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The Hypercoagulability Paradox of Chronic Kidney Disease: The Role of Fibrinogen

Geoffrey R Nunns, MD¹, Ernest E Moore, MD^{1,2}, Michael P Chapman, MD³, Hunter B Moore, MD¹, Gregory R Stettler, MD¹, Erik Peltz, DO¹, Clay C Burlew, MD², Christopher C Silliman, MD PhD^{4,5}, Anirban Banerjee, PhD¹, and Angela Sauaia, MD PhD^{1,6}

¹Department of Surgery, University of Colorado Denver, Aurora, CO

²Department of Surgery, Denver Health Medical Center, Denver, CO

³Department of Radiology, University of Colorado Denver, Aurora, CO

⁴Department of Pediatrics, University of Colorado Denver, Aurora, CO

⁵Research Laboratory, Bonfils Blood Center, Denver, CO

⁶School of Public Health, University of Colorado Denver, Aurora, CO

Abstract

Background—Chronic kidney disease (CKD) patients have increased rates of bleeding as well as thrombosis. Fibrinogen and platelets combine to generate a mature clot, but in CKD platelets are dysfunctional. Therefore, we hypothesize that CKD patients have increased clot strength due to elevated fibrinogen levels.

Methods—Retrospective review of CKD patients (n=84) who had rTEG and fibrinogen levels measured. They were compared to healthy controls (n=134).

Results—CKD patients had statistically significant increases in ACT, angle, MA and decreases in LY30 compared to controls. Fibrinogen levels were increased in CKD patients compared to reference range. Fibrinogen levels had a positive correlation with MA ($\rho = 0.709$, $p < 0.0001$) in CKD patients.

Conclusions—Patients with CKD manifest a coagulopathy consisting of delayed clot formation, but increased final clot strength and decreased clot breakdown. Furthermore, the elevated clot strength is mediated by increased fibrinogen levels in CKD patients.

Keywords

Kidney Failure; Chronic; Hypercoagulability; TEG; Fibrinogen

Corresponding Author: Ernest E Moore, MD, ernest.moore@dhha.org Phone: 303-724-2685 Fax: 303-720-2682, Mailing Address: 655 Bannock Street Denver, CO 80203.

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Introduction

Chronic Kidney Disease (CKD) patients have a paradoxical hemostatic potential, with increased rates of bleeding, but are prone to thrombosis.^{2, 3} Increased bleeding is thought to be driven principally by platelet dysfunction, with additional contributions from alterations in the coagulation cascade with deranged vWF and platelet interactions, increased nitric oxide and impaired fibrinolysis, as well as the sequelae of anemia.^{2, 4, 5} Clinically relevant bleeding has been reported in 24–50% of patients on HD, with a >2-fold increased prevalence compared to patients without ESRD.^{2, 6}

Increased rates of thrombosis, on the other hand, manifest as deep venous thrombosis (DVT), pulmonary embolus (PE), thrombosis of arteriovenous fistula or hemodialysis access catheter, or acute coronary syndromes.^{2, 6} VTE event rates are doubled in the presence of CKD.⁶ The mechanisms driving this pro-thrombotic state are unclear.³

Thrombelastography (TEG) is a viscoelastic hemostatic assay that has been widely used in clinical settings as it more closely approximates the *in vivo* clotting characteristics compared to standard coagulation assays.¹ Standard coagulation assays use platelet poor plasma (PPP), while TEG used whole blood and therefore represents contributions from red blood cells, platelets, white blood cells in addition to clotting factors found in PPP.¹ TEG measures different hemostatic variables: the rate of clot formation (activated clotting time (ACT)), rate of clot propagation (angle), clot strength (maximal amplitude(MA)) and clot breakdown 30 minutes after achieving maximum clot strength (LY30). TEG has been shown to predict thrombotic complications in a wide variety of patient populations, with an elevated MA as the best predictor.^{7–9} As TEG provides detailed descriptions of the different phases of clot formation and predicts clinical outcomes, it provides a good tool to characterize the hemostatic potential in CKD.

MA is composed of contributions from platelets as well as fibrinogen that combine to generate a mature clot.^{10, 11} CKD has been associated with both platelet dysfunction as well as hyperfibrinogenemia.^{2, 5, 12} Thrombocytopenia has been successfully compensated for by the addition of fibrinogen concentrate.¹³ Additionally, fibrinogen concentrates have been used clinically used in European centers for the treatment of traumatic coagulopathy.^{13–15} Therefore, it seems reasonable that despite the presence of platelet dysfunction in renal failure, the elevated fibrinogen levels could compensate for this to drive increased clot strength. We hypothesize that increased fibrinogen levels in patients with CKD will correlate with increased clot strength and an increased MA on TEG.

Material and methods

Study Design

This was a single center, retrospective review of patients undergoing dialysis access surgery by a single surgeon at Denver Health Medical Center from 4/2013–10/2016. This group of CKD patients was compared to healthy controls.

Blood Samples from Healthy Volunteers

Nursing staff collected samples from volunteers at an outpatient clinic after approval by the Colorado Multi-institutional Review Board. The study was open to patients and hospital staff not taking antiplatelet or anticoagulant medication. Volunteers with any medical comorbidities, including diabetes, renal disease, hypertension or liver disease, were excluded. While reference ranges are available through the manufacturer, we elected to perform analysis of healthy volunteers to control for the effect of altitude in Denver and exclude patients with comorbid conditions.¹⁶ Blood samples were obtained via venous puncture, and collected in tubes containing no anticoagulants.

Blood Samples from Dialysis Access Patients

Clinical data was collected from the medical record after approval was obtained by the Colorado Multi-institutional Review Board. Patients undergoing dialysis access by a single surgeon at Denver Health Medical Center were included in the study. Clinical data included age, sex, and whether or not the patient was on dialysis prior to surgery and type of dialysis (hemodialysis (HD) or peritoneal dialysis (PD)). Patients who had multiple surgeries within the study period only had one surgical event included in a random fashion. Laboratory data collected includes preoperative Rapid Thrombelastography (rTEG), fibrinogen levels and glomerular filtration rate (GFR). Rapid thrombelastography and fibrinogen levels were obtained routinely on all patients undergoing dialysis access surgery in the preoperative holding area. Blood samples were collected and run in accordance with clinical guidelines at DHMC.

Rapid Thrombelastography

Blood was collected from healthy volunteers and dialysis access patients in sample tubes without any anticoagulant (Vacutainer; Becton-Dickinson, Franklin Lakes, NJ). For healthy controls, samples were run in a research lab within 10 minutes of collection by trained research staff. For dialysis access patients, samples were run in the DHMC clinical lab within 10 minutes of collection by trained laboratory personnel. In both cases, rTEG assays were run according to the manufacturer's instructions on a TEG 5000 Thrombelastograph Hemostasis Analyzer System (Haemonetics, Niles, IL, USA), with all supplies and reagents supplied by the same manufacturer. Machines were calibrated according to manufacturer suggestions before use. All samples were run with the Rapid TEG Reagent which adds Tissue Factor and Kaolin to blood prior to the assay being performed. The following parameters were recorded from the tracings of the rTEG: Activated Clotting Time (ACT, seconds), angle (α , degrees), maximal amplitude (MA, mm), and lysis 30 minutes after MA (LY30, %).

Statistical Analysis

GraphPad Prism version 7.0a (GraphPad Software, Inc; La Jolla, CA) and SPSS software (SPSS Institute, Cary, NC) were used for statistical analysis. The proportion of patients with an elevated ACT in different groups was compared with Fishers Exact Test. TEG variables were compared between groups using Mann-Whitney U Test. In the CKD subgroup,

correlation between fibrinogen and rTEG parameters was analyzed using the Spearman Rho test.

Results

Patient Population

134 healthy volunteers and 84 CKD patients were included in the study. Healthy volunteers had a median age of 31 (27–38) and were 47% male. CKD patients had a median age of 57 years (52.5–62), were 60.7% male, and 66% of patients were on dialysis (65% on HD, 1.1% on PD). Healthy patients and controls differed in age ($p<0.0001$) but not in proportion of patients that were male or female. Of patients not on dialysis ($n=28$), 25 had a GFR available preoperatively. These patients were stratified based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) chronic kidney disease (CKD) staging. One patient was in CKD Stage 3 (GFR 30–59), 7 patients were in CKD Stage 4 (GFR 15–29) and 17 patients in CKD Stage 5 (GFR <15).

Comparison of Healthy Controls and CKD Patients

All TEG values demonstrated statistically significant differences from healthy controls (Table 1). ACT was prolonged (>128 seconds) in 18% of CKD patients compared to 4.5% of healthy controls ($p=0.0025$). Angle was increased in CKD (79.8 IQR: 76.4–81.9 vs. 73.85 IQR: 70.85–76.3 degrees in controls) ($p<0.0001$). MA was increased in CKD (71.6 IQR: 66.95–77.18 vs. 65 IQR: 61.5–68 mm in controls) ($p<0.0001$). LY30 was decreased in CKD (0.9 IQR: 0.1–2.5 vs. 2.7 IQR: 1.975–3.7 % in controls) ($p<0.0001$). Fibrinogen levels were increased in CKD patients (median 406.5, IQR 333–513 mg/dL) compared to the clinical reference range of 150–400 mg/dL.

Effect of Dialysis

Patients undergoing HD ($n=55$) were compared to patients not on dialysis ($n=28$). Patients on peritoneal dialysis were excluded from this analysis due to the low sample size. There were no significant differences in ACT or angle between groups (Table 2). Patients on HD, however, had a decreased MA compared to those not on dialysis. Additionally, patients on HD had an increased clot breakdown compared to those not on dialysis. There was a trend towards decreased fibrinogen levels in the HD group, although this did not reach significance ($p<0.1$). In both groups (patients receiving HD or not on dialysis) all rTEG variables still showed statistically significant differences from healthy controls ($p<0.05$ for all). The differences between these groups and healthy controls mirrored the changes between healthy controls and the aggregate CKD patient cohort (increased ACT, angle, MA and decreased LY30).

Correlation with TEG values

ACT did not correlate with fibrinogen levels. Angle and MA had a positive correlation with fibrinogen ($\rho = 0.427$, $p=0.0007$ and $\rho = 0.709$, $p<0.0001$), respectively (Figures 1 and 2). Correlation still existed between MA and fibrinogen for subgroups of patients on HD and not on dialysis (Figure 3). There was no correlation between fibrinogen and LY30.

Discussion

Chronic kidney disease generates a distinct hemostatic potential as compared to normal controls. CKD patients manifest a coagulopathy consisting of delayed clot formation with increased final clot strength and decreased clot breakdown when compared to healthy patients. The increased clot strength (MA) that is seen in this population is mediated by supra-normal fibrinogen levels. The increased clot strength and decreased clot breakdown is attenuated in patients receiving HD.

Our data aligns with prior work showing increased clot strength in CKD.^{12, 17, 18} Additionally, the findings of a delayed clot formation, decreased lysis and increased fibrinogen levels have been seen in some prior studies.^{12, 17, 18} The delayed clot formation seen may predispose to bleeding complications. Furthermore, the increased clot strength and decreased breakdown in this group may account for the increased thrombotic complications in this group.^{2, 6}

This increased clot strength is mediated by increasing levels of fibrinogen. Given the known platelet dysfunction in CKD, increased fibrinogen appears to be responsible for the observed hypercoagulability as a compensatory mechanism to normalize hemostasis in the presence of platelet dysfunction.^{2, 12, 13} Elevated fibrinogen levels have been shown to correlate with myocardial complications in patients with Stage 5 CKD.¹⁹ This supports the theory that hyperfibrinogenemia and associated increased clot strength as assessed by increased MA, is mechanistic in the physiologic coagulopathy and the complications with thrombosis in CKD patients clinically.

HD patients have moderation of the hypercoagulable profile, with a decreased MA and increased clot breakdown compared to CKD patients not on dialysis. While their coagulation indices do not reach healthy controls, the moderation may have implications for hypercoagulable events in this group. The mechanisms for this remain to be fully explained, although some studies show decreased levels of fibrinogen and vWF after dialysis, other suggest changes arise from increased tPA levels following dialysis.^{20, 21}

Several limitations in this study warrant discussion. While our control group was chosen to exclude any patients with comorbid conditions, they are significantly younger than the CKD group. Some of the differences between groups may represent additional comorbid conditions that coexist in the CKD population as well as the effect of increasing age. The endotheliopathy seen in CKD is not reproduced in the TEG cup.² This may lead to overestimation of the tendency for thrombosis, as the platelet vessel wall binding may be decreased due to decreased vWF-platelet binding, or alternatively underestimation if endothelial damage and increased platelet activation is present.² The small population size, short term follow up and a heterogeneous patient population limit our ability to directly evaluate hyperfibrinogenemia and a hypercoagulable state seen with increased MA on TEG against clinical thrombotic events. CKD patients have variable histories of upper extremity percutaneous dialysis access, different AV fistula sites / sizes, different conduits and AV graft materials which all add confounding variables to consider when assessing the impact of fibrinogen or clot strength on clinical thrombotic potential. However, increased MA and

fibrinogen have been shown to correlate well with increased thrombotic complications in CKD patients and other populations and taken with evidence from this study strongly suggest that hyperfibrinogenemia contributes to the increased clot strength and associated thrombotic risk.^{7, 9, 19} These important clinical outcomes could be improved upon with a larger, multicenter, prospective evaluation.

These data suggest that a distinct hemostatic potential exists in CKD, consisting of a decreased speed of clot formation, but a stronger clot that is resistant to breakdown compared to healthy patients. The increased clot strength and therefore hypercoagulability seen in the CKD population appears to be mediated by fibrinogen. Thus, methods to treat hypercoagulability in this population should target fibrinogen. Additionally, the hypercoagulable state in CKD may improve with dialysis through an unknown mechanism. Prospective studies are needed to evaluate the ability of TEG and fibrinogen to predict clinical postoperative complications including thrombosis.

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Thank you,

Angela Sauaia, MD PhD

University of Colorado Denver

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Figure 1.
Correlation of angle with fibrinogen levels

Figure 2.
Correlation of MA with fibrinogen levels

Figure 3.
Correlation of MA with fibrinogen levels in groups receiving HD or not receiving dialysis.

Table 1

TEG parameters of healthy controls and CKD patients

	<i>Control (n=134)</i>	<i>CKD (n=84)</i>	<i>P</i>
<i>ACT>128 seconds (% of population)</i>	4.5%	18%	0.0025
<i>Angle (degrees)</i>	73.85 (70.85–76.3)	79.8 (76.4–81.9)	<0.0001
<i>MA (mm)</i>	65 (61.5–68)	71.6 (66.95–77.18)	<0.0001
<i>LY30 (percent)</i>	2.7 (1.975–3.7)	0.9 (0.1–2.5)	<0.0001

Comparisons between continuous variables was done with Mann-Whitney U Test. Discrete variables were analyzed using the Fishers Exact Test.

Table 2

Hemostatic variables of CKD patients stratified by those receiving dialysis.

	<i>HD (n=55)</i>	<i>No Dialysis (n=22)</i>	<i>P</i>
<i>ACT>128 seconds (% of population)</i>	<i>11.5%</i>	<i>26.9%</i>	<i>0.11</i>
<i>Angle (degrees)</i>	<i>79.45 (76.38–81.9)</i>	<i>80.45 (76.6–82.35)</i>	<i>0.49</i>
<i>MA (mm)</i>	<i>69.8 (64.65–75.1)</i>	<i>73.75(69.23–78.4)</i>	<i>0.0165</i>
<i>LY30 (percent)</i>	<i>1.3 (0.2–2.85)</i>	<i>0.4 (0.025–1.525)</i>	<i>0.0355</i>
Fibrinogen (mg/dL)	394 (317.5–498)	483 (386–541.5)	0.0671

Comparisons between continuous variables was done with Mann-Whitney U Test. Discrete variables were analyzed using the Fishers Exact Test.