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Review

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Altered platelet quality and dynamics in patients undergoing hemodialysis

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Abstract

Patients undergoing hemodialysis (HD) are at high risk for both atherothrombosis and hemorrhage. Compared to healthy individuals, these patients show significant alterations in platelet dynamics, potentially contributing to cardiovascular complications and bleeding. This review presents a hypothesis-generating model to elucidate the mechanisms of platelet turnover, reactivity, and premature aging in HD patients. It also examines the roles of pulmonary thrombopoiesis, inflammation, and oxidative stress in platelet dysfunction. Furthermore, the review highlights the importance of platelet heterogeneity and proposes a strategy for developing personalized antiplatelet therapies for HD patients. Future research directions, such as single-cell analyses, are recommended to enhance understanding of platelet dynamics in HD and improve patient care.

Keywords: Clonal hematopoiesis, extramedullary hematopoiesis, hematopoietic stem cells, inflammation, megakaryocytes, oxidative stress

INTRODUCTION

Patients with end-stage renal disease (ESRD) are at high risk for bleeding, atherothrombosis, and resistance to antithrombotic therapies[1]. These complications largely arise from uremia and the underlying disease burden associated with kidney dysfunction, both of which result in changes to the endothelium, coagulation factors, and blood cells, including platelets. Although hemodialysis (HD) helps reduce uremic toxicity, patients on HD remain vulnerable to both thrombotic and hemorrhagic complications[2-4]. One contributing

factor is the deterioration of their overall condition during treatment. Additionally, hypoalbuminemia and hypovolemia may develop, further increasing coagulability[5]. The use of anticoagulants during HD increases the risk of systemic bleeding, while bioincompatibility can promote thrombosis[6]. More importantly, altered platelet quality and function drive these risks. This review examines the role of platelets in the adverse outcomes observed in HD patients and presents a hypothetical model of how HD impacts platelet quality and function. We also identify key areas of platelet research relevant to HD that support this hypothesis. A deeper understanding of these mechanisms could lead to the development of personalized antithrombotic therapies aimed at preventing both atherothrombosis and hemorrhage.

Platelet dynamics under physiological conditions

Platelets, involved in the hemostatic process, are unique to mammals[7]. They are produced in the bone marrow through thrombopoiesis, much like other blood cells. Megakaryocytes (MgKs), the precursors of platelets, originate from hematopoietic stem cells (HSCs) in response to growth factors such as thrombopoietin (Tpo). After undergoing sufficient nuclear division through endomitosis, MgKs terminally differentiate and produce platelets, generating approximately 100 billion platelets daily[8]. Tpo, continuously produced by the liver, is cleared from the bloodstream by platelets. When platelet counts decrease, plasma Tpo levels rise, thereby stimulating platelet production[9]. Aged platelets activate an intrinsic apoptotic pathway, likely regulated by an unidentified internal timer[10]. This mechanism facilitates their recognition and clearance by the reticuloendothelial system, concluding their lifespan of approximately ten days. Under healthy conditions, platelets function optimally to maintain proper blood clotting.

Platelet dynamics in bleeding

When bleeding occurs, platelets are exposed to elements in the extravascular space, such as collagen bound to von Willebrand factor. This exposure activates the platelets, triggering the release of soluble factors that attract additional platelets and amplify the clotting cascade. The coordinated consumption of platelets and clotting factors forms a thrombus to stop bleeding. When platelet demand increases, larger, denser, and more reactive platelets are produced[11], enhancing hemostasis[12]. These platelets are thought to originate from MgKs with higher ploidy, which have undergone additional endomitosis in response to Tpo and inflammatory cytokines[13,14]. Erythropoietin (Epo), a stimulant for red blood cell production, has also been linked to increased MgK ploidy in mice[15], possibly making platelets more reactive during blood loss. While Tpo and Epo take days to impact platelet production[9,15], rapid mechanisms like MgK rupture may provide platelets within hours, as observed in mouse models of acute platelet depletion[16]. This rapid response may help meet urgent platelet demands in cases of acute bleeding in humans.

HYPOTHETICAL MODEL: PLATELET DYNAMICS IN HD PATIENTS

Platelet activation and exhaustion in ESRD patients on HD

Compared to physiological conditions, the production and function of blood cells in ESRD patients are significantly altered. Decreased Epo production by the kidneys, iron deficiency, secondary hyperparathyroidism, and bone marrow fibrosis contribute to severe anemia in these patients[17]. Changes in the innate immune system, such as reduced monocyte activity and impaired neutrophil function, are also common[18,19]. Uremic toxins and malnutrition further alter T cell-induced adaptive immune responses[19,20]. Similarly, platelets in ESRD are characterized by hyporeactivity associated with altered surface receptors and granule content[21,22]. Uremia also disrupts the balance between coagulation and platelet function, leading to either thrombosis or bleeding[23,24] [Table 1].

Although HD reduces uremia, it temporarily exacerbates immune alterations due to interactions with the HD circuit[25]. Analogously, while HD partially corrects coagulation imbalances and improves platelet function[22,26], it also activates platelets as blood flows through the dialyzer[27]. Platelets exhibit increased

Table 1. Mechanisms of thrombosis and hemorrhage in hemodialysis patients

Thrombosis		Causing factors		Bleeding
		Changes due to uremia		
Enhanced coagulability[5]	←	Uremia	→	Surface receptor alterations[21,22]
Hypovolemia/hypoalbuminemia[5]	←	Overall health complications in ESRD patients		
		Changes due to HD		
Bio-incompatibility[6]	←	Anticoagulants used during HD	→	Hypocoagulability
Platelet-leukocyte aggregation[29,30]	←	Platelet over-activation	→	Exhausted platelets[34]
Antiplatelet resistance[53]	←	Increased platelet turnover		
Altered platelet priming/biogenesis[68]	←	Inflammatory mediators/ROS		
Increase inMgK ploidy[13]	←	Excessive platelet consumption	→	Thrombocytopenia
		Changes due to biological aging		
Altered platelet priming by SASP[103]	←	Senescent leukocytes		
Rapid release of larger & hyperactive platelets[110,111]	←	Fast-tracked emergency MgK production		
Potentially thrombotic mutations[120]	←	CHIP-related mutations	→	Potentially hemorrhagic mutations[120]
(e.g., DNMT3A, TET2, JAK2)[118,121]				(e.g., GFI1B)[122]

CHIP: Clonal hematopoiesis of indeterminate potential; ESRD: end-stage renal disease; HD: hemodialysis; MgK: megakaryocytes; ROS: reactive oxygen species; SASP: senescence-associated secretory phenotype.

activation, evidenced by higher levels of platelet CD62P on the venous side of the HD circuit[28]. Some activated platelets aggregate with leukocytes[29,30], while others undergo degranulation[31]. Although platelet activation starts immediately after HD begins[6], it gradually diminishes over the course of the session, accompanied by a reduction in platelet size[32]. Electron microscopy reveals that these smaller platelets contain fewer dense granules, confirming degranulation[33]. These platelets are likely overactivated and are unable to participate in subsequent hemostatic processes, representing exhausted platelets[34]. Exhausted platelets are also observed in trauma[35], stroke[36], and cancer[37], contributing to their bleeding complications. Given that up to 80% of platelets are exhausted in HD patients[32], this is likely the cause of increased bleeding risk in these patients.

Robust consumption of platelets

A study by Dewanjee *et al.* investigates platelet consumption in a swine model of HD[38]. They inject autologous 111-indium-labeled platelets into pigs and find that radioactivity counts from the lungs increase by 1.5-fold immediately after starting HD, indicating significant platelet trapping in the lung vasculature. The radioisotope counts in the spleen and liver also increase, suggesting that activated platelets are phagocytized by macrophages in these organs. Twenty-four hours after injection, HD animals retain twice as many platelets in the lungs compared to control animals, confirming the lungs' role in capturing HD-induced thrombi. Remarkably, platelet levels in the blood drop by nearly half after three hours of HD. The isotope count lost from the bloodstream was nearly equal to the sum of that trapped in the HD circuit, adhered to the lung vasculature, and presumably embolized to other organs. Robust platelet consumption following intense activation mirrors the pathology of disseminated intravascular coagulation (DIC)[39], heparin-induced thrombocytopenia (HIT)[40], and thrombotic thrombocytopenic purpura (TTP)[41]. These conditions are characterized by a bleeding tendency despite a hypercoagulable state, supporting the idea that excessive platelet consumption may contribute to both thrombosis and bleeding in HD patients. Moreover, significant platelet loss due to HD aligns with findings from a clinical study on cardiopulmonary bypass circuits, where several days are needed to restore platelet counts[42]. A single session of extracorporeal circulation induces the production of larger, hyperreactive platelets, resembling the response to bleeding

events that increase megakaryocyte ploidy[11,13]. Notably, larger platelets are linked to atherothrombosis in HD patients[43,44]. This supports the idea that HD activates compensatory mechanisms for bleeding, which may, in turn, lead to thrombotic events.

Accelerated turnover of platelets

In the swine study, indium-bound proteins from platelets degrade within macrophage phagosomes in the spleen and liver, with the isotope likely remaining inside and potentially binding to other intracellular proteins[45]. Despite the accumulation of significant residual isotopes through this process, the levels of radioactivity in the spleen and liver remain comparable between sham-operated animals and those after HD. This suggests that these organs provide live platelets to compensate for platelet consumption[46], which may explain the rapid recovery of platelet counts in HD patients. More importantly, increased platelet turnover might indicate significantly heightened thrombopoiesis. We hypothesize that, with the fast and repetitive turnover of platelets, patients may eventually reach a threshold where even a slight reduction in thrombopoiesis leads to mild thrombocytopenia. This aligns with reports showing that HD patients tend to have lower platelet counts[47-49], which decline further with age[49] much faster than in the general population[50]. Notably, mild thrombocytopenia appears to be associated with worse cardiovascular outcomes in chronic HD patients, particularly those resistant to antiplatelet therapy[51], similar to patients with venous thrombosis and exhausted platelets[52]. These observations are in line with the notion that increased platelet turnover contributes to antiplatelet therapy resistance[53] [Table 1].

Variance in platelet reactivity among HD patients

The impact of platelet activation, exhaustion, and consumption on overall platelet reactivity remains unclear, and the prognostic significance of accelerated platelet turnover and the resulting mild thrombocytopenia[51] requires further validation. Interestingly, some studies indicate that platelet reactivity varies significantly among HD patients. Gäckler *et al.* report that up to 15% of HD patients show extreme increases or decreases in *ex-vivo* platelet aggregation[54]. This variability may result from differences in platelet reactivity before and after HD[55], which could partially explain the mixed results in studies examining platelet function in these patients[56]. Notably, patients who experience thrombotic vascular access failure exhibit increased platelet reactivity[57], while those with bleeding events display altered platelet function[58]. Therefore, we hypothesize that the outliers in platelet reactivity identified by Gäckler *et al.* may be linked to either thrombotic or bleeding diatheses[54]. It is also important to note that platelet reactivity is not consistently high or low within the same individual; rather, both hyperactive and exhausted platelets likely coexist. Proteomics studies reveal a mixed activation pattern in platelets from patients with acute coronary syndrome[59,60] or COVID-19[61,62]. In a chronological analysis of patients with critical limb-threatening ischemia, researchers observe a dramatic decrease in platelet alpha granule secretion prior to cardiovascular events (and unpublished data[63]). These studies suggest that both hyperactive and exhausted platelets can be present in a single individual. This may also apply to HD patients.

The extent of accelerated platelet turnover may also differ among patients. Although reticulated platelets, detected by mRNA-binding thiazole orange and corresponding to younger platelets, indicate rapid turnover[64], conflicting studies report varying levels of these cells in HD patients[65,66]. Tassies *et al.* find that in HD patients with renal anemia, thiazole orange-dim platelets do not reach the threshold for detecting immature platelets[67]. Interestingly, after treatment with recombinant human Epo, thiazole orange intensity normalizes, and platelet function improves. Given that Epo may influence MgK ploidy[15], the findings of Tassies *et al.* suggest that the mechanism of thrombopoiesis significantly impacts platelet quality and reactivity[67]. Notably, patient responses to Epo vary[67], implying that differences in progenitor or stem cell susceptibility to thrombopoietic stimuli may also affect platelet reactivity, thereby contributing to variations in platelet quality. Collectively, we hypothesize that some HD patients are under a precarious balance

between hyperactive and exhausted platelets, and when either side shifts, patients may experience thrombosis or hemorrhage.

Central role of the lungs in hyperactive platelet formation

Platelet subpopulations with varying reactivity likely arise from the diversity of MgK, different modes of thrombopoiesis, and environmental priming[68]. However, the exact origins, characterizations, and mechanisms behind these variations in platelet quality remain unclear. It is plausible that multiple pathways, including some yet to be identified, regulate platelet reactivity to maintain hemostatic balance, even in HD patients. Thus, when outliers in platelet function occur, it is likely that extreme conditions or environments in platelet biogenesis and maintenance exist beyond the typical homeostatic controls. In this context, we hypothesize that platelet biogenesis and retention in the lung may play a critical role for two reasons. First, although thrombopoiesis in HD patients is expected to accelerate significantly to meet the increased platelet demand, it is surprising that the bone marrow MgK count remains low despite thrombocytopenia[69]. This suggests the presence of substantial extramedullary thrombopoiesis. The role of MgK in the pulmonary vessels in platelet production has been debated[70-73] since it was first reported nearly fifty years ago[74,75]. Notably, recent research by Lefrançais *et al.* reveals that bone marrow-derived MgKs contribute significantly to platelet biogenesis in the mouse lungs, accounting for nearly 50% of total platelet production[76]. They also discover that hematopoietic stem and progenitor cells in the lungs can reconstitute bone marrow in response to thrombocytopenia and bone marrow stem cell deficiency. Given that thrombocytopenia[47-49] and bone marrow fibrosis[77-79] are relevant in HD patients, replenishment of HSC from the lungs may be vital for HD patients.

Second, the lung vasculature receives venous blood directly from the HD circuit. As mentioned, platelets lose their granule contents in the HD circuit, releasing platelet-secreted molecules including thrombopoietic and inflammatory cytokines[14] directly into the hematopoietic niche. Thus, it is hypothesized that thrombopoiesis may occur significantly in the lungs of HD patients. Recent studies have identified MgK in the extravascular space of the lungs, where it participates in the local immune response rather than being involved in thrombopoiesis[80,81]. However, Qiu *et al.* observe that inhaled particles increase MgKs in the alveoli and rapidly boost activated platelets in circulating blood[82]. Although the impact of intravascular mediators on MgKs and resident hematopoietic progenitor cells in the lungs remains unclear[83], this may support the hypothesis that HD-derived contents in the venous blood alter platelet biogenesis in the lungs.

Notably, blood collected from the dialyzer also contains high levels of reactive oxygen species (ROS), mainly generated by activated polymorphonuclear neutrophils during HD[84-86]. Conversely, reduced erythropoiesis in renal anemia and increased apoptotic death from eryptosis[87] compromise the antioxidant properties of red blood cells[88], significantly increasing oxidative stress in venous blood[84,89]. Since inflammation and ROS are associated with platelet hyper-reactivity[68,90,91], both fresh platelets produced in the lungs and other platelets passing through the lung vasculature may be primed by inflammatory cytokines and ROS in venous blood[68]. This priming may contribute to the development of hyperactive platelets.

Role of premature aging in platelet priming

Inflammation and oxidative stress are hallmarks of cellular aging processes involving telomere attrition (i.e., Hayflick's replicative cellular senescence)[92-94]. Cellular senescence is believed to contribute significantly to biological aging, and various age-related diseases have been associated with premature aging[95,96]. Previous reports show that hematopoiesis in HD patients exhibits features of premature aging, such as producing leukocytes with aged phenotypes. For instance, 40% of peripheral blood mononuclear cells display telomere shortening, compared to 5% in age-matched control[97], which is associated with increased p53 expression and altered cell surface markers from a CD14-bright/CD16-dim to a CD14-dim/CD16-bright phenotype.

Telomere shortening correlates with future cardiovascular events in HD patients[98], highlighting the role of premature senescence in adverse HD outcomes. Cellular senescence is generally linked to the secretion of proinflammatory cytokines[99], known as the senescence-associated secretory phenotype (SASP), which is mainly attributed to prematurely aged cells, including monocytes and endothelial cells[100,101]. SASP factors like IL-6, IL-1β, and TNF-α from these cells create an inflammatory environment that may sensitize platelets to activation signals[101]. Studies indicate that SASP significantly alters platelet function in prematurely aged patients, including those with cardiovascular diseases, diabetes, obesity, and chronic kidney diseases[101-103]. This supports the notion that platelet priming by senescent cells is a mechanism that makes platelets hyperactive in HD patients.

Role of premature aging in thrombopoiesis

In contrast, interpreting how cellular senescence alters platelet biogenesis is complex, as Hayflick's senescence machinery is crucial for the physiological differentiation of MgKs[93,104]. However, telomere attrition skews hematopoietic stem cells (HSC) toward MgK lineages[105]. Studies in rodents[106,107] and humans[108] reveal that platelet-skewed hematopoiesis is associated with the thrombogenic features of aging[109]. Remarkably, this pathway of thrombopoiesis in this pathway rapidly produces hyperactive platelets during acute platelet depletion[110,111]. Moreover, reports show that platelets from aged individuals exhibit higher reactivity to classical agonists than those from younger individuals, with aggregability increasing by up to 8% per decade[112]. Transcriptome studies reveal differentially expressed platelet RNA with age[113], potentially shifting platelets toward a proinflammatory state[114], which is associated with age-related diseases. This body of evidence supports the view that altered thrombopoiesis driven by stem cell aging may be a pivotal factor contributing to the generation of hyperactive platelets in HD patients.

An alternate feature of hematopoietic aging is clonal hematopoiesis of indeterminate potential (CHIP)[115], which refers to the expansion of HSC with age-related somatic mutations without apparent hematologic malignancies. CHIP occurs in 10% of individuals over 65 years of age[116] and is a prominent risk factor for atherothrombosis[117]. Specific CHIP mutations, such as those in DNMT3A and TET2, are linked to genome instability that drives excessive production of inflammatory cytokines, potentially contributing to cardiovascular impairment[118]. A study shows a higher prevalence of these CHIP mutations among ESRD patients, which is associated with the progression of kidney disease[119]. Other CHIP mutations may affect platelet function, especially considering the thrombogenic and bleeding risks previously associated with mutations in these genes from other contexts[120]. For instance, the JAK2 mutation, linked to ischemic stroke in individuals with CHIP[121], also contributes to increased thrombosis risk through enhanced platelet activation in essential thrombocythemia. Similarly, mutations in GFI1B, found in CHIP, are associated with gray platelet syndrome, an inherited bleeding disorder characterized by reduced alpha-granules in platelets[122]. These mutations can affect platelet quality, potentially leading to either thrombosis or hemorrhage in HD patients.

The exact mechanism behind HSC mutation remains unclear. However, we hypothesize that HSC in HD patients are more susceptible to mutations for several reasons. First, the proportion of activated to quiescent HSC is presumably higher in HD patients due to the increased demand for MgK resulting from platelet consumption. Second, activated HSCs are more prone to mutations because of exposure to replication-associated errors[123,124]. Finally, HD induces significant stimuli in the lung hematopoietic niche as HD-stimulated blood cells and soluble factors, arriving via venous circulation, increase chronic inflammation and oxidative stress. This may enhance both HSC activation[102] and mutation[125]. These factors support the view that hyperactive platelets in HD patients may result from biological aging of the hematopoietic system.

Hypothetical mechanism of bleeding and thrombotic risks in hd patients

Altogether, we hypothesize that HD-induced inflammatory mediators and oxidative stress likely skew lung hematopoietic differentiation toward aged phenotypes[51]. This leads to the production of hyperactive platelets through the direct impact on thrombopoiesis. Alternatively, platelets may be primed by the senescence-associated secretory phenotype (SASP) and other proinflammatory signals from aged leukocytes[126]. These hyperactive platelets then enter the HD circuit and become activated, creating a feedback loop that generates excessive inflammatory cytokines and ROS, which are subsequently reintroduced to the lungs. In HD patients, this cycle repeats three times a week over a lifetime, promoting chronic inflammation in the vessel walls and contributing to atherothrombosis[51,127]. Alternatively, when this process leads to a predominance of exhausted platelets, it may increase the risk of bleeding [Figure 1].

FUTURE DIRECTIONS AND CONCLUSIONS

Therapeutic strategies for individualized antithrombotic therapy

Efforts to mitigate thrombosis while preventing bleeding have explored various dialysis membranes, ranging from cellulose diacetate to polysulfone, that reduce inflammatory substances or oxidative stress in the effluent[128]. Individualized anticoagulant treatments, such as fractionated heparin, citrates, or even anticoagulation-free HD, have shown promise in reducing platelet activity and bleeding risks[129]. However, the effectiveness of these strategies for preventing cardiovascular events in HD patients remains uncertain. Furthermore, antiplatelet therapy should be precisely tailored based on drug types, combinations, doses, and treatment durations[130]. The thrombotic and hemorrhagic mechanisms in HD are complex and vary significantly among patients. These conditions may also evolve with hematopoietic aging[131], and hematological changes can arise spontaneously due to other conditions, such as infections[132] and malnutrition[133], complicating individualized antithrombotic therapies. To address the paradox of antiplatelet resistance and bleeding risks, it is essential to identify distinct platelet subpopulations, including the roles of hyperactive and exhausted platelets. Although methods like aggregation analyses and hematology analyzers are commonly used, most studies prepare platelet samples from whole blood or platelet-rich plasma separated via centrifugation, leading to the analysis of platelets as a bulk population. Since varying platelet reactivity in HD patients may be linked to different distributions of platelet subpopulations, a more detailed classification of these bulk populations is needed.

Single-cell analyses are crucial for identifying specific subpopulations. Fluorescence flow cytometry can distinguish several surface marker expression patterns, identifying a few platelet subpopulations. Advances in cytometry, such as time-of-flight mass spectrometry, now enable the staining of up to 100 different parameters in a single cell. This technology has been used for immunophenotyping various cells[134], including platelets. Computational clustering of identical cell populations has successfully identified novel platelet subtypes in both healthy individuals and patients with Glanzmann thrombasthenia[135]. Recently, single-cell RNA sequencing (scRNA-seq) has provided detailed snapshots of gene expression in anucleated red blood cells, helping to identify their subpopulations[136]. Applied to platelets, scRNA-seq could become a powerful tool for defining platelet subpopulations and understanding their functional roles. Leveraging single-cell analyses to quantify the relative proportions of hyperactive and exhausted platelets may help to unravel the complexities of platelet reactivity in HD patients, ultimately paving the way for personalized antiplatelet therapies that can effectively mitigate thrombotic events while minimizing bleeding risks.

Conclusions

HD patients experience the paradoxical coexistence of thrombotic and hemorrhagic diatheses, hindering antithrombotic therapy. In these patients, the HD circuit over-activates platelets, increasing inflammation and oxidative stress while simultaneously promoting platelet exhaustion. This over-activation accelerates hematopoietic aging, likely involving hematopoietic stem and progenitor cells in the lungs, leading to the

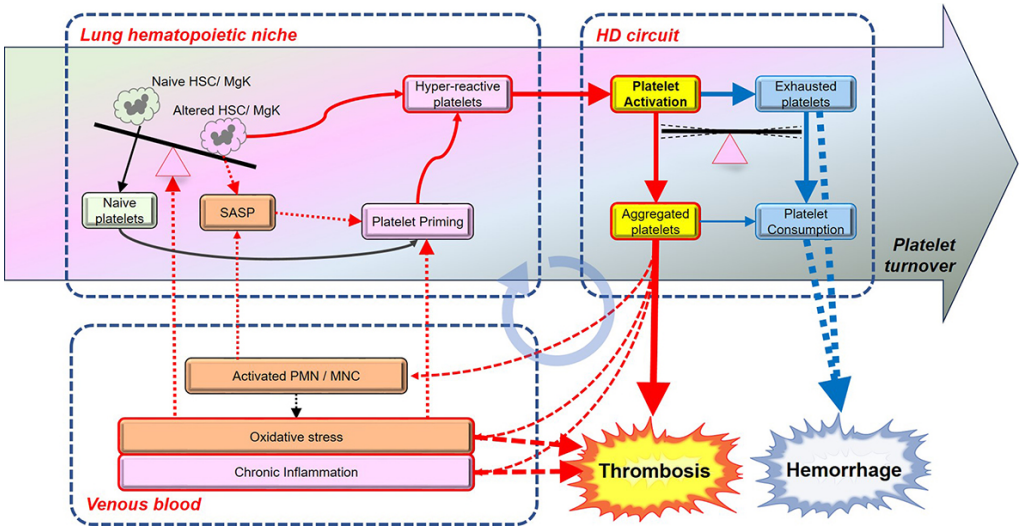

Figure 1. Hypothetical mechanism of bleeding and thrombotic risks in patients undergoing hemodialysis. Platelets become activated upon entering the hemodialysis circuit, either losing their granule content and becoming exhausted or aggregating with activated polymorphonuclear neutrophils. These aggregates carry oxidative stress and inflammatory mediators, which are transported to the hematopoietic niche in the lungs, skewing the differentiation of hematopoietic stem cells (HSCs) and megakaryocytes (MgKs) toward biologically aged phenotypes. Aged HSCs and MgKs directly impact thrombopoiesis or indirectly prime platelets to become more sensitive to activation stimuli through the senescence-associated secretory phenotype (SASP) and other proinflammatory signaling in the presence of aged leukocytes. These hyperactive platelets re-enter the HD circuit, creating a positive feedback loop that increases inflammatory cytokines and oxidative stress, which are once again delivered to the lungs. The balance between naïve, activated, and exhausted platelets is maintained by homeostatic buffering mechanisms. However, when this vicious cycle sustains chronic inflammation in vessel walls, it may promote atherothrombosis. Alternatively, if this process leads to significant qualitative changes in platelets or a depletion of thrombopoietic capacity, the prevalence of exhausted platelets could increase bleeding risk. The bold arrows indicate cell dynamics while the dotted arrows represent their functional properties. HSC: Hematopoietic stem cell; HD: hemodialysis; MgK: megakaryocyte; MNC: mononuclear cell; PMN: polymorphonuclear cell; SASP: senescence-associated secretory phenotype.

production of hyperactive platelets and perpetuating a vicious cycle. Meanwhile, platelet exhaustion heightens the risk of bleeding. Future research focused on characterizing hyperactive platelets and measuring their proportions relative to exhausted platelets will be crucial for developing tailored antiplatelet therapies.

DECLARATIONS

Authors' Contributions

Made substantial contributions to the conception of the review: Tateno K

Provided valuable insights into the roles of lung vasculature and coronary heart disease: Sugimura K, Fujimoto Y, Kawamura A

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

Not applicable.

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