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Article

Kaolin thromboelastography as an index of diabetic foot severity: Preliminary results in summary

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Abstract

Background: This observational study compares the use of thromboelastography (TEG) in the diagnosis of Normal Foot (NP/C), Diabetic Foot (DF), Diabetic Foot with Ulcer (DFU), and Ulcer without Diabetic Foot (WDFU). Research suggests that blood fibrinogen (Fib) concentrations are used to assess the onset and severity of diabetic foot (DF) and to monitor its progression in patients. However, a correlation between TEG and Fib has not been reported in these patients. Methods: This study correlates DF, DFU, NP, and WDFU with α-angle values, clot formation time (*k*), and Max Amplitude (MA) from Thromboelastography (which reflect Fib function), as well as blood fibrinogen. Patients studied were divided into five groups, and their blood samples underwent TEG. Subsequently, the parameters R, k, α-angle, and MA were analyzed. Primary and secondary hemostatic profile was examined using TEG and fibrinogen levels and was classified as hypo-, hyper-, and normo-coagulable. Results: Presence of an ulcer had a positive effect on the correlation between Fib and MA parameter in TEG both before (☐=0.65, p=0.36) and after surgery (☐=0.64, p=0.32), in both diabetic and non-diabetic patients; Median k and fibrinogen levels significantly increased in subjects with DF compared to those without, particularly in those with ulcer (DFU). α angle levels (median) significantly decreased in subjects with DF with ulcer compared to those without (p<0.01). Spearman correlation analysis (☐) showed that α angle and Fib were weakly negatively correlated in the DF classification (☐= -0.27, p = 0.12) preoperatively and positively (☐ = 0.25, p = 0.16) postoperatively. α value was positively correlated in the DF (☐☐= 0.40, p < 0.05) preoperatively and negatively correlated in the DF (☐ = -0.2, p = 0.26) postoperatively. ROC curve analysis showed that in patients with pre-surgery fibrinogen levels between 401 and 600 mg/dL, the optimal cutoff point for the α angle to distinguish patients with DF from those without was 53.5°, with a sensitivity and specificity of 63.6%. In the same patients, the

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optimal cutoff point for the k value was 3.8 min, with a sensitivity of 87.5% and a specificity of 50%. Optimal cutoff point for pre-surgery fibrinogen was 3.98 g/L, with a sensitivity and specificity of 100%. For post-surgery fibrinogen, the cutoff was >4.18 g/L, with a sensitivity of 50% and a specificity of 0%. Optimal cutoff point in patients with pre-surgery fibrinogen >600 mg/dL to assess the risk of progression of diabetic foot was >665 mg/dL, with a sensitivity and specificity of 100%. Optimal cutoff point for the k value was 2.40 min, with a sensitivity and specificity of 100%. Optimal cutoff point in the control group (C) for pre-surgery fibrinogen was 2.78 g/L, with a sensitivity of 66.7% and a specificity of 100%. Conclusion: α angle, k value, and pre-surgery fibrinogen have clinical significance for the risk of onset and development of diabetic foot and its progression to ulceration and may contribute to early diagnosis and early clinical intervention in diabetic foot.

Introduction

Globally, the age-adjusted prevalence of type 2 diabetes mellitus (T2DM) is projected to increase from 9.3% to 10.9% by 2045. Renal and cardiovascular disease remain the prevalent chronic complications, occurring in 50% and 15% of patients, respectively, followed by diabetic retinopathy (12%). The global prevalence of diabetic foot is 6.3% [1]. Patients with diabetes mellitus, due to vascular endothelial damage and platelet dysfunction, are seventeen times more likely to develop gangrene and five out of six to undergo major limb amputations. Clinical observation and case history suggest that fibrinogen (Fib) concentrations could be used to assess the onset and severity of diabetic foot and to monitor its progression in patients [2]. Comprehensively assessing coagulation status is challenging because the coagulation cascade is dynamic and depends on the interaction of several factors, including primary hemostasis, platelet clot formation, secondary hemostasis, thrombin generation, and fibrinolysis. Viscoelastic coagulation tests such as thromboelastography (TEG®) are designed for rapid, comprehensive assessment of hemostasis, most closely resembling in vivo hemostasis by continuously monitoring the coagulation process from initiation, amplification, propagation, and termination through fibrinolysis. Thrombelastography (TEG®) is one of the most important methods for monitoring coagulation function in clinical practice. TEG® monitors the blood coagulation and dissolution process based on fibrin and platelet levels and functions. Currently, TEG is widely used to guide clinical blood transfusion and the use of medications that affect platelet function, for real-time monitoring of coagulation in patients with a variety of conditions, and to predict the risk of venous thrombosis [3]. Indeed, many studies demonstrate that preoperative TEG is the most appropriate option for predicting postoperative thromboembolic events. TEG can be considered a point-of-care test (POCT) that is performed in approximately 20 minutes. However, as mentioned, it is not routinely used in patients with T2DM [4].

The present study therefore aims to detect hemostasis abnormalities in association with glycemic levels and diabetic foot type (ulcerated or non-ulcerated) among patients with T2DM using TEG, also in the presence of anticoagulants such as aspirin and enoxaparin.

Meaning of TEG values

Hyperglycemia causes protein glycation (including fibrinogen), making fibrin fibers more resistant to lysis. TEG is the only tool capable of measuring this dynamic "resistance." Furthermore, it has been shown that in diabetic patients, even if the platelet count is normal, their reactivity is increased, contributing to the increase in AD.

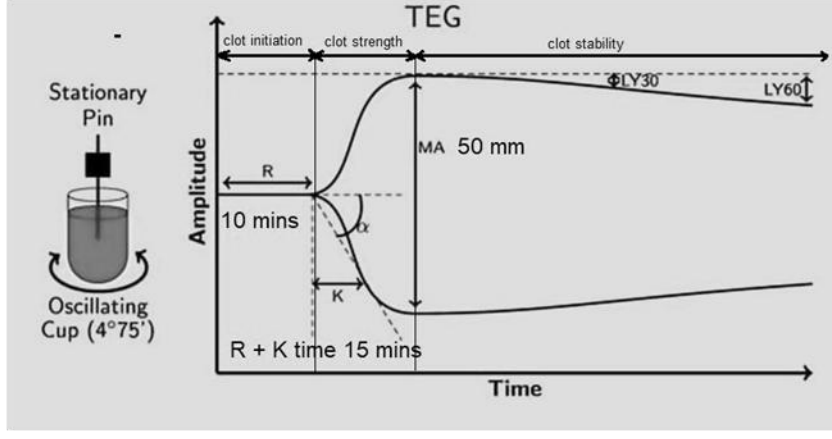

Figure 1. Schematic diagram of the TEG trace. TEG parameters illustrate the functional activity of clot initiation, kinetics, maximum strength, and clot stability

R. reaction time (minutes): An elevated or prolonged R value (more than eight minutes) may indicate a deficiency of coagulation factors, hemodilution, the presence of heparin (anticoagulant substances), and/or severe hypofibrinogenemia. A short R time (less than four minutes) may indicate hypercoagulopathy requiring the use of anticoagulants.

k. (clot formation time): represents clot formation and is closely related to platelet function, plasma factors, and fibrinogen. An increased *k* value indicates slower clot formation; a reduced value indicates hypercoagulability (n.v.: 1-3 minutes). The length of the *k* value is primarily influenced by the level of fibrinogen.

Alpha angle: The α angle is greater if there is greater platelet and fibrinogen activity in the blood and is smaller if anticoagulants or platelet inhibitors are present. The normal range of values is between 47 and 74° (deg). Fibrinogen levels determine the angle.

MA. Maximum Amplitude (mm): This measure of clot strength depends primarily on the interaction between platelets and fibrin. The normal range is between 55 and 73 mm. It correlates 80% with platelet function and 20% with fibrinogen.

Maximum amplitude is considered the most sensitive parameter for assessing platelet function in thromboelastography [4].

A low MA value indicates low clot strength, which may be caused by decreased fibrinogen levels, a low platelet count, or reduced platelet function [5-7].

In short, a quick interpretation of the results could benefit from the observation that the lower the R and k values and the higher the α value, the greater the blood coagulability.

Purpose of the study

1) Some of the questions we asked in this study are:
2) Does TEG-MA predict platelet count in diabetic patients? To evaluate this, we correlated TEG-MA with platelet count (Plt).
3) Can TEG-MA, TEG-*k*, and TEG-α angle predict the onset of Diabetic Foot and/or Diabetic Foot Ulcer? To evaluate this effect, we correlated these values with pre- and post-intervention fibrinogen levels in the four diseased patient groups compared to the control group (C).
4) Can TEG parameters, therefore, predict both coagulopathy and thrombotic events? The literature has reported that the use of TEG-MA, TEG R-time, TEG-*k*, and TEG-α angle in cardiac patients is predictive of coagulopathy and could predict thrombotic events [8-10]. This study aims to demonstrate whether the same is true in diabetic patients and whether they may be novel biomarkers of DFU.

State of research on TEG

The existing research on thromboelastography (TEG) in diabetic patients undergoing general surgical procedures is limited. However, these studies indicate that using TEG or rotational thromboelastometry (ROTEM) in diabetic patients enhances the detection of coagulopathy. Additionally, certain TEG parameters have been shown to predict early sepsis in this population [8]. To date, no studies have specifically examined the correlation between TEG parameters and moderate to severe hyperfibrinogenemia in patients with Diabetic Foot.

Critical issues of TEG

The respective sources of errors in TEG tracings are: 1) a false value of time k=0 in a severe hypocoagulable state which would indicate a hypercoagulable state; 2) spikes due to vibrations in the surrounding environment; 3) inappropriate positioning of the cup in the instrument resulting in a beak-shaped tracing; 4) falsely high MA value due to evaporation of the sample during the run; 5) failed self-calibration before a sample run resulting in a hypercoagulable state; 6) delayed onset of clotting due to the use of calcium chloride older than 24 hours after reconstitution [11].

Materials and methods

This study correlates Normality (NP)(C), Diabetic Foot (DF), Diabetic Foot with Ulcer (DFU), and Ulcer without Diabetic Foot (WDFU) with the α angle and k (clot formation time) values of kaolin thromboelastography (which reflect Fib function) and baseline and post-operative fibrinogen levels, as well as with TEG MA values and blood CRP, ESR, and Plt values.

Viscoelastic tests are crucial in targeted and modern coagulation management for assessing patients' coagulation status. Therefore, in the absence of uniform quantitative standards for biomarkers that can serve as benchmarks for the risk of diabetic foot onset and progression, and considering that an increase in the α angle and a decrease in the k value can be an important indicator of the development of vascular lesions, it is

hypothesized whether they could be considered new biomarkers in the diabetic foot. All subjects examined (165) were classified as normocoagulable and hypercoagulable for each of the groups examined (NP, DF, DFU, WDFU, C) based on the fibrinogen level (<400, 401~600, >600 mg/dL) pre- and post-intervention.

TEGs that were not performed within 15 minutes of standard coagulation tests were excluded from our analysis.

In our study, a test was concluded when all values appeared on the TEG recordings. When no values were provided, due to blood samples not forming a clot, the test was stopped after 60 minutes and discarded.

Statistical analysis

The patients studied were divided into 5 groups and their blood samples were subjected to TEG. Subsequently, the parameters R, k, α angle, and MA were analyzed. Spearman's correlation analysis (□) was used to analyze the correlation between groups of nonparametric data. The Kursaal-Wallis test and the $\square^2$ test were used to analyze continuous variables. Ordinal categorical variables were compared using ordinal logistic regression analysis and by estimating the odds ratio of risk factors and the relative risk. A receiver operating characteristic (ROC) curve was constructed to assess the TEG's ability to recognize various parameters, and the areas under the curve (AUROC) were compared using the Delong test for diagnosis. The primary and secondary hemostatic profile was examined using TEG and fibrinogen levels and was classified as hypo-, hyper-, and normo-coagulable.

The ROC curve has been used to measure the accuracy of a diagnostic test across the entire range of possible values. Since the ROC curve measures the agreement between the test of interest and the presence/absence of a specific disease (as identified by a golden standard), it represents the method of choice for validating a diagnostic test. The ROC curve also allows us to identify the optimal threshold value (the so-called best cut-off), that is, the test value that maximizes the difference between true positives (i.e., the proportion of individuals with an abnormal test value among all those actually affected by the disease) and false positives (i.e., the proportion of individuals with an abnormal test value who are not affected by the disease of interest).

Results and statistical correlations

1) The data showed that plasma fibrinogen was significantly higher in diabetic patients than in controls.
2) Fib/MA Correlation: There was a strong positive pre-intervention correlation between fibrinogen levels and the MA parameter of the TEG (□=0.65, p=0.36). The higher the fibrinogen, the stiffer the clot and the more difficult it was to break down.
3) Differences between the DF vs. DFU Group: Patients with active ulcers (DFU) showed a shortened k-time and an increase in the α angle and MA, a sign of a state of "consumptive hypercoagulability" or reactive to wound inflammation.

4) The α angle as a predictor: The study identifies the α angle as a highly sensitive parameter for distinguishing the transition from a "stable" diabetic patient to one with ulcer complications.

5) Diagnosis of Diabetic Foot: A *k* value ≤ 3.8 min and an α angle ≥ 53.5° identify the presence of the disease with high sensitivity.

6) Risk Severity: In the presence of very high fibrinogen (>600 mg/dL), a *k* value < 2.40 min predicts with 100% specificity and sensitivity a critical hypercoagulable state in diabetic foot and a tendency to progress to ulcerative form.

Conclusion

TEG is superior to traditional tests for monitoring thrombotic risk in diabetic feet. The *k* and α angle parameters are reliable biomarkers for early diagnosis. The tool allows for personalized anticoagulant or antiplatelet therapy, identifying patients who do not respond to standard doses (drug resistance) or who are at risk of small vessel occlusion, the main cause of amputations. The α angle, *k* value, and pre-surgery fibrinogen levels have clinical significance for the risk of onset and development of diabetic foot and its progression to ulceration and can contribute to early diagnosis and early clinical intervention in diabetic foot. The authors reserve the right to publish the complete and definitive data in a subsequent article.

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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