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Review Article

Abnormalities in Hemostatic Parameters Related to Hemodialysis in End-stage Kidney Pathology: A Narrative Review

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ABSTRACT

Chronic kidney disease (CKD) is a progressively prevalent global health issue. During the initial phases of the condition, CKD is commonly linked to a tendency for excessive blood clotting. While in the end-stage of disease, patients undergoing hemodialysis have a multitude of hemostatic abnormalities. These include prolonged bleeding time, altered platelet count, prolonged PT and aPTT, elevated FDPs and D-dimer, dysregulated vWF activity, and abnormal thrombin generation. These changes result from a combination of uremic toxicity, endothelial dysfunction, inflammatory states, and the effects of the hemodialysis procedure itself. Understanding these mechanisms is crucial for managing and mitigating the bleeding and thrombotic risks in this patient population. This review aims to systematically investigate the effects of hemodialysis on key hemostasis parameters in CKD patients.

Keywords: Coagulation, Hemostasis, Hemodialysis, End-stage Kidney Disease (ESKD).

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INTRODUCTION

Chronic kidney disease (CKD) places a substantial burden on global healthcare systems. This prominent non-communicable ailment is associated with unfavorable clinical and economic consequences. However, the recognition of CKD remains limited. Early identification is crucial for preventing and delaying the progression of CKD. CKD is correlated with an elevated risk of mortality, cardiovascular disorders (CVD), and increased medical expenses. Many CKD patients struggle with hypertension (HT), diabetes (DM), and/or CVD, driven by an interconnected association among these principal chronic conditions that complicate appropriate management.[1]

Hemodialysis (HD) has emerged as a cornerstone in the management of advanced CKD, serving as a vital therapeutic modality to alleviate uremic symptoms and maintain fluid and electrolyte balance. While hemodialysis undeniably contributes to the overall well-being of CKD patients, its influence on hemostasis parameters remains an area of growing concern and scientific interest.[2] Several studies have indicated that CKD patients, particularly those undergoing hemodialysis, may experience alterations in hemostasis parameters, leading to an increased risk of bleeding or thrombotic events. The intricate interplay between renal dysfunction, the dialysis process itself, and the resulting impact on hemostasis is not yet fully understood. Observable activation of leukocytes due to hemodialysis serves as a visible indicator of this biological incompatibility, leading to the initiation of cardiovascular changes. The activation of platelets plays a role in the adverse outcomes linked to hemodialysis therapy, as demonstrated by an elevated susceptibility to thromboembolic ailments. Despite systemic anticoagulation during hemodialysis sessions, the extracorporeal configuration continues to incite coagulation activation.[3]

This research aims to systematically investigate the effects of hemodialysis on key hemostasis parameters in CKD patients.

Hemostasis

Hemostasis is an intricate mechanism through which the body naturally halts bleeding and keeps blood in a liquid state within the vascular compartment. It denotes the process responsible for arresting bleeding from a blood vessel and comprises a series of interconnected phases, culminating in the creation of a "plug" that seals the wounded section of the blood vessel, thereby controlling the bleeding. Initiated by injury to the blood vessel lining, this hemostatic cascade can be segmented into four distinct stages: (1) the contraction of the blood vessel, (2) formation of a provisional "platelet plug," (3) initiation of the coagulation cascade, and (4) development of the ultimate "fibrin plug" or clot formation.[4]

The study of hemostasis physiology necessitates focused attention, particularly recognizing the significance of pre-analytical factors that could impact the overall outcomes of tests. Adhering to CLSI recommendations for collecting and preserving coagulation study samples ensures precise results and accurately reflects the condition of the specimen based on the patient's clinical state.[5]

In end-stage kidney disease (ESKD), hemostasis is significantly disrupted, leading to a complex interplay of bleeding and thrombotic tendencies. The underlying perturbed intracellular pathways contribute to the dysregulation of hemostatic processes, impacting platelet function, endothelial cell behavior, and coagulation pathways. This review focuses on the key intracellular mechanisms altered in ESKD that contribute to these hemostatic abnormalities.

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Table 1: Illustrate studies in Hemostatic Parameter abnormalities related to HD in ESKD.

Authors and source	Study design	Sample size	Outcomes	Notes
Schoorl et al. [63]	Descriptive study		Variations in platelet and immature platelet numbers, morphological characteristics, and expression of Platelet Factor 4 (PF4), serotonin, β-Thromboglobulin (β-TG), Prothrombin Fragment 1 + 2 (F1 + 2), and Thrombin-Antithrombin III (TAT) levels were observed during the progression of HD therapy.	
Milburn et al.a [64]	Descriptive study	55 HD patients	Platelet performance was evaluated, and stimulated platelet fibrinogen binding exhibited elevated levels post-hemodialysis ($p < 0.001$). Aggregation responses were diminished post-hemodialysis. Noteworthy increments were recorded post-hemodialysis in TAT ($p < 0.001$), D-dimer ($p < 0.001$), vWF ($p < 0.001$), and high-sensitivity C-Reactive Protein (hs-CRP) ($p = 0.011$).	Blood samples were drawn just before and immediately after a hemodialysis session.
Milburn et al.b [65]	Descriptive study	70 HD patients	TAT, hs-CR, and D-dimer were elevated in patients on HD compared to controls.	However, the significant distinction in platelet activation was maintained only in the group that did not use antiplatelet agents.
Khan et al. [66]	Cross-sectional descriptive study	100 CRF patients and 100 control subjects	PT and APTT were extended after hemodialysis, while platelet counts decreased.	The coagulation profile was assessed before and after hemodialysis. The decline in platelet counts post-hemodialysis could be attributed to the usage of heparin.
Khalid and Zafar [67]	A cross-sectional investigation	84 patients aged 16 to 70	Following the dialysis procedure, the hemostatic parameters were significantly elevated, with average PT and APTT values reaching 15.64 ± 3.18 and 46.54 ± 24.68 seconds, respectively, with a p-value of < 0.001 for both parameters.	Assessments of PT and APTT were conducted before and after dialysis.
Habib, Ahmad, and Rehman [68]	Descriptive study	42 CRF patients and 40 healthy adults	The findings revealed noteworthy reductions in RBC count and hemoglobin levels among patients with CRF. Moreover, the process of hemodialysis further exacerbated the decrease in all hematological parameters. Conversely, a minor increase was noted in total leukocyte count, while a substantial elevation in ESR was detected.	
Huang et al. [69]	A Prospective Observational Study	95 CKD patients and 20 healthy controls	Both adjusted and unadjusted levels of vWF antigen (vWF:Ag), vWF ristocetin cofactor activity (vWF:RCo), antithrombin III, fibrinogen, D-dimer, factor V, VII, VIII (FV) (FVII) (FVIII), and protein C and S were significantly increased in CKD patients. These levels showed an increase with the progression of CKD. Factors such as platelet aggregation, Protein C, Protein S, AT III, and D-dimer exhibited notable differences with a significance of $p < 0.001$.	
Aziz et al. [70]	Descriptive study	20 healthy participants, 60 CKD patients, and 40 HD patients	The mean values of platelet distribution width (PDW), mean platelet volume (MPV), plateletcrit (PCT), and platelet large cell ratio (PLCR) were higher in both CKD and ESRD patients compared to healthy controls.	
Hernaningsih and Aprianto [71]	An observational-analytical study	50 HD patients	A noteworthy extension in APTT was identified in post-hemodialysis patients with CKD V. Hemodialysis procedures also contributed to a reduction in the activity of coagulation factors II, IX, X, and XII, leading to APTT prolongation post-hemodialysis.	The study involved pre- and post-hemodialysis assessments with a minimal dose of heparin. The elongation of APTT following hemodialysis can be attributed to the utilization of heparin as an anticoagulant, which raises both PT and APTT by obstructing antithrombin III.
Gäckler et al. [72]		20 HD patients, 10 peritoneal dialysis patients, 10 (CKD5), and 10 healthy controls (HC).	Patients with advancing kidney disease exhibited a noticeable decrease in hemoglobin levels compared to healthy controls (both with $p < 0.01$). Approximately 44% of CKD5 patients and 41% of hemodialysis patients exhibited extended platelet function analyzer (PFA) ADP-test results ($p < 0.05$), a phenomenon absent in peritoneal dialysis patients and the HC group. Patients undergoing hemodialysis displayed notably reduced thrombin-generating potential, while the clot lysis time revealed a state of reduced fibrinolysis among those undergoing hemodialysis and peritoneal dialysis compared to HC ($p < 0.001$).	

Pavlou et al. [73]		32 HD patients and 50 HC	Analysis of platelet function revealed deviant outcomes among patients with ESRD, even though heightened activation indicators (PS, CD62P, iROS) levels were present. HD triggered an elevation in the activities of most coagulation, fibrinolytic, and inhibitory proteins. Notably, PS and iROS levels in red blood cells were detected, closely correlating with differences in platelet traits and several coagulation factors.	Blood samples were drawn before and after HD.
Abdelmaguid et al. [74]	A cross-sectional investigation	30 HC and 120 CKD patients	Concentrations of D-dimer, TAT, and intercellular adhesion molecule-1 (ICAM-1) exhibited considerable elevation in CKD patients compared to HC ($p < 0.01$). Notably, the maximum clot firmness in rotational thromboelastometry (ROTEM) was significantly elevated among patients compared to HC ($p < 0.01$). Within CKD Stage 5 patients (both pre-HD and post-HD initiation), multiple electrode aggregometry (MEA) tests for adenosine diphosphate and thrombin receptor activating peptide disclosed significantly diminished outcomes compared to HC, signifying a defect in platelet aggregation ($p < 0.05$).	The study included 120 CKD patients (70 who did not require RRT, 20 with transplants, and 30 on HD). The CKD patient group displayed attributes of concurrent hypercoagulability, as measured by ROTEM, alongside platelet dysfunction, as quantified by MEA. Noteworthy is that the estimated eGFR emerged as an independent determinant for platelet dysfunction and hypercoagulability.
Nosseir et al. [75]	A descriptive study	21 males and 9 females HD patients and 30 HC	Notably, patients with CKD undergoing hemodialysis exhibited elevation in plasma FVIII levels and a distinct reduction in plasma PC levels compared to the HC group ($p = 0.0226$ and 0.000103, respectively). Additionally, a substantial elevation in GFR (measured in mL/min/1.73 m^2), PT (measured in seconds), and APTT (measured in seconds) was evident ($p < 0.00001$). The levels of FVIII exhibited an inversely proportional relationship with kidney function, while the relation between renal function and plasma PC levels was positive within the patient cohort ($r = -0.27$ and 0.53, respectively).	These atypical hemostatic profiles are potentially related to the sharp susceptibility to thrombotic events. The levels of FVIII demonstrated an inverse relationship with kidney function, while there was a noticeable positive association between kidney function and plasma PC levels among the patient cohort ($r = -0.27$ and 0.53, respectively).

Uremic Toxins and Platelet Dysfunction

Calcium Signaling: Uremic toxins impair intracellular calcium mobilization in platelets, which is crucial for activation and aggregation. Disrupted calcium homeostasis affects the secretion of granules containing ADP, serotonin, and thromboxane A2, impairing platelet recruitment and stabilization of the platelet plug.[6, 7]

cAMP Pathway: Elevated levels of cyclic adenosine monophosphate (cAMP) in platelets inhibit platelet aggregation. Uremic toxins can modulate cAMP levels, reducing platelet responsiveness to activating stimuli.[8-10]

Protein Kinase C (PKC) Pathway: PKC plays a vital role in platelet activation through the phosphorylation of various substrates. Uremia-induced oxidative stress can alter PKC activity, affecting platelet granule release and aggregation.[9]

Endothelial Dysfunction

Nitric Oxide (NO) Production: Endothelial cells produce NO, a potent vasodilator and inhibitor of platelet aggregation. Uremic toxins downregulate endothelial nitric oxide synthase (eNOS) expression and activity, reducing NO production. This increases platelet adhesion and a pro-thrombotic state.[11-13]

Reactive Oxygen Species (ROS) Generation: Uremic conditions enhance ROS production within endothelial cells, causing oxidative stress. Elevated ROS levels can damage cellular components, disrupt endothelial barrier function, and promote a pro-inflammatory and pro-coagulant environment.[13-15]

Endothelin-1 (ET-1) Pathway: Increased production of ET-1, a potent vasoconstrictor, is observed in ESKD. ET-1 signaling involves the activation of mitogen-activated protein kinases (MAPKs) and intracellular calcium mobilization, contributing to endothelial dysfunction and vascular constriction.[12, 13, 16]

Coagulation Cascade Alterations

Tissue Factor (TF) Expression: Uremic conditions upregulate TF expression on endothelial cells and monocytes. TF initiates the extrinsic coagulation pathway by binding to factor VIIa, leading to thrombin generation. Intracellular signaling pathways involving nuclear factor-kappa B (NF-κB) and MAPKs regulate TF expression in response to inflammatory stimuli.[8, 9, 16, 17]

Protein C Pathway: The anticoagulant protein C pathway is impaired in ESKD due to the downregulation of the endothelial protein C receptor (EPCR) and thrombomodulin. Intracellular pathways involving MAPKs and NF-κB can influence the expression of these receptors, reducing protein C activation and its anticoagulant effects.[18-22]

Platelet-Derived Microparticles (PMPs): PMPs are released from activated platelets and contain pro-coagulant phospholipids and TF. Uremia enhances PMP generation through intracellular calcium signaling and cytoskeletal reorganization, contributing to a hypercoagulable state.[23-25]

Fibrinolytic System Imbalance

Plasminogen Activator Inhibitor-1 (PAI-1): Increased levels of PAI-1 in ESKD inhibit tissue plasminogen activator (tPA), reducing fibrinolysis. Intracellular pathways involving transforming growth factor-beta (TGF-β) and MAPKs regulate PAI-1 expression in endothelial cells and platelets.[26-28]

Urokinase-Type Plasminogen Activator (uPA): Uremic conditions alter the expression of uPA and its receptor (uPAR), affecting localized fibrinolysis. Intracellular signaling through the Janus kinase (JAK)/

signal transducer and activator of transcription (STAT) pathway can modulate uPA/uPAR levels.[8, 9, 16, 17]

Abnormal Hemostatic Parameters in End-Stage Kidney Disease and Underlying Mechanisms

Prolonged Bleeding Time: Prolonged bleeding time is commonly observed in patients undergoing hemodialysis due to end-stage kidney disease (ESKD).[29]

• *Uremic Platelet Dysfunction:* Uremia impairs platelet function, affecting adhesion, aggregation, and secretion due to toxins accumulating in the blood.[17]

• *Endothelial Dysfunction:* Uremic toxins and hemodynamic stress can lead to endothelial cell damage, reducing the production of von Willebrand factor (vWF) and nitric oxide, which are crucial for platelet adhesion and vasodilation, respectively.[9]

Altered Platelet Count: Patients may exhibit either thrombocytosis (high platelet count) or thrombocytopenia (low platelet count).[30]

• *Thrombocytopenia:* Frequent blood sampling, mechanical trauma to platelets during dialysis, and sequestration in the spleen can reduce platelet count.[30, 31]

• *Thrombocytosis:* Compensatory mechanisms in response to chronic inflammation or iron deficiency anemia can lead to increased platelet production.[30]

Increased Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT): Prolonged PT and aPTT indicate a deficiency or dysfunction in the clotting factors of the extrinsic and intrinsic pathways, respectively.[32]

• *Vitamin K Deficiency:* Malabsorption or dietary restrictions common in ESKD patients can lead to vitamin K deficiency, affecting clotting factor synthesis.[33]

• *Liver Dysfunction:* Reduced hepatic synthesis of clotting factors due to liver dysfunction is often associated with ESKD.[34]

• *Heparin Use:* Heparin, used during hemodialysis to prevent clotting in the dialysis circuit, can extend PT and aPTT.[35]

Elevated Fibrin Degradation Products (FDPs) and D-dimer Levels: High levels of FDPs and D-dimer indicate increased fibrinolytic activity and ongoing clot breakdown.[33]

• *Chronic Inflammation:* ESKD is associated with chronic inflammatory states that promote coagulation and subsequent fibrinolysis.[36]

• *Dialysis-Related Stress:* The hemodialysis procedure itself can induce a transient pro-thrombotic state, followed by increased fibrinolysis.[37]

Dysregulated von Willebrand Factor (vWF) Activity: Elevated or dysfunctional vWF activity is commonly seen in ESKD.[38]

• *Endothelial Injury:* Chronic endothelial activation or damage due to uremic toxins increases vWF release.[39]

• *Altered Clearance:* Impaired renal function reduces the clearance of vWF, leading to elevated levels and potentially dysfunctional multimers that affect normal clot formation [38].

Abnormal Thrombin Generation: Enhanced or impaired thrombin generation affects the balance between coagulation and anticoagulation.[40]

• *Pro-coagulant State:* Increased levels of pro-inflammatory cytokines and exposure to dialysis membranes can enhance thrombin generation.[41]

• *Anticoagulant Therapy:* The use of anticoagulants during dialysis to prevent extracorporeal clotting can alter thrombin dynamics, potentially leading to bleeding complications.[42]

Abnormalities in Coagulation in End-Stage Kidney Disease

Hypercoagulability in CKD

Upon vascular injury, the coagulation process leads to the reinforcement of the platelet cluster through the assembly of fibrin. Among patients undergoing conservative management for CKD and those on hemodialysis, there is a distinct trend of hypercoagulability. This state is characterized by heightened levels of fibrinogen, tissue factor, D-dimer, tissue plasminogen activator, Factor VIII, and thrombin-antithrombin complexes, accompanied by decreased levels of proteins C and S (coagulation proteins).[43] Furthermore, fibrin clots generated from the plasma of hemodialysis patients manifest a more compact and thrombogenic structure combined with reduced permeability. This unique clot composition is linked to an augmented risk of cardiovascular mortality. Additionally, post-translational glycosylation and guanidinylation are observed in fibrinogen from patients undergoing hemodialysis, leading to the formation of finer fibrin filaments.[44]

Coagulation and Fibrinolysis Dysbalance in CKD

Even though platelet function is diminished and there is a predisposition to bleeding, individuals with uremia still exhibit activation within the coagulation system. Disturbances in coagulation and fibrinolysis indicate an increased tendency toward coagulation, accompanied by cardiovascular and thrombotic complications. Patients with uremia undergoing hemodialysis remain susceptible to vascular access thrombotic complications. Thrombotic occlusions are associated with procedures like percutaneous cannulation, central vein catheter insertion, and the establishment of native vein or prosthetic arteriovenous fistulas. Contributing factors to the emergence of a hypercoagulable condition include elevated platelet aggregability, fibrinogen concentrations, von Willebrand factor, and FVIII in the plasma. Contradictory results concerning the fibrinolytic process reveal both reduced functionality and stimulation of fibrinolysis following hemodialysis.[45]

Plasma prothrombin time (PT) and activated partial thromboplastin time (APTT) are standard coagulation assessments commonly conducted in clinical laboratories to evaluate the functionality of the coagulation cascade. The PT assay gauges the extrinsic pathway, while the APTT test examines activities within the intrinsic pathway. Both tests are susceptible to variations from pre-analytical factors such as the venipuncture procedure, citrate anticoagulant dosage, and sample handling during transportation, processing, and storage. The presence of hemolysis, icterus, and lipemia poses significant challenges in coagulation tests utilizing photo-optical detection methods. The accuracy of outcomes can be influenced by errors occurring in both the pre-analytical and analytical phases.[46]

It is not necessary to outright reject all samples displaying signs of hemolysis when utilizing photo-optical methods for PT and/or APTT assays. The prevailing practice of discarding all samples affected by hemolysis should be reevaluated, as obtaining new samples is time-intensive, introduces additional operational expenses for the laboratory, and causes inconvenience to patients.[47]

The role of pro-coagulant phospholipids on the surface of circulating blood cells in thrombosis and hemostasis.

Phospholipids (PLs) are essential components present in all cell types, providing structural integrity and playing a role in cell signaling. Under

normal conditions, pro-coagulant aminophospholipids (aPLs) are kept on the inner side of the plasma membrane. When platelets are activated, these aPLs translocate to the outer membrane layer, where they are vital for the coagulation process by facilitating the binding of coagulation factors. Recent studies have highlighted that enzymatically oxidized phospholipids (eoxPLs) also participate in the coagulation process alongside native aPLs. However, the specific functions of aPLs and eoxPLs in thrombo-inflammatory diseases, such as arterial and venous thrombosis, are not yet fully understood.[48]

In addition to native aPLs, HETE-PLs, which are produced by LOX enzymes in innate immune cells, play a role in coagulation processes. All positional isomers of HETE-PLs have been shown to increase thrombin generation in vitro in a dose-dependent manner, likely due to changes in the biophysical properties of the activated cell membrane. These changes, induced by eoxPLs, increase membrane electronegativity, which in turn enhances the calcium-dependent binding of coagulation factors. Unlike unoxidized PC, 12-HETE-PC directly promotes thrombin generation. Molecular dynamics simulations and calcium-binding assays further indicate that a higher proportion of HETE-PLs on liposomal surfaces leads to increased calcium binding.[49, 50]

In vivo studies using Alox12−/− mice reveal smaller clots and a bleeding phenotype, rescued by injecting 12-HETE-PL-containing liposomes. Alox15−/− mice with defective fibrin clot formation demonstrate the importance of 12/15-LOX in eosinophils, with rescue by 12-HETE-PL-containing liposomes. Alox12 and Alox15 deletions protect against aneurysm formation in murine models of abdominal aortic aneurysm. Human studies show elevated eoxPLs in patients with antiphospholipid syndrome experiencing venous thrombotic events. Patients undergoing cardiopulmonary bypass surgery exhibit reduced post-operative platelet 12-HETE-PL levels, potentially contributing to an increased risk of bleeding. These findings suggest a significant role for HETE-PL in thrombosis and hemostasis.[49, 50]

The provided evidence outlines current knowledge about aPL distribution and eoxPL generation in response to inflammation and immune cell activation. It explores the roles of aPLs and eoxPLs in promoting coagulation reactions in vitro and murine thrombosis models. However, the impact of thrombotic diseases on aPL and eoxPL profiles in circulating blood cells in humans remains unknown. To address this, more clinical and translational studies using contemporary lipidomic techniques, such as LC-MS/MS and derivatization methods, are essential for detecting and quantifying these lipids. Additionally, a mechanistic understanding of how these lipids influence inflammation and coagulation is crucial for advancing our knowledge of their modulation and modification.[48]

Clinical Issues and Management Challenges in Thrombotic and Bleeding Disorders in ESKD

Thrombotic Disorders in ESKD

Increased Thrombotic Risk

- Patients with ESKD have a pro-thrombotic state due to enhanced platelet reactivity, elevated fibrinogen levels, endothelial dysfunction, and chronic inflammation.
- This increased risk manifests as deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), and stroke.[51]

Arteriovenous Fistula/Graft Thrombosis

- Hemodialysis patients often experience thrombosis of their vascular access sites, such as arteriovenous fistulas or grafts. This is due to endothelial injury and turbulent blood flow.
- Thrombosis of these sites can lead to the loss of dialysis access, requiring surgical revision or the creation of new access points.[52]

Challenges in Management

Balancing Anticoagulation

- Therapeutic Window: There is a narrow therapeutic window for anticoagulants in ESKD due to altered drug metabolism and excretion.[53]
- Bleeding Risk: A high risk of bleeding complicates the management of anticoagulants like warfarin or direct oral anticoagulants (DOACs).[53]
- Frequent Monitoring: Regular monitoring of coagulation parameters (e.g., INR for warfarin) is challenging due to fluctuating renal function and frequent dialysis sessions.[53]

Monitoring and Dose Adjustment

- Dose Adjustments: It is difficult to adjust doses to maintain efficacy while minimizing bleeding risk.
- Interaction with Dialysis: Dialysis can remove certain anticoagulants, necessitating dose adjustments on dialysis days.[53]

Risk of Calciphylaxis

- Warfarin Use: Warfarin increases the risk of calciphylaxis, a severe condition involving vascular calcification and thrombosis, requiring careful risk-benefit analysis before use.[53]

Bleeding Disorders in ESKD

Increased Bleeding Tendency

- Uremic toxins impair platelet function, causing prolonged bleeding time. Hemodialysis can exacerbate this issue due to heparin use.[17]
- Patients may present with mucosal bleeding, bruising, or more serious bleeding complications such as gastrointestinal bleeding or hemorrhagic stroke.[54]

Gastrointestinal Bleeding

- There is a higher incidence due to mucosal vulnerability, uremic platelet dysfunction, and the use of anticoagulants/antiplatelet agents.[55]
- This condition presents as hematemesis, melena, or occult blood loss, leading to anemia.[55]

Challenges in Management

Heparin Use During Hemodialysis

- Bleeding vs. Clotting: Balancing is necessary to prevent clotting in the dialysis circuit with the risk of systemic bleeding.[56]
- Heparin Alternatives: Considering alternative anticoagulants like low molecular weight heparin (LMWH) or regional citrate anticoagulation may offer a better safety profile.[57]

Antiplatelet Therapy

- Bleeding Risk: There is a high bleeding risk associated with antiplatelet agents like aspirin or clopidogrel, particularly in patients with a history of bleeding.[58]
- Balancing Cardiovascular Protection: It is necessary to balance the cardiovascular benefits of antiplatelet therapy with the increased risk of bleeding.[59]

Management of Acute Bleeding

- Reversal Agents: Use of reversal agents (e.g., vitamin K for warfarin, idarucizumab for dabigatran) in the event of severe bleeding.[60]
- Blood Product Transfusion: There is a frequent need for blood product transfusions, which can be logistically challenging and carry risks of transfusion reactions.[61]
- Local Hemostatic Measures: Use of local hemostatic agents and techniques to control bleeding, especially during surgical or endoscopic procedures.[6]

DISCUSSION

Hemodialysis (HD) appears to amplify the potential for thrombotic events, although the sustained malfunction of platelets may counterbalance the heightened vulnerability to post-dialysis thrombotic occurrences. An intricate interplay involving red blood cells, platelets, thrombus formation, endothelial interaction, and soluble components within the coagulation pathways was observed. Secondary hemostasis screening tests, as well as measurements of coagulation, fibrinolysis, and inhibition proteins, displayed noteworthy differences in pre-HD results compared to both controls and post-HD outcomes.

While small sample size studies have provided initial insights into the significant elevation of hemostatic parameters following dialysis in ESKD patients, their limitations highlight the need for further research. Small sample size studies have significant limitations, including reduced generalizability, lower statistical power, increased variability, and challenges in controlling for confounding factors.

Large-scale cohort studies, randomized controlled trials, mechanistic investigations, comparative effectiveness research, and advanced statistical techniques are necessary to validate these findings and enhance our understanding of the clinical implications. These approaches will provide more comprehensive and reliable data, guiding evidence-based management strategies for improving patient outcomes in ESKD.

CONCLUSION

An association is established exclusively between the high level of coagulation activation markers and the lower normal and immature platelet counts during the HD procedure. As a result, it is suggested that all patients be appropriately screened for coagulation profile and platelet count before and after dialysis to mitigate potential complications. The outcomes suggest that chronic renal failure entails varying hematological parameter abnormalities, necessitating meticulous evaluation and management.

The management of thrombotic and bleeding disorders in patients with ESKD is fraught with challenges. Thrombotic disorders necessitate a careful balance between preventing clot formation and avoiding excessive bleeding, particularly given the altered pharmacokinetics and pharmacodynamics in these patients. Bleeding disorders, on the other hand, require meticulous management of heparin and antiplatelet therapy to prevent serious hemorrhagic complications. Regular monitoring, individualized dosing, and a multidisciplinary approach are essential to optimize outcomes and mitigate risks in this complex patient population. Further research and the development of tailored therapeutic strategies are needed to improve the management of these disorders in ESKD.

AUTHOR'S RECOMMENDATION

Further investigation is imperative to attain a deeper comprehension of the persistent pro-thrombotic state in CKD patients, to elucidate its contribution to amplified morbidity and mortality within this patient cohort, and to identify prospective therapeutic strategies capable of translating into enhanced renal outcomes for these individuals.

AUTHORS CONTRIBUTION

All authors contributed equally to the review, concept, literature search, and Manuscript preparation and editing.

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CONFLICTS OF INTEREST

None declared

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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