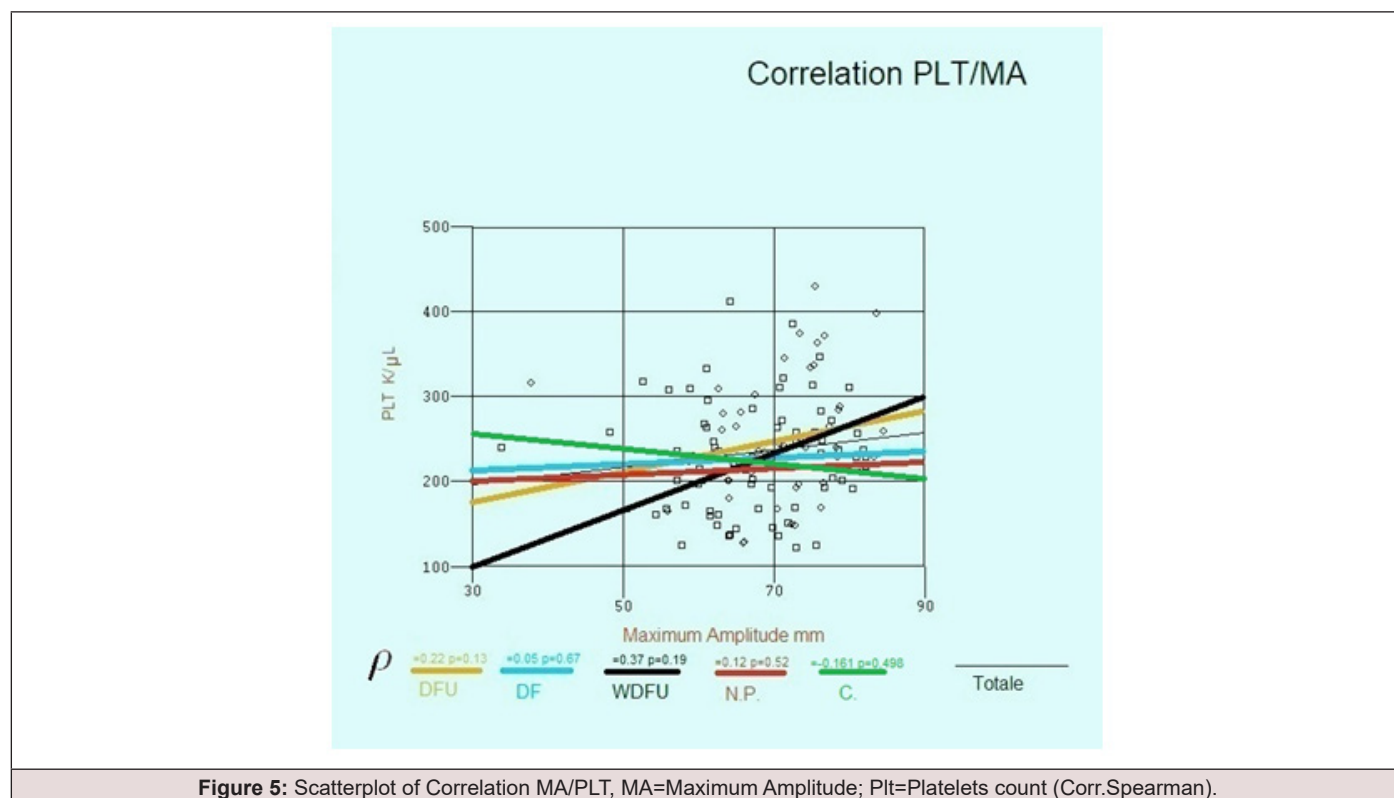
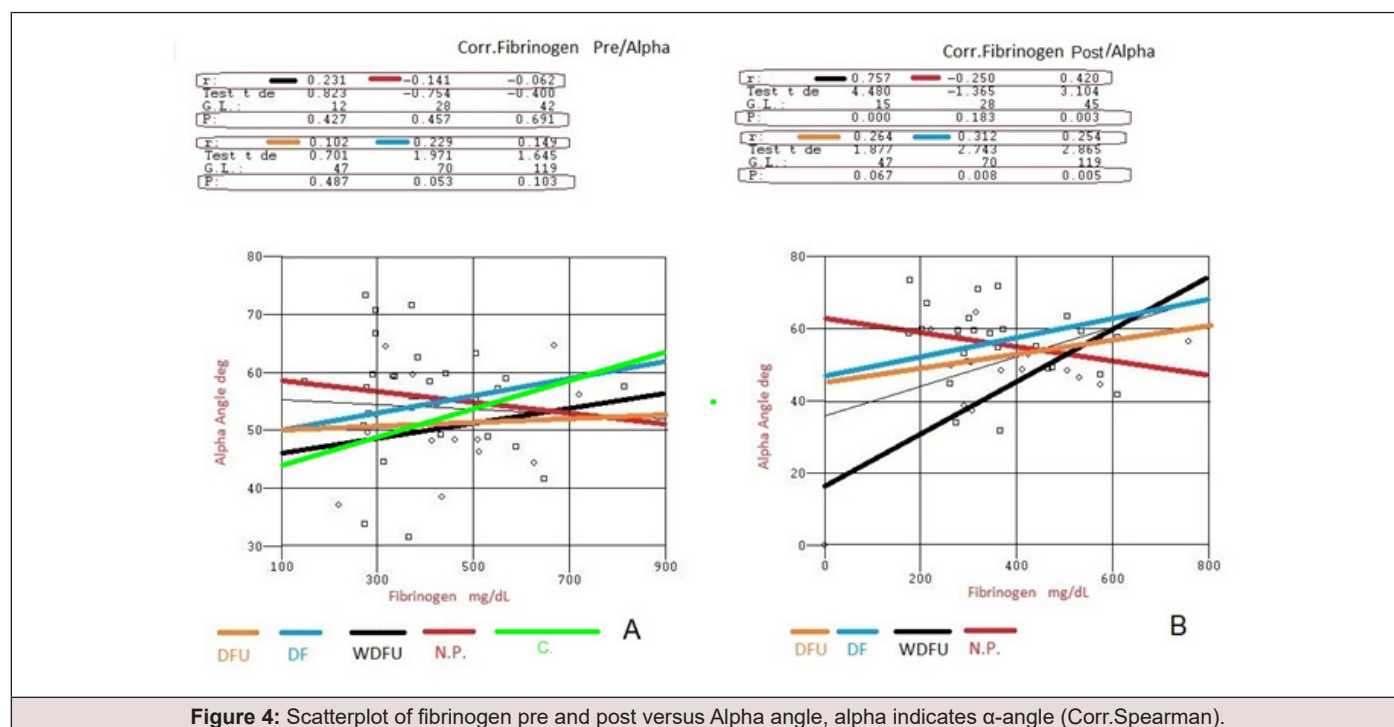
Analisi	N.P.	D.F.	D.F.U.	W.D.F.U.	C.	Corr. di Bonferroni
Pre/MA	0,19	0,12	0,38 ^①	0,65 ^①	0,59 ^①	0,025
Post/MA	0,10	0,30 ^①	0,32 ^①	0,64 ^①		0,017
Pre/ α	-0,14	0,22	0,1	0,23	0,38	>0,05
Post/ α	-0,25	0,31 ^①	0,76 ^①	0,31		0,025
Pre/K	0,13	-0,19	0,02	-0,51 ^①	-0,38	0,05
Post/K	0,25	0,31 ^①	-0,26 ^①	-0,45		0,025
Pre/R	0,3	0,11	0,22	-0,22	0,34	>0,05
Post/R	0,34 ^①	-0,02	0,04	-0,2		0,05

$p \leq 0.05$;

Table 3: Correlation of clinical-chemical parameters (ρ) with basal and post-intervention Fibrinogenemia with Plt, CRP and VES and of Max Amplitude with PLT of each experimental group after excluding the effect of age.

Analisi	N.P.	D.F.	D.F.U.	W.D.F.U.	C.	Corr. di Bonferroni
Pre/PCR	0,53 ^①	0,51 ^①	0,44 ^①	0.25	0.61 ^①	0,017
Post/PCR	0,45 ^①	0,36 ^①	0,43 ^①	0.46 ^①		0,0125
Pre/VES	0,67 ^①	0.46 ^①	0.70 ^①	0.70 ^①	0.32	0,0125
Post/VES	0,50 ^①	0,43 ^①	0.63 ^①	0.78 ^①		0,0125
Pre/PLT	0,19	0.11	0,40 ^①	0.05	-0,32	0,05
Post/PLT	0.14	0,2	0.1	0.75 ^①		0,05
MA/PLT	0,12	0.05	0,22	0.37	-0,076	>0.05





Results

Across all groups, TEG parameters deviated from normality under the Shapiro-Wilk W test; hence, data are presented as Median and Q1 (Quartile at 25%), depending on the considered group and parameters in exam (Table 1).

38% of patients (n=63) had at admission normal fibrinogen (<400 mg/dL), while 41% (n=68) shown fibrinogen level between 401 e 600 mg/dL; lastly 21% (n=34) had fibrinogen >600 mg/dL.

No patient had low fibrinogen levels (<190 mg/dL).

Nel gruppo C (Controllo) $\frac{1}{5}$ circa (il 15%, 3 su 20) dei pazienti hanno riportato fibrinogenemia tra 400 e 600 mg/dL, lo 0% >600 mg/dL e l'85% <400 mg/dL.

The primary outcome was AUROC for diagnosing hyperfibrinogenemia (defined as fibrinogen >400 mg/dL). Sensitivity analysis was performed also for severe hyperfibrinogenemia (>600 mg/dL), median HbA1c was higher in ulcerated diabetic foot than non-ulcerated (median 7.2 mmol/mol, IQR 6.3 for DFU vs. median 6.1 mmol/mol, IQR 5.4 for DF). Median CRP and ESR were highest in DFU (CRP: 9.0 mg/L; ESR: 50 mm/h; Table 1), demonstrating specificity for ulceration.

Four key preoperative TEG parameters (R, MA, k, α) were compared across cohorts (Table 2 and Figure 2-4) against baseline and postoperative fibrinogen, CRP, ESR, and Plt (Table 3).

Kruskal-Wallis and χ^2 tests showed statistically significant correlations between pre-/ postoperative fibrinogen and CRP/ ESR across all groups ($p=0.000$). A strong correlation was found between postoperative Fib and Plt in the WDFU group (Table 3). Preoperative fibrinogen was consistently higher than postoperative fibrinogen across all groups (Table 1), likely due to intraoperative hemodilution.

Spearman test showed a strong correlation (ρ) between TMA (Time to MA) and pre-/postoperative Fib in WDFU (0.65 and 0.64, $p<0.05$ and a substantial correlation between postoperative α angle and Fib in DFU group (0.76, $p<0.05$). A moderate negative correlation was noted between pre-/postoperative Fib and k time in WDFU group (-0.51 and -0.45, $p<0.05$) and a weak negative correlation in DFU (-0.26 $p<0.05$) Conversely, postoperative Fib correlated weakly positively with α -angle and k (0.31 $p<0.05$, Table 2, Figure 4B) in DF. Pre- and postoperative Fib correlated weakly positively with MA in DFU (respectively 0.38, 0.32, $p<0.05$) (Table 2, Figure 2A e B), indicating a thrombotic tendency in ulcerated (both in diabetic and non-diabetic patients) cohorts.

A moderate correlation was observed between baseline fibrinogen and MA in Control group C (0.59 $p=0.006$) (Table 2 and Figure 2A) and a weak correlation (0.38 $p=0.09$) with α angle (Table

2 and Figure 4A); lastly, a non-significant weak negative correlation (-0.38 $p=0.09$) was found with Clot Formation Time (k) (Table 2 and Figure 3A).

A weak, non-significant correlation was found between MA and Platelet Count (Plt) exclusively in ulcerated groups (DFU: 0.22; WDFU: 0.37) (Table 3, Figure 5). Across all cohorts, moderate-to-strong correlations were observed between CRP/ESR and pre-/ postoperative Fib (Table 3) ($p<0.05$). No pathological group demonstrated a correlation between Reaction Time (R) and pre-/ postoperative Fib (Table 2). Only in control Group C a weak, non-significant correlation was found.

Across all cohorts, Procalcitonin (PCT) was found to be ≤ 0.5 ng/dL, pertanto non ha avuto significato diagnostico and yielded no diagnostic utility; only 1% exceeded 0.5 ng/dL with a mean of

1.04 ng/dL (range: 0.52-2.5) [18].

Xuan e al., 2021 [19] studies demonstrated that, concerning TEG parameters, k, α angle and MA in deceased patients group was lower in a statistically significant way compared to non-deceased patients ($p<0.05$). Differently, in our current work, authors found that median k values (min) are lower in control group, compared to groups of patients without and with ulceration (diabetic or non-diabetic) (Table 1). α angle values were highest in control group, whereas R and MA (mm) were highest in DFU (Table 1).

Pre-operative Fib mean values $\pm$ standard deviation were significantly higher in DFU of grade higher than 1 compared to DF of grade lesser than 1 (545.0 ± 165.0 mg/dL versus 433.5 ± 138.3 mg/dL; $p=0.0001$). Postoperative blood fibrinogen remained higher in DFU than DF (503.9 ± 150.9 mg/dL versus 394.5 ± 120.7 mg/dL; $p=0.0001$) though medians dropped postoperatively in both DFU (537.0 vs 479.0 mg/dL) and DF (426.0 vs 380.0 mg/dL) (Figure 6, 7) compared to group C. Confirming the authors findings, shown in a previous work⁹, fibrinogen correlated with CRP, neutrophil count, ESR, and leukocyte count, while monocyte count differed significantly between non-diabetics patients with vs. without ulcers (0.41 vs 0.29 k/ ρ L; $p=0.000$) and between DF and NP (0.39 vs 0.29 k/ ρ L; $p=0.000$) [20].

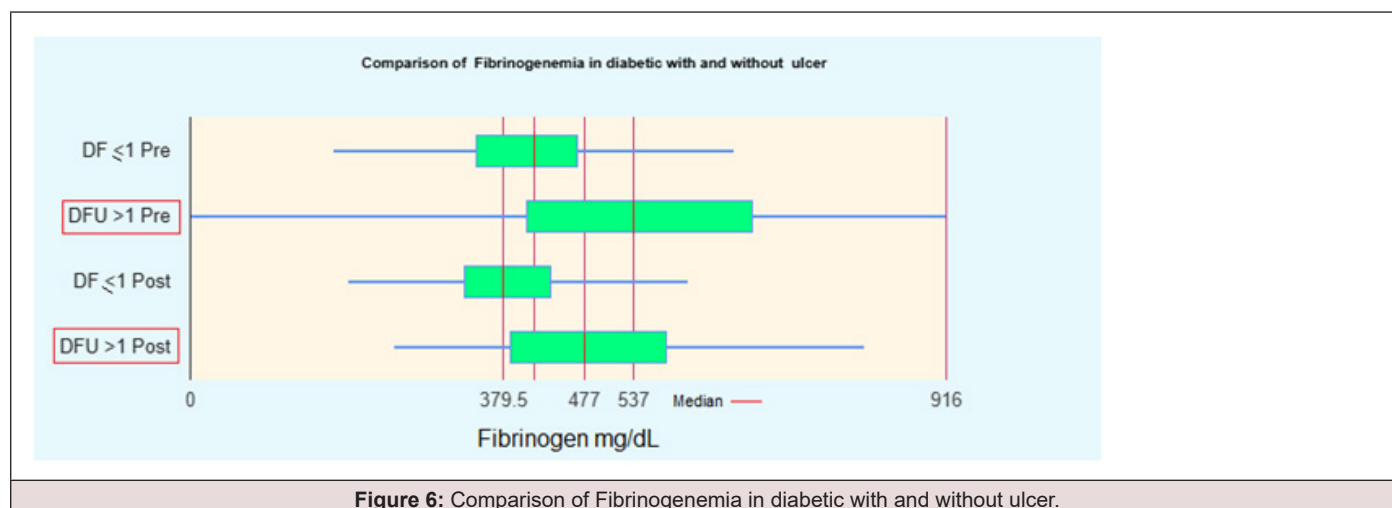


Figure 6: Comparison of Fibrinogenemia in diabetic with and without ulcer.

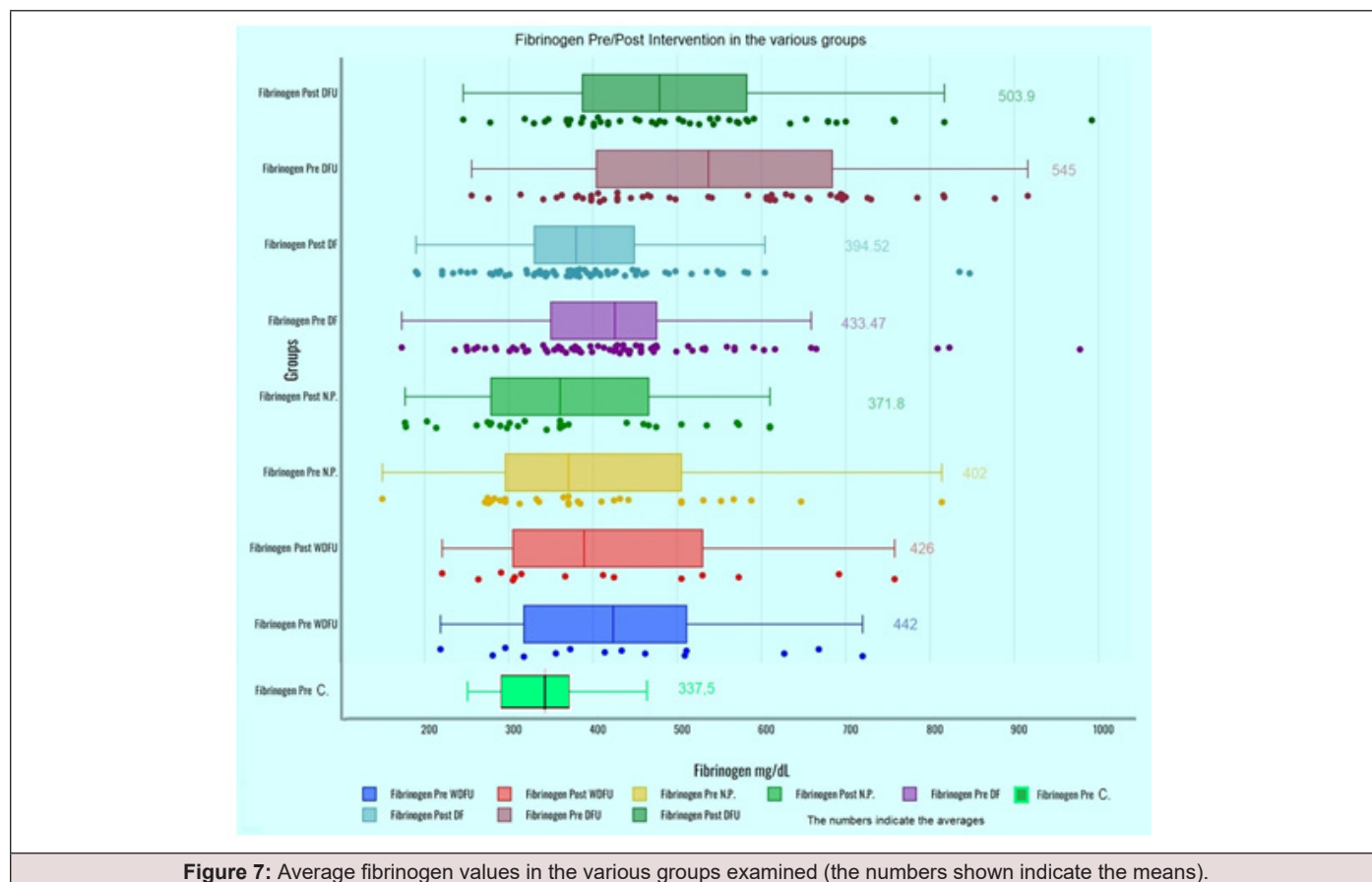


Figure 7: Average fibrinogen values in the various groups examined (the numbers shown indicate the means).

Thus, neither monocytes nor HbA1c serve as specific biomarkers for diabetic foot ulceration risk, functioning merely as general type 2 diabetes markers. In contrast, fibrinogenemia, its pre/post-operative ratio, TEG α angle and k values exhibit clear clinical significance regarding onset and ulcer development risk.

TEG® diagnostic results in patients with Fib >400 mg/dL

Median and mean pre- and postoperative Fib and TEG values for patients with Fib >400 mg/dL are reported in Table 4. Highest R, k-time, Angle- α , MA, Fib Pre- and Post- occurred in patients with Fib >600 mg/dL in DFU and DF, peaking in DFU (Figure 7).

Spearman correlation for patients with pre- and postoperative fibrinogen >600 mg/dL in DFU and DF was also considered, taking in account k-time, α angle and MA. (Figure 8). Results showed that preoperative Fib correlated strongly positively with k-time in DF ($\rho=0.69$ $p=0.09$) and weakly positively in DFU ($\rho=0.37$ $p=0.09$), while weakly negative correlating in DF post-operatively ($\rho=-0.33$ $p=0.47$) in a non-significant way (Figure 8 A, B). This shows that preoperative k (min) is a possible important marker of non-ulcerating diabetic foot.

Preoperative Fib correlated strongly negatively with α angle in DF ($\rho=-0.82$ $p=0.02$) and weakly negatively in DFU ($\rho=-0.26$ $p=0.24$), whereas postoperative Fib correlated strongly positively in

DF ($\rho=0.68$ $p=0.09$) and weakly positively in DFU ($\rho=0.25$ $p=0.25$) (Figure 8 C,D). Thus, preoperative α angle values are inversely proportional to baseline Fib but positive with postoperative Fib, highlighting the presence of non-ulcerated diabetic foot, with weak correlation in DFU.

Postoperative MA correlated strongly negatively with Fib ($\rho=-0.79$ $p=0.03$) ed è anch'esso indicatore di presenza di DF nei pazienti con Fib >600 mg/dL. serving as another indicator of DF in patients with Fib >600 mg/dL. None of these parameters alone were specific for ulceration, indicating only the presence of DF generally (Figure 8 F).

ROC analysis showed preoperative fibrinogen had the best diagnostic accuracy for both DF and DFU in patients with Fib =401-600 mg/dL (respectively: AUC=1.00; sensibility 100%; $z=n.v.$; $p<0.001$; and =0.818; sensibility 81.8%; $z=2.604$; $p=0.009$;) with a cutoff of respectively 499 (DFU) and 398 (DF) mg/dL. Post operation AUC in DFU patients (401-600 mg/dL) was 0.5; sensibility 50%; $z=0.00$; $p=1.00$; with a cutoff of 418 mg/dL. AUROC of k, α angle and MA in the same set of patients was found to be near chance level (=0.6).

In DF patients with preoperative Fib between 401 and 600 mg/dL ROC values of post-operative Fib, k, α Angle and MA, were respectively 0.818, 0.636, 0.64 and 0.626 with respective cutoffs of >499 mg/dL, >2.7 mm, ≤ 53.5 deg and 54,5 mm.

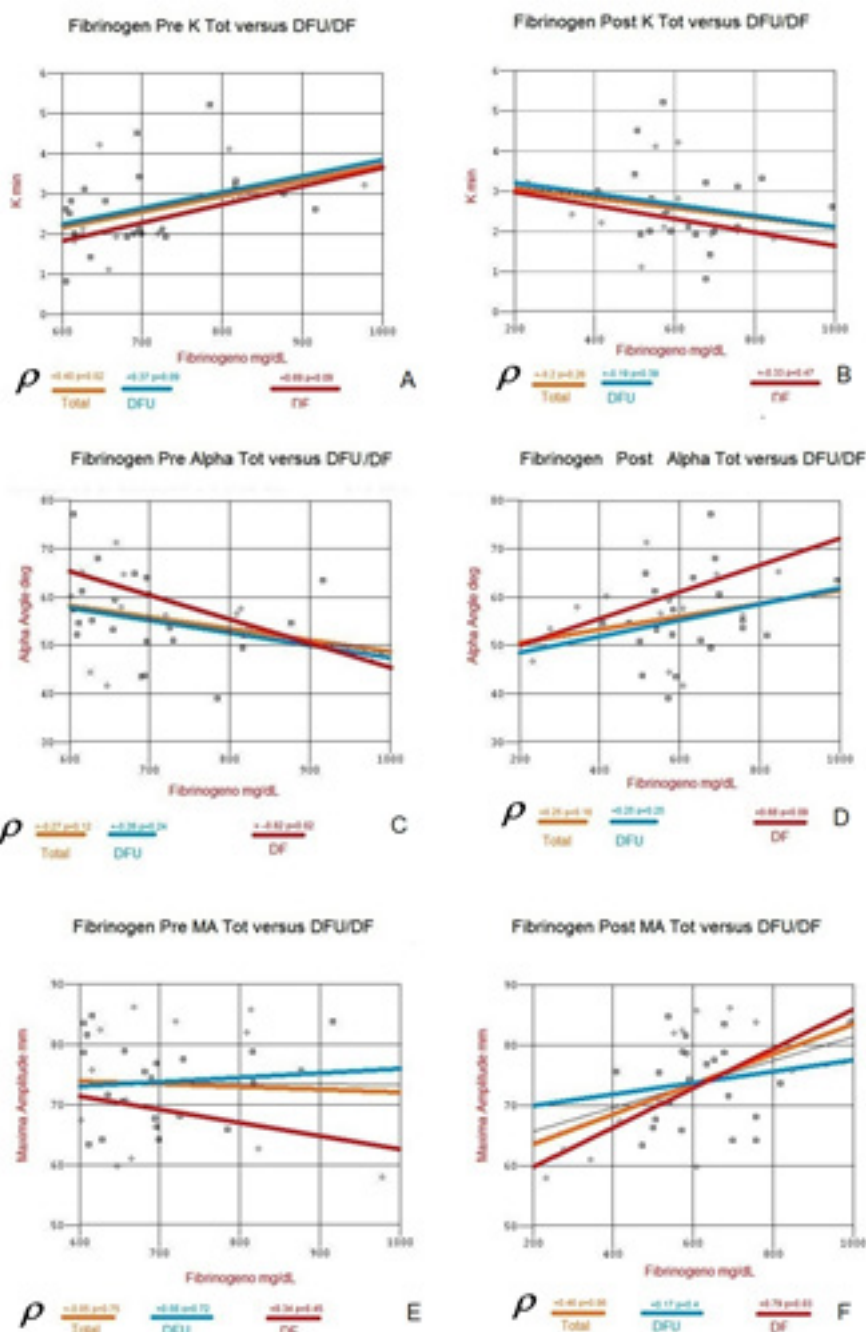


Figure 8: Scatterplot of fibrinogen pre and post >600 mg/dL versus α -angle, k-time, and MA. k-time indicates kinetic time; MA, Maximum amplitude; Alpha, α -angle on DFU and DF Patients (Corr.Spearman).

In this group (33 patients) postoperative Fib was ≤ 3.54 g/dL (Youden) with optimal cutoff of ≤ 2.21 g/dL. In DFU patients, with preoperative Fib between 401 and 600 mg/dL (18 patients), cutoff was >3.98 g/dL, while with postoperative Fib, Youden cutoff was >4.18 g/dL; the optimal cutoff for ulceration risk is >4.51 g/dL.

Combining indicators in patients with preoperative Fib >600 mg/dL, in DF patients (7 p) and DFU patients (22 p), results shown

that α angle, k, pre operative Fib, had AUC of 1.00, sensibility and specificity of 100% $p<0.001$ (Figure 9A and B) and predicted progression from DF to DFU in a better way compared to other parameters, that is ulceration risk in diabetic foot, with a cutoff (Youden test) of respectively 54.5%, 2.8 mm and 6.34 g/dL. Post operative Fib cutoff (Youden) in patients with levels >601 mg/dL is >634 , with optimal cutoff of >7.57 g/dL (Figure 10).

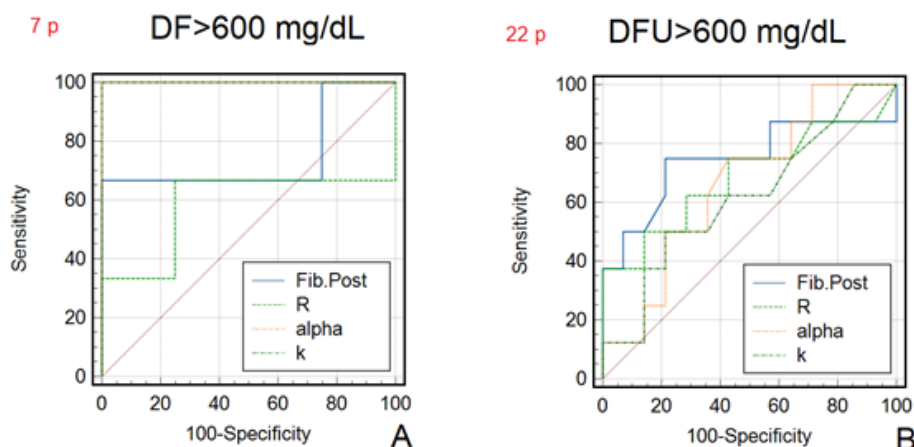


Figure 9: Delong test; Area under the curve (AUC) DF (A) and DFU (B) >600 mg/dL of Fibrinogen Post-intervention, Alpha angle, k and R.

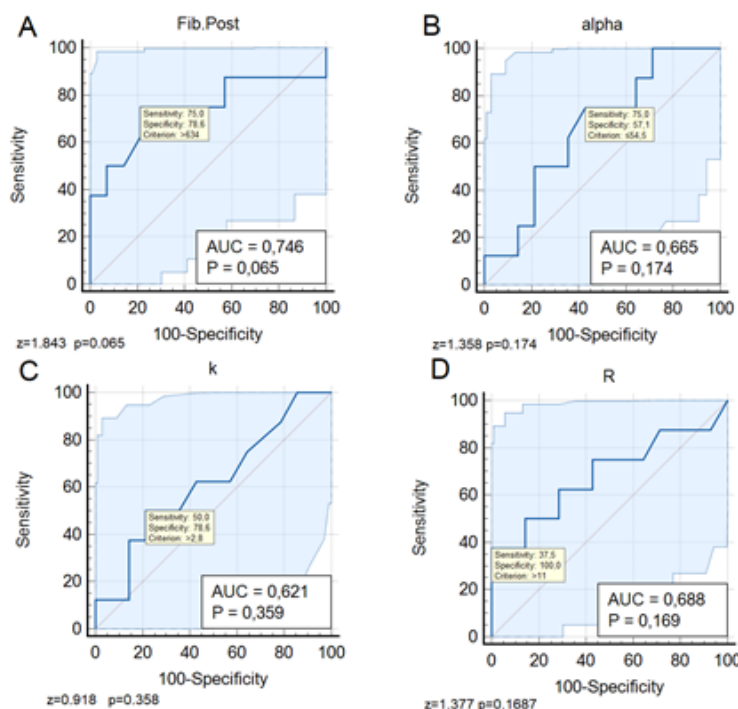


Figure 10: Area under the curve (AUC) DFU >601 mg/dL of Fibrinogen Post-intervention (A), Angle α (B), k (C) and R (D).

McNemar's exact tests for TEG parameter cut-offs in patients with Fib >400 mg/dL yielded: for pre and post operational Fib in DFU 401-600 mg/dL, $p=0.000$, $\chi^2=16.007$; in DFU >600 mg/dL, $p=0.07$, $\chi^2=3.291$; in DF 401-600 mg/dL $p=0.006$, $\chi^2=7.660$; in DF >600 mg/dL, $p=0.01$, $\chi^2=6.258$; k, Alpha Angle, R and MA in the same patients, comparing preoperation Fib 401-600 with >600 mg/dL, yielded: k $\leftrightarrow$ DF $p=0.045$, $\chi^2=4.005$; DFU $p=0.92$, $\chi^2=0.010$; α -angle $\leftrightarrow$ DF $p=0.006$, $\chi^2=7.660$; DFU $p=0.032$, $\chi^2=4.608$; R $\leftrightarrow$ DF $p=0.000$, $\chi^2=20.682$; DFU $p=0.000$, $\chi^2=27.507$; ; MA $\leftrightarrow$ DF $p=0.012$,

$\chi^2=6.258$; DFU $p=0.401$, $\chi^2=0.705$.

ROC for k-time, α -angle, R-time and MA, especially in DF, diagnosed with greater precision hyperfibrinogenemia >400 mg/dL preoperative (0.636, 0.64, 0.58 and 0.626 respectively); it must be said that, in kaolin-TEG k time is expressed in several minutes, while MA needs much more time.

Odds Ratio=1.8715 (I.C.95% 1.1342-3.0881); $z = 2.453$; $p=0.0142$;

Table 4: Median TEG Values in relation to Fibrinogenemia >400 mg/dL;

Fib	401-600 mg/dL						>600 mg/dL					
Group	R	k	Angle α	MA	Fib Pre	Fib Post	R	k	Angle α	MA	Fib Pre	Fib Post
WDFU	4.45	2.90	48.20	62.80	448.0	418.5						
N.P.	4.1	2.80	55.00	76.20	505.0	466.0						
DFU	4.9	2.35	51.60	66.20	437.0	441.5	6.85	2.55	54.50	74.85	692.0	587.5
DF	6.2	2.40	54.90	67.20	457.0	379.0	8.80	2.40	57.80	67.30	665.0	417.0

■ = non-representative values;

Relative Risk=1.2324 (I.C.95% 1.0362-1.4658); $z = 2.362$; $p=0.0182$;

This demonstrates that preoperative Fib >600 mg/dL, alongside α angle and k-time, serves as a significant marker for the evolution of ulcerative diabetic disease.

Discussion

TEG® is a modern method for evaluating coagulation, dynamically capturing the entire sequence from clot initiation through fibrinolysis. It is simple, rapid, and accurate, providing essential insights into global hemostatic status. Comprehensive

understanding of the underlying assay principles and operational competence minimizes analytical errors, the majority of which are preventable [21].

In particular, 1a TEG assesses the rate of clot development and overall clot strength, making it valuable for gauging bleeding risk, platelet dysfunction, clotting factor deficiencies, and hyperfibrinolysis in hyperthyroidism. Parker et al., 2012 demonstrated that surgical patients with an elevated functional fibrinogen-to-platelet ratio on TEG experienced a significantly higher incidence of thrombosis ($8/13 = 61.5\%$) (Figure 11) with sensitivity of 89% and specificity of 75% [22].

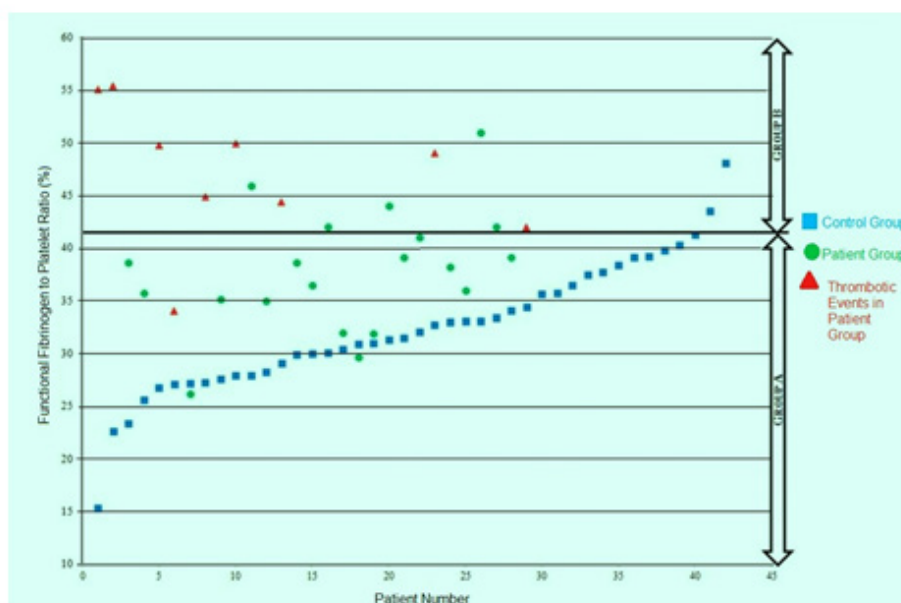


Figure 11: Graph showing the functional fibrinogen contributions of the patient group (green) compared to healthy controls (blue) as measured by TEG analysis. Patients who experienced thrombotic events are highlighted (▲) (from Parker et al. 2012 modified) [22].

Sustained hyperglycemia in type 2 diabetes could result in impaired endothelial structure and function, causing metabolic disturbances, and reducing nitric oxide availability, thus enhancing endothelin-1, angiotensin-II, and advanced glycation end-product production, and ultimately promoting systemic hypercoagulability.

k value and α angle primarily reflect fibrinogen and platelet function; a reduction of both levels suggests that increased k values shows an increased speed of clot formation. k value length is primarily influenced by Fib levels, while platelet function has a weaker influence. Factors that can influence k value length include

(1) anticoagulant drugs; (2) platelet defects and (3) coagulation factor deficits. α angle results from combined fibrin and platelet action at clot formation; α angle and k value are strictly correlated, reflecting clot adhesion, and the same factors can influence both α angle and k . In severely hypocoagulable states where amplitude fails to reach 20 mm, k cannot be calculated, making α clinically more important than k .

The results of this study showed that the combined model, in patients with type 2 diabetes mellitus, had a medium diagnostic effect (PCT was the indicator with the largest AUC, CRP was the indicator with the best sensitivity, and the TEG model had the best specificity).

This indicates that the blood of these patients is in a state of significant hypercoagulation and that they are therefore at increased risk of thrombosis and embolism.

In this study, we used TEG in combination with CRP and Fib to diagnose and assess ulcer risk in diabetic and non-diabetic patients, focusing on the correlation between TEG parameters. We highlighted that the quantification of fibrinogen levels, both pre- and 48-hour post-surgery, plays an important role in defining the risk of diabetic foot and/or ulcer development in T₂DM.

Even at baseline, the median values of pre-intervention fibrinogen, R, α , MA, and ESR were significantly higher in the DF and DFU groups than in the other groups. By analyzing the relationship between TEG-MA and platelet count (Plt), we highlighted that both diabetic (DFU) and non-diabetic (WDFU) ulceration showed a weak correlation ($\rho = 0.22$; $\rho = 0.37$) with a non-significant difference. This indicates that in the patients examined in this study, TEG-MA does not represent Plt concentration. In our opinion, it may be useful to perform the TEG test upon admission and at discharge because a thrombotic event can be predicted in these patients; hence it can be used to guide potential anticoagulant therapy given the presence of hyperfibrinogenemia in diabetic patients.

Autor's found that median k values were lower in the N.P. control group and also, to a lesser extent, in the C group, compared to the groups without and with ulcers (diabetic and non-diabetic). The mean $\pm$ SD and median preoperative fibrinogen values were significantly higher in patients with diabetic foot ulcers (DFUs) than in patients with DFs. The median postoperative blood fibrinogen values were also higher in patients with DFUs than in patients with DFs, but lower than the preoperative values. This indicates that preoperative fibrinogen values are specific to patients with diabetic foot ulceration. A correlation between preoperative fibrinogen levels and Time to DM in the diabetic and non-diabetic ulcer groups demonstrates a tendency for patients in these two groups to develop thrombosis, demonstrating that the mere presence of ulceration predisposes to thrombosis and, furthermore, a high DM value (>65 mm) predicts the onset of an ulcer.

Based on the optimal estimated balance between sensitivity and specificity determined in our study, we suggest that an α angle

$>55^\circ$, k -time >2.4 minutes, $R >5$ minutes, and $MA <55$ mm can be used to diagnose a baseline fibrinogen level between 400 and 600 mg/dL. Our results indicate that, instead, an α angle $>60^\circ$, k -time >2.8 minutes, $R >11$ minutes, and $MA \leq 79$ mm could be used as optimal estimated cutoffs to detect severe hyperfibrinogenemia (>600 mg/dL) and, consequently, a tendency to ulceration in diabetic foot.

The k (min) and α angle ($^\circ$) values assessed at patient admission are, however, good indicators of a diabetic foot that is not prone to ulceration. The results of this study demonstrate that patients with preoperative fibrinogenemia >601 mg/dL have cutoffs for α , k , and PreFib of 54.5° , 2.8 mm, and 6.34 g/dL, respectively, with an optimal cutoff of PreFib >7.57 g/dL. We therefore recommend the use of TEG[®] for assessing preoperative blood coagulation function as it can aid in the timely diagnosis of blood hypercoagulability. TEG[®] may also help predict the risk of intraoperative and postoperative deep vein thrombosis and pulmonary embolism.

However, its role in predicting thrombotic events, hypercoagulability, or complications is still under debate. This is due to an intrinsic lack of contact with collagen (representing endothelial disruption) in this test and the lack of variability in shear stress to assess the arterial and venous systems in the cup-and-pin technology, so the fluid mechanics of the Viscoelastic Hemostatic Assay do not replicate vascular hemodynamics. Other limitations of TEG[®] are their inability to detect (due to the overwhelming effect of thrombin) specific abnormalities of platelet receptors without the use of specialized tests. Standard TEG parameters, however, demonstrate poor sensitivity to aspirin and enoxaparin concentrations in therapeutic ranges. TEG without platelet mapping are unable to measure the outcomes of antiplatelet therapies (clopidogrel and aspirin) on the level of inhibition of specific platelet receptor activities.

Conclusions

TEG can quickly characterize patients' dynamic coagulation profile, detect high and low blood coagulation and fibrinolysis, and simulate the entire human coagulation process. Therefore, TEG has a high clinical guidance value. The results of this study indicate that these patients' blood was significantly hypercoagulable, and they were at increased risk of thrombosis and embolism. We therefore recommend using TEG for preoperative assessment of coagulation function, as it can aid in the timely diagnosis of hypercoagulation. TEG has also proven to be a useful tool in detecting the risk of diabetic foot ulceration. We therefore recommend conducting multi-platform randomized clinical trials (mpRCTs) comparing TEG parameters with standardized tools, and performing meta-analyses to pool data from all related studies to resolve the controversy among studies. Further clinical studies are also needed to investigate the use of TEG in critically ill patients, particularly geriatric patients, and to standardize its use in different perioperative settings. Our group plans to design a comparative study comparing the TEG parameters detected in these patients with thermographic analysis

of the surfaces of diabetic feet. It should be noted, however, that neuropathic feet do not ulcerate spontaneously, and that the path to ulceration requires, in addition to neuropathy, extrinsic factors such as trauma, and intrinsic factors such as deformities or hyperkeratosis resulting from plantar overload.

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