Hypercoagulability and Vascular Disease

Ali T. Taher, MD, PhD, FRCP[a,*], Maria Domenica Cappellini, MD[b,c], Rayan Bou-Fakhredin, BSc[d], Daniel Coriu, MD, PhD[e], Khaled M. Musallam, MD, PhD[f]

KEYWORDS

• Thrombosis • Pulmonary hypertension • Cerebrovascular disease
• Hypercoagulable state

KEY POINTS

- Hypercoagulability in β-thalassemia is attributed to several factors, including the prothrombotic potential of red blood cells, activated platelets, and endothelial damage.
- Clinical thrombotic events are more commonly observed in splenectomized or nontransfused patients and include venous, arterial, and cerebrovascular events.
- Clinical trials to determine the best prevention or treatment approaches are absent and management should remain individualized, focusing on high risk patients.

INTRODUCTION

A hypercoagulable state has been identified in patients with β-thalassemias, especially in those with nontransfusion-dependent thalassemia (NTDT), which can be present since childhood.[1–3] This hypercoagulable state primarily results from abnormalities in pathologic red blood cells and platelets, ultimately leading to thrombosis or other types of vascular disease (**Fig. 1**).[4–9] This article summarizes current knowledge on such mechanisms and highlights available evidence on clinical sequelae and their management. Although hypercoagulability is thought to play a crucial role in the development of pulmonary hypertension in patients with β-thalassemia, other factors and disease dynamics are also involved and these will not be discussed in the scope of this review.

Conflicts of Interest: None to disclose.

[a] Department of Internal Medicine, Naef K. Basile Cancer Institute, American University of Beirut Medical Center, PO Box 11-0236, Beirut 11072020, Lebanon; [b] Department of Medicine, Ca' Granda Foundation IRCCS, Milan 20122, Italy; [c] Department of Clinical Science and Community, University of Milan, Milan 20122, Italy; [d] Department of Internal Medicine, American University of Beirut Medical Center, Beirut 11072020, Lebanon; [e] Department of Hematology, Fundeni Clinical Institute, University of Medicine and Pharmacy "Carol Davila", Bucharest 030167, Romania; [f] International Network of Hematology, London WC1V 6AX, UK
* Corresponding author.
E-mail address: ataher@aub.edu.lb

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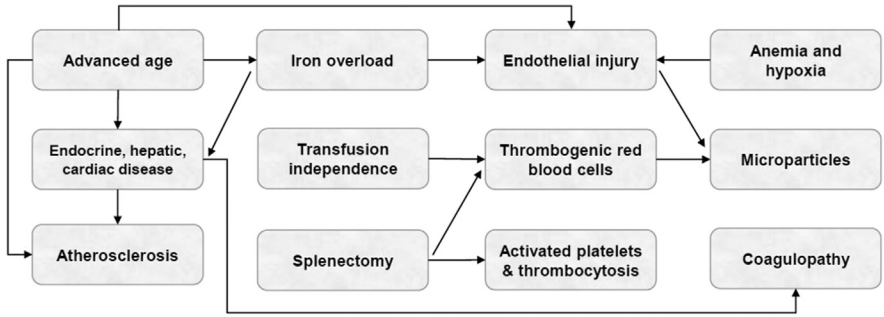

Fig. 1. Pathophysiologic and risk factors contributing to a hypercoagulable state and subsequent thrombotic and vascular events in β-thalassemia. Relevant associations between different factors are highlighted.

PATHOPHYSIOLOGY

Patients with β-thalassemia have enhanced platelet aggregation and chronically activated platelets,[10] as confirmed by the increased expression of CD62P (P-selectin) and CD63, which are markers of in vivo platelet activation.[11,12] β-thalassemia patients have been shown to have 4 to 10 times higher metabolites of thromboxane A2 and prostacyclin (PG I2), which are markers of hemostatic activity, than healthy individuals.[13] It has also been demonstrated that splenectomized patients have high platelet counts[14,15] but with a shorter life-span due to enhanced consumption.[16] One study showed that increased platelet adhesion is a finding that is commonly seen in splenectomized β-thalassemia patients. This is induced by mechanisms that involve both red blood cells and platelets, and is a strong contributor to occlusive thrombus formation in the carotid arteries of thalassemic mice.[17,18]

The role red blood cells play in the hypercoagulability of β-thalassemia has received great deal of attention. In thalassemia, the oxidation of globin subunits in erythroid cells leads to the formation of hemichromes,[19] which precipitate, prompting heme disintegration and the subsequent release of toxic iron species.[20] In turn, the free iron catalyzes the formation of reactive oxygen species, thereby leading to the oxidation of membrane proteins and the formation of red-cell senescence antigens such as phosphatidylserine,[21] which cause the red blood cells to aggregate and become rigid and deformed, resulting in premature cell removal.[22] Thalassemic red blood cells containing a high content of such negatively charged phospholipids often lead to an increase in thrombin generation,[23,24] as demonstrated by studies using annexin V, a protein with high specificity and affinity for anionic phospholipids.[24] Splenectomized patients have a considerably higher number of these negatively charged pathologic red blood cells and, as a result, higher thrombin generation is seen in these patients.[25,26] Compared with controls, β-thalassemia subjects were also found to have higher levels of procoagulant microparticles of red blood cell, leukocytic, and endothelial origins.[27]

The presence of other peripheral blood elements in patients with thalassemia, such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin, and von Willebrand factor, shows that endothelial cell activation or injury may be an aspect of the disease itself, aiding in the recruitment of red and white blood cells, thus promoting thrombosis.[28,29] In fact, studies have revealed that red blood cells from β-thalassemia subjects often express an increased adhesion to cultured endothelial cells.[30] Although inherited thrombophilia does not play a role in the