THROMBOTIC COMPLICATIONS OF SICKLE CELL ANEMIA

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BACKGROUND

Sickle cell anemia (SCA) is an inherited blood disorder caused by a mutation in the HBB gene that produces abnormal hemoglobin S (HbS), which distorts red blood cells into rigid, sickle-shaped forms. These cells are fragile, hemolyze prematurely, and block vessels, resulting in chronic anemia and vaso-occlusive crises (Figures 1 & 2). Typical red blood cells usually live for about 120 days before they need to be replaced. But sickle cells usually die in 10-20 days, leaving a shortage of red blood cells, causing the anemia part. It is well known that SCA is a prothrombotic condition, with patients exhibiting severe risks of VTE, stroke, and other thrombotic events. However, the precise mechanisms underlying this hypercoagulable state in SCA patients remain unclear. The objective of this study was to review the literature to better understand how and why thrombosis develops in SCA patients, identify key biological pathways involved, and highlight treatment options targeting platelet-driven thromboinflammation to guide the development of more effective therapies.

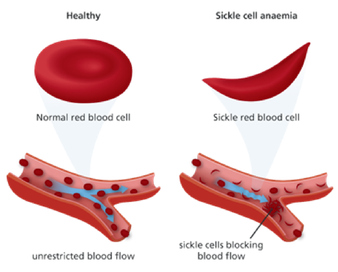

Figure 1: Comparison of a healthy red blood cell and a sickle cell in SCA.

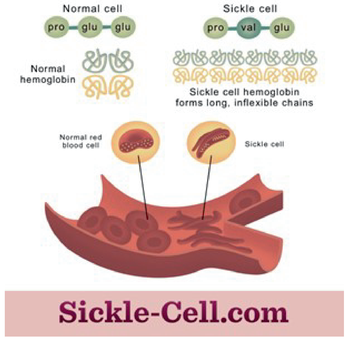

Figure 2: Blood flow in a vessel with normal RBC versus sickle cell.

OBJECTIVES

We reviewed findings from peer-reviewed, population-based studies to elucidate the mechanisms of thrombosis associated with SCA. Cellular and molecular mediators of thrombosis, including platelet activation, natural anticoagulants, and microparticle release, were examined.

METHODS

We incorporated findings from a single-center retrospective observational study titled "Interplay Between Sickle Cell Disease and Thrombosis", the review article "Sickle Cell Disease and Venous Thromboembolism: What the Anticoagulation Experts Need to Know", and the study "Factor XII Contributes to Thrombotic Complications and Vaso-Occlusions in Sickle Cell Disease."

RESULTS

SCA produces a chronic hypercoagulable state driven by hemolysis. Chronic hemolysis releases free hemoglobin and heme which consume nitric oxide and promote oxidative stress. TNF-alpha drives endothelial cell activation, thereby increasing the expression of adhesion molecules like VCAM-1 and ICAM-1, which makes the endothelium "stickier" for sickled RBCs, activated platelets, and leukocytes. This promotes vaso-occlusion, which triggers local thrombin generation and microparticle release.

Endothelial cells, monocytes, and microparticles express higher levels of Tissue Factor (TF, a key initiator of the coagulation cascade). Patients with SCD have persistently elevated TF expression, leading to ongoing thrombin production. Circulating microparticles derived from RBCs and from previous elements are elevated in both steady-state and crisis conditions. These microparticles carry tissue factor and phosphatidylserine (PS), further amplifying thrombin generation and vascular occlusion. Patients have slow circulation due to slowed blood flow caused by sickle cells, allowing clotting factors and platelets to accumulate.

Platelets in SCA are chronically activated, with elevated P-selectin expression. Decreased levels of these natural anticoagulants may contribute to the increased risk of thrombosis and vaso-occlusion in SCA, explaining why patients may develop complications such as stroke and organ damage even outside of acute crises.

SCA patients show signs of reduced clot breakdown, specifically during inflammatory states. This reduced fibrinolytic activity was likely caused by damage to blood vessel linings from widespread red cell sickling, which likely reduces the body's production of plasminogen activator, a key factor in breaking down clots. This impaired fibrinolysis can increase the risk of vascular blockage because clots and/or fibrin build up but are not efficiently cleared. Decreased plasminogen activator production and endothelial injury impair fibrinolysis, allowing fibrin build-up and sustained vascular obstruction.

Anticoagulation management is complex due to baseline anemia, renal dysfunction, central venous catheters, frequent hospitalization, and ongoing inflammatory activation. A single-center retrospective observational study of 46 SCD patients found that 12 developed thrombosis and 17.4% showed signs of VTE, while 75% of those affected carried the HbS gene (Figure 3). Significant associations with thrombosis included old age, anticoagulant therapy and dosage, Antiplatelet therapy, and type of transfusion received.

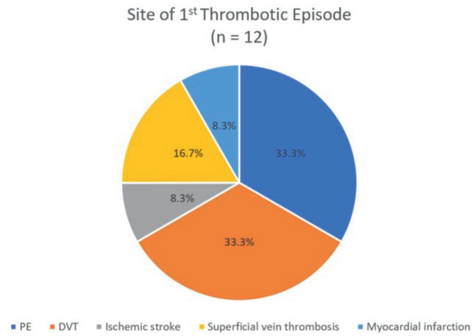

Figure 3: Anatomical classification of the first thrombotic episode

RESULTS CONT.

In experimental mouse models mimicking patient SCD, Factor XII activation significantly increased thrombin production and inflammation (Figure 4). More importantly, inhibition of Factor XII reduced thrombotic and vaso-occlusive events. These findings suggest that the intrinsic pathway may actively contribute to thromboinflammation in SCA, particularly during crisis. Unlike other coagulation factors, Factor XII inhibition may reduce thrombosis with minimal bleeding risk, making it a promising therapeutic target.

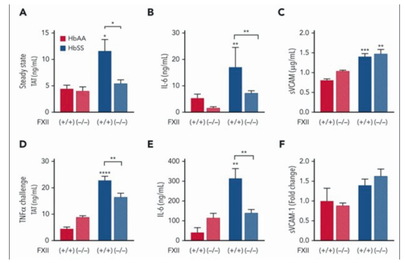

Figure 4: Factor XII contributes to increased thrombin generation and inflammation in HbSS mice at steady state.

DISCUSSION

Thrombosis in SCA is characterized by continuous interaction between hemolysis, inflammation, endothelial dysfunction, and dysregulated coagulation. Unlike short-lived risk factors seen in the general population, SCA represents a persistent prothrombotic environment. Hydroxyurea may indirectly reduce thrombotic risk by lowering leukocyte and monocyte counts and reducing endothelial activation. Anti-P selectin therapy, such as crizanlizumab, reduces adhesion and vaso-occlusive events, and may influence thromboinflammatory pathways. Many have opted to take a more curative approach using gene therapy to eliminate defective RBC production entirely. Despite the many treatment regimens available, prevention and long-term management of VTE in SCD remain complex and require additional evidence-based guidance.

CONCLUSIONS

Thrombosis in SCA results from the combined effects of hemolysis, chronic inflammation, platelet hyperactivation, and endothelial dysfunction. These mechanisms create a sustained hypercoagulable state, significantly increasing the risk of VTE. Management strategies, such as antiplatelet therapy and anticoagulation, may help reduce the risk of thrombosis, and treatment regimens such as hydroxyurea, blood transfusions, and crizanlizumab show promising results. A deeper understanding of these mechanisms is critical for improving thrombotic prevention and optimizing care for patients with SCA. We have reviewed the complex mechanisms that promote thrombotic complications in SCA, discussing the pathophysiology, complications, and advances in targeted therapies aimed at reducing thrombotic complications and improving patient outcomes.