The Hypercoagulable State in Thalassemia Patients

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Learning Outcomes

- Thalassemia: symptoms and signs
- Types of thalassemia and pathophysiology
- Diagnosis and treatment
- Complications - thrombosis - molecular mechanisms
- Current potential antithrombotic drugs
- Conclusions

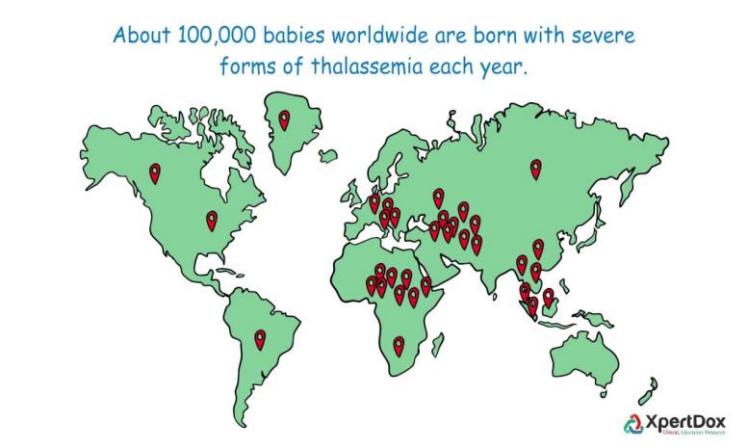
What is Thalassemia?

What?

Thalassemia is a genetic blood disorder that affects the production of hemoglobin and red blood cells in the body. Hemoglobin is a protein in red blood cells that carry oxygen. The function of red blood cells is to transport oxygen throughout the body via the bloodstream.

Symptoms and Signs?

Thalassemia can cause symptoms of anemia such as fatigue, trouble breathing, dizziness, and pale skin. Thalassemia also causes bone structure abnormalities, an enlarged spleen, discolored urine and skin, and poor appetite.



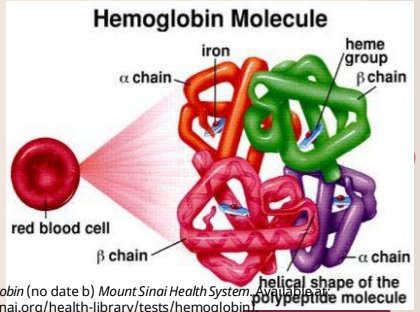
Adapted from *What is thalassemia?* (2018) *YouTube*. Available at: https://www.youtube.com/watch?app=desktop&v=JxuupecxHO8.

Incidence

- Approximately 1 in 100000 people in the general population possess thalassemia.
- Thalassemia affects African Americans, Southeast Asians, and people of Mediterranean descent.

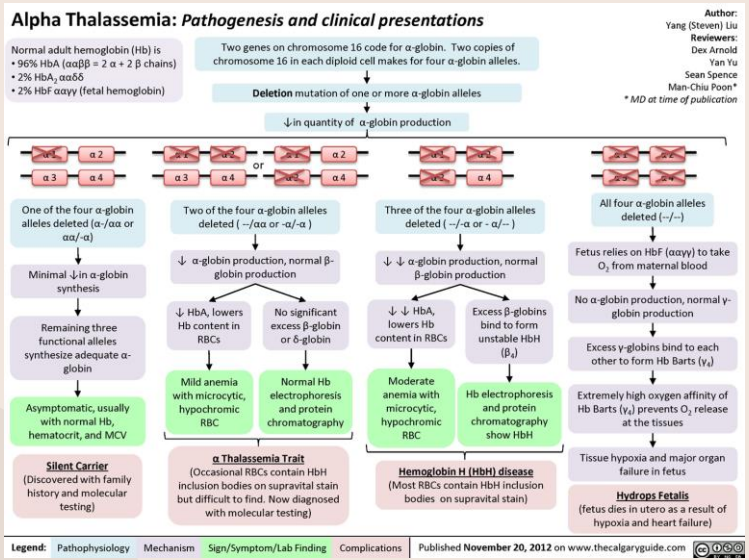
Alpha Thalassemia

- There are 4 genes (2 inherited from each parent) that make up alpha globin protein chains. Thalassemia occurs if one or more of these genes are defective.
- One defective gene results in an asymptomatic condition called alpha thalassemia minima.
- Two defective genes results in minor symptoms and is called alpha thalassemia minor.
- Three defective genes causes minor to severe conditions. This is called Hemoglobin H disease.
- Four defective genes (Hemoglobin Barts) are typically fatal.



Adapted from *Hemoglobin* (no date b) *Mount Sinai Health System*. Available at: https://www.mountsinai.org/health-library/tests/hemoglobin

Pathophysiology of Alpha Thalassemia

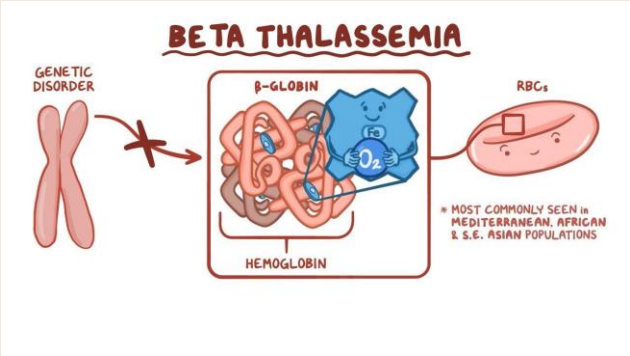


Adapted from *Alpha thalassemia: Pathogenesis and clinical presentations: Calgary guide* (2015) *The Calgary Guide to Understanding Disease.* Available at: https://calgaryguide.ucalgary.ca/alpha-thalassemia-pathogenesis-and-clinical-presentations/.

- The oxygen transport system depends on the affinity of hemoglobin for oxygen.
- 2 α-globin genes are located on each chromosome 16 making up the 4 α-gene loci (αα/αα)
- Severity of α-thalassemia depends on the number of inactivated or deleted alpha loci

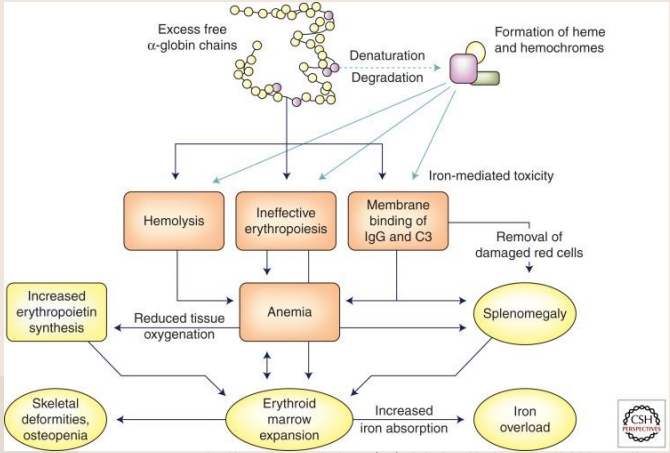
Beta Thalassemia

- Each person inherits 2 beta-globin genes, one from each parent.
- One defective beta-globin gene results in mild symptoms and is called beta thalassemia minor.
- Two defective beta-globin genes causes moderate to severe symptoms. The moderate version is called thalassemia intermedia, while the severe condition is called beta thalassemia major.



Adapted from *Osmosis - beta-thalassemia: Video, anatomy, definition & function | osmosis*. Available at: https://www.osmosis.org/learn/Beta-thalassemia.

Pathophysiology of Beta Thalassemia



Adapted from Nienhuis, A.W. and Nathan, D.G. (2012) *Pathophysiology and clinical manifestations of the β-thalassemias, Cold Spring Harbor perspectives in medicine.* Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3543079/.

- Freed a globin chains build up in RBCs
- Aggregation, denaturation, and degradation of these chains creates hemichromes, which damage cell membranes.
- This leads to bone marrow expansion, hemolysis of RBCs, and loss of red cells in the spleen.
- Bone marrow expansion causes skeletal deformities and osteopenia.
- Hemolysis leads to excessive iron levels.

Diagnosis

Prenatal Testing

Chorionic Villus Sampling

This test is done during around the 11th week of pregnancy; the process involves removing a small piece of the placenta for testing.

Amniocentesis

This test is done around the 16th week of pregnancy; the process involves evaluating a sample of amniotic fluid.

	Controls (n = 35)		β-Thalassemia (n = 56)[a]	
	Mean	SE	Mean	SE
Serum ferritin, pmol/L	ND[b]	NA	4885.76	356.70
Hb, g/L	134	1.9	99[c]	1.2
RBCs, $\times 10^{12}$/L	4.63	0.07	3.51[c]	0.05
WBCs, $\times 10^{9}$/L	9.3	0.65	7.4[c]	0.30
Plts, $\times 10^{9}$/L	269	18	255	9
Hct, ratio	0.40	0.01	0.29[c]	0.00
MCV, fL	87	0.66	83[c]	0.34
MCH, pg	29	0.24	28[c]	0.16
MCHC, g/L	330	1.1	340[c]	1.2

[a] One patient with Hb H disease.

[b] ND, not done; NA, not applicable; WBC, white blood cell; Plt, platelet; Hct, hematocrit; MCV, mean cell volume; MCH, mean cell Hb; MCHC, mean cell Hb concentration.

[c] Statistically significant ($P < 0.05$, one-way ANOVA).

Adapted from *The clinical and laboratory data of the two beta-...* Available at: https://www.researchgate.net/figure/The-clinical-and-laboratory-data-of-the-two-beta-Thalassemia-major-BTM-groups_tbl1_302027060.

CBC Testing

- measures the amount of hemoglobin and different types of blood cells
- Thalassemic patients have fewer healthy RBCs and hemoglobin than healthy patients.
- RBCs may appear smaller than normal.

	Male (n=96)	Female (n=397)	P
HbF	0.64±0.70	0.70±0.85	0.523
HbA2	3.29±1.16	3.17±0.97	0.303
HbA0	84.18±8.77	84.25±7.94	0.936
S Window	24.70±1.59	27.58±3.86	0.158
Hemoglobinopathies			
No	76 (79.2%)	309 (77.8%)	0.884
Yes	20 (20.8%)	88 (22.2%)	
Types of hemoglobinopathies			
β-Thalassemia Trait	13 (65%)	51 (57.95%)	0.915
HbS Heterozygous	4 (20%)	33 (37.5%)	0.270
Compound heterozygous HbS and β-Thalassemia trait	3 (15%)	4 (4.55%)	0.300

Adapted from Khera, R. *et al.* (2015) *HPLC in characterization of hemoglobin profile in thalassemia syndromes and hemoglobinopathies: A clinicohematological correlation, Indian journal of hematology & blood transfusion : an official journal of Indian Society of Hematology and Blood Transfusion.* Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4275515/.

Hemoglobinopathy Screen

- Tests for abnormal forms of hemoglobin

Who is at risk?

Genetic factors

Those with family history of thalassemia have a greater risk, since the mutated hemoglobin genes are passed down from parent to offspring.

Ancestry

Thalassemia occurs in African Americans and in people of Mediterranean and Southeast Asian descent.

Three main types of treatments

Blood Transfusion

The more severe the thalassemia, the more frequent blood transfusions are required. This can cause excessive iron levels, which can cause issues with the heart, liver, and other organs.

Chelation Therapy

This is done in order to reduce the excessive iron from the blood after frequent transfusions and breakdown of red blood cells. Also medications such as deferasirox, deferiprone, and deferoxamine can be used as well to reduce iron levels.

Stem Cell Transplant

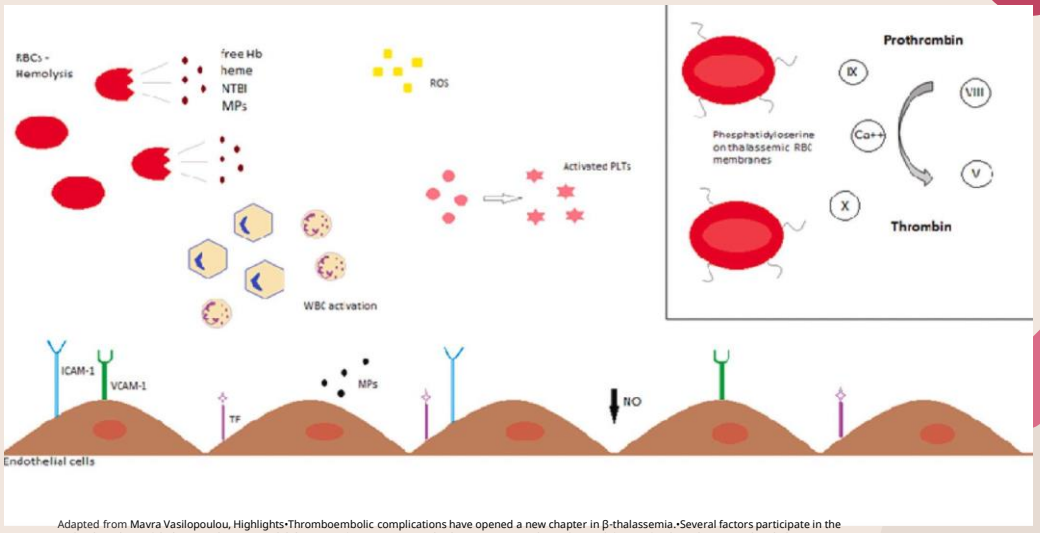
This process involves taking stem cells from a compatible donor. This can bypass the excessive iron levels associated with blood transfusions with severe thalassemic patients.

Newer technologies for treatment in thalassemia patients

- Gene therapy: stem cells
- Allogeneic hematopoietic stem and progenitor cells (HSPCs) are harvested and then the hemoglobin genome is edited to express more b globin and is transferred using a lentiviral vector.
- Induced pluripotent stem cells (iPSCs) might be used to avoid the requirement for high-variation proficiencies in future gene therapies and can be distinguished into HSPCs.
- HSCs are transferred from the bone marrow of a healthy individual to thalassemia patients
- 80% success rate
- **Complications**: Graft versus host disease can lead to death of transfer recipients due to the rejection of the graft by the patient's immune system.
- Gene editing
- CRISPR and CAS9 is technology that can edit the genome by removing or adding base pairs.
- CRISPR and CAS9 can edit the defective b globin genes involved in b thalassemia.
- **Complications**: immune responses to viral vectors and stable expression of the edited gene
- In utero transplantation
- Uses maternal stem cells as the donor
- High doses of maternal cells, infused intravenously into the fetus is currently being tested as a treatment option.

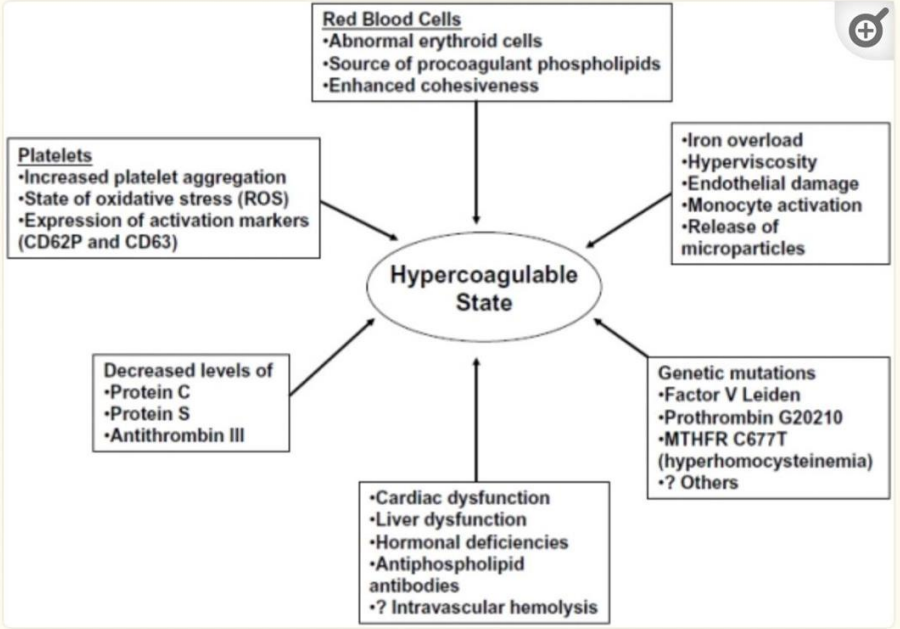
Complications in Thalassemia

- Increased platelet activation (specifically, an increased number platelets express P-selectin and CD63 due to enhanced platelet consumption)
- High levels of endothelial adhesion proteins demonstrate that endothelial injury may contribute to high levels of white blood cells and RBCs, thu promoting thrombosis at vascular inflammation sites.
- Hemolysis of RBCs and pulmonary hypertension



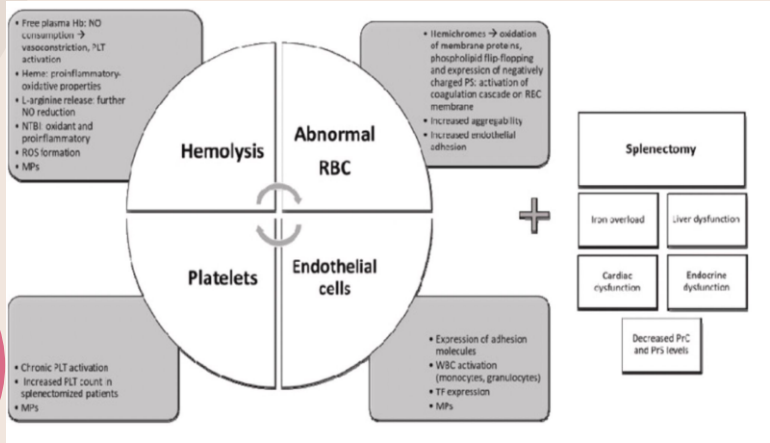
Adapted from Mavra Vasilopoulou, Highlights•Thromboembolic complications have opened a new chapter in β-thalassemia.•Several factors participate in the pathophysiology of thalassemic hypercoagulability.•Transfusion naivety and splenectomy are independent risk factors for thrombosis.•Guid and AbstractB-thalassemia is one of the most common recessive monogenic disorders (2022a) *The thrombotic spectrum of B-Thalassemia, Thrombosis Update*. Available at: https://www.sciencedirect.com/science/article/pii/S2666572722000062.

Hypercoagulability in Thalassemia Patients



Adapted from (No date a) *(PDF) thalassemia and hypercoagulability - researchgate*. Available at: https://www.researchgate.net/publication/5340071_Thalassemia_and_hypercoagulability.

Pathophysiology of Thalassemia and Thrombosis



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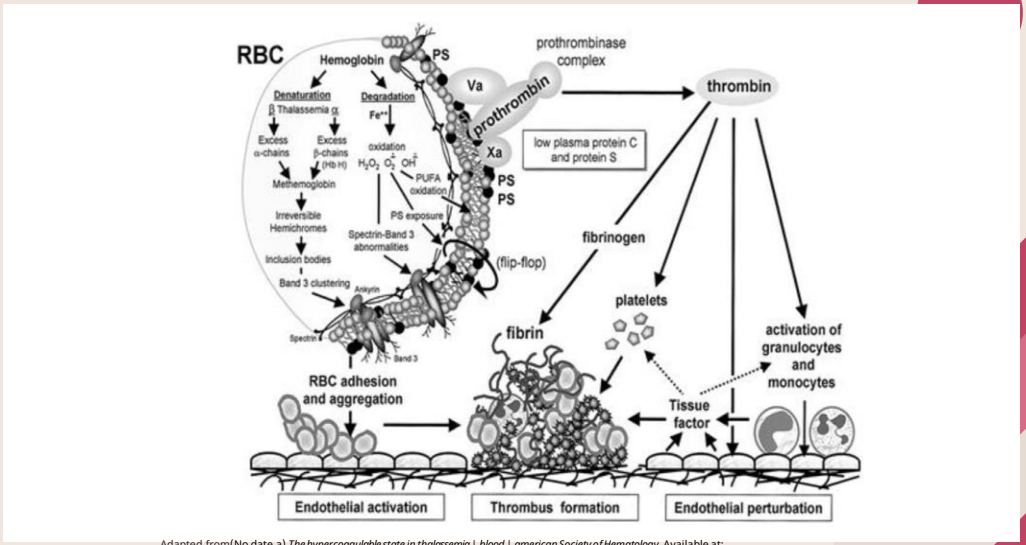


Adapted from(No date a) *The hypercoagulable state in thalassemia | blood | american Society of Hematology*. Available at: https://ashpublications.org/blood/article/99/1/36/107240/The-hypercoagulable-state-in-thalassemia.

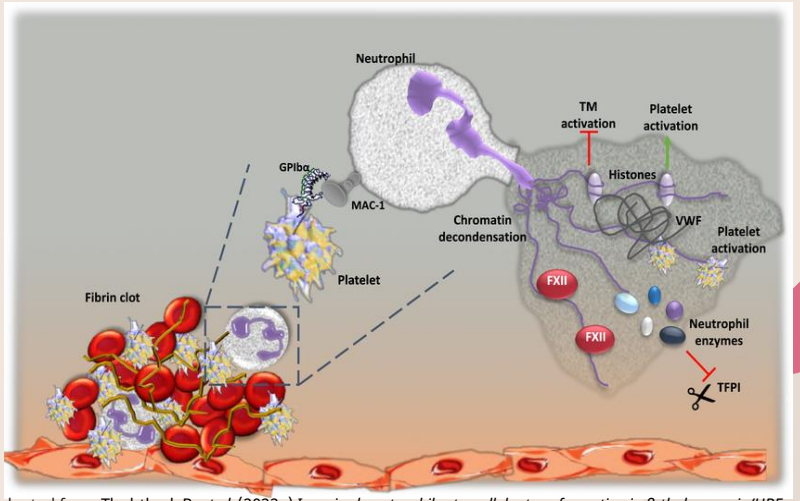
Hemostatic Parameters in Thalassemia Patients

	Assay	β-TM	β-TI	α-Thalassemia	SCD
Platelet	Life span	Short	Short		
	Aggregation	Impaired	Impaired		Impaired
	Urinary TXA_2	High	High		High
	Circulating platelet aggregates	Present	Present	Present	Present
	CD62, CD63	High	High		High
	PF3	High	High	High	
	PF4, β-TG	High	High		High
Vascular endothelium	Thrombomodulin	High	High		High
	ICAM-1	High	High		High
	VCAM-1	High	High		High
	VWF	High	High		High
	E-selectin	High	High		High
	Urinary PGI_2	High	High		High
RBC	Annexin V binding	Increased	Increased		Increased
	Thrombin generation	Increased	Increased		Increased
Coagulation factors	Factor II	Low	Low		
	Factors V, VII, X	Normal	Normal		
Coagulation inhibitors	Protein C (antigen, activity)	Low	Low		Low
	Protein S (free)	Low	Low		Low
	ATIII	Normal	Low		Normal
	HCII	Low			
Thrombin generation	TAT	High	High	High	High
	$F_{1,2}$	Normal	High		Normal
	FPA		High		High
	D-dimer		High		High

Adapted from(No date a) *The hypercoagulable state in thalassemia | blood | american Society of Hematology*. Available at: https://ashpublications.org/blood/article/99/1/36/107240/The-hypercoagulable-state-in-thalassemia.

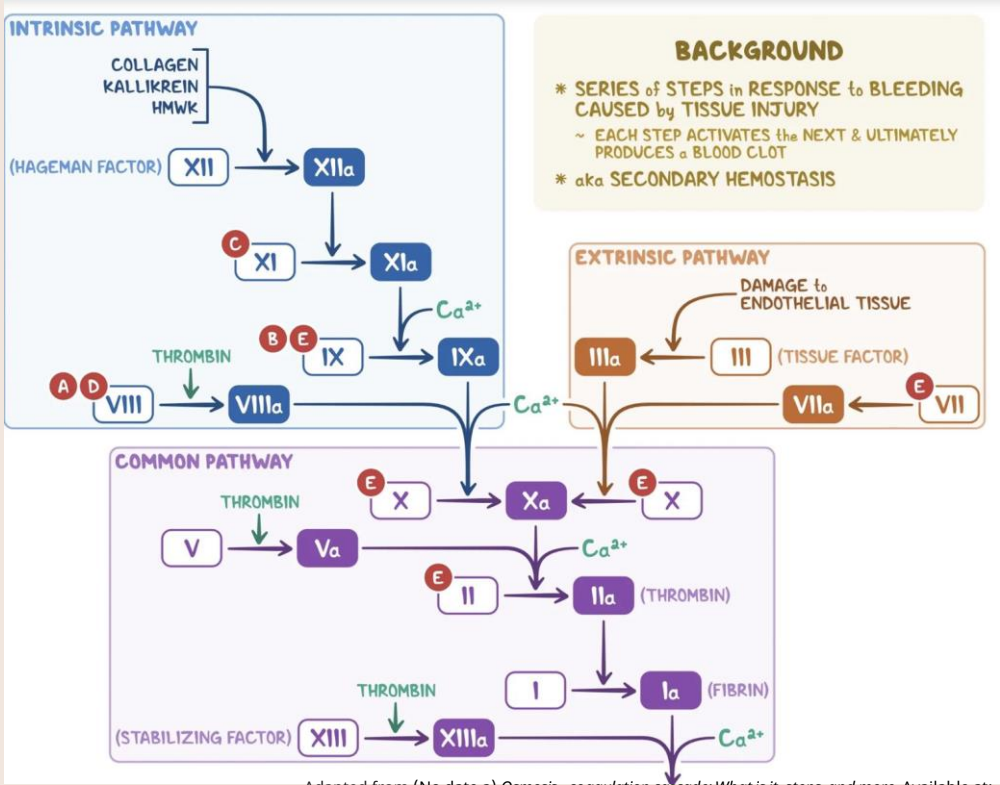
NETosis

- Via the inflammatory response, neutrophils are sent to infection sites and fight pathogens.
- Neutrophil extracellular traps (NETs) are a function of neutrophils that trap and eliminate pathogens by releasing extracellular structures and neutrophil elastase.
- According to a study conducted in 2022 by R. Thubthed and colleagues, splenectomized b thalassemia patients have impaired NET function, leading to high susceptibility to infection.
- Iron overload contributes to impaired NET function. Hemin from transfusion treatments could play a role in priming neutrophils to induce inflammation.
- The study recognizes that the neutrophils in b thalassemia patients had increased reactive oxygen species (causes platelet aggregation) and increased levels of inflammatory cytokines (M-CSF, TNF-α, IFN-γ and IL-1β).



Adapted from Thubthed, R. *et al.* (2022a) *Impaired neutrophil extracellular trap formation in β-thalassaemia/HBE*, *Scientific reports*. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8816948/.

Activation of the Coagulation Cascade



Adapted from (No date a) *Osmosis - coagulation cascade: What is it, steps, and more*. Available at: https://www.osmosis.org/answers/coagulation-cascade.

Observations

- As clinically observed, thalassemia patients that have had a splenectomy have a higher risk of thrombosis.
- This is likely due to high platelet counts following the procedure and abnormal RBCs. These patients also have reported higher numbers of thrombin in comparison to the patients in the control group.
- Additionally, patients with thrombosis and thalassemia intermedia reported decreased levels of protein C and S, which serve as anticoagulants, which can serve as reasoning for high risk of thrombosis in these patients.
- Other risk factors can depend on the patient’s family history, transfusion frequency, and age.

Thromboembolic event incidence in thalassemia patients

Thromboembolic Event	Incidence in Thalassemia Patients
DVT	Increased incidence
PE	Higher risk in these patients
Stroke	Higher risks in b thalassemia patients
Heart Attack	Higher risk due to increased iron levels and anemic symptoms

Clinical Study 1

Clinical Trial > Hematol Oncol Stem Cell Ther. 2018 Jun;11(2):65-74.
doi: 10.1016/j.hemonc.2017.05.028. Epub 2017 Jun 15.

Study of platelet activation, hypercoagulable state, and the association with pulmonary hypertension in children with β-thalassemia

Mahmoud Alhosiny Fayed [1], Hesham El-Sayed Abdel-Hady [2], Mona Mohammed Hafez [3], Osama Saad Salama [4], Youssef Abdelhalim Al-Tonbary [5]

Affiliations + expand

PMID: 28633041 DOI: 10.1016/j.hemonc.2017.05.028

Free article

Abstract

Background: The increased survival rate of thalassemic patients has led to unmasking of management related complications which were infrequently encountered.

Objective: Study the increased coagulation and platelet activation in children with β-thalassemia, to analyze the factors that lead to such hypercoagulable state and to study pulmonary hypertension (PH) in conjunction with platelet activation and hypercoagulable state in children with β-thalassemia.

Methods: 36 Egyptian children with β-thalassemia with a mean age of 9.9years (±4.7 SD). In addition, 20 healthy Egyptian children matched for age and sex were enrolled as a control group. Both were subjected to clinical and laboratory assessments. Echocardiography was done to the patient group and PH was diagnosed based on calculated mean pulmonary artery pressure [MPAP] >25mmHg.

Adapted from Fayed MA;Abdel-Hady HE;Hafez MM;Salama OS;Al-Tonbary YA; (no date) *Study of platelet activation, hypercoagulable state, and the association with pulmonary hypertension in children with β-thalassemia, Hematology/oncology and stem cell therapy*. Available at: https://pubmed.ncbi.nlm.nih.gov/28633041/.

Clinical Study 1 Results

Marker	Trends in Beta Thalassemia Patients	Correlation with Pulmonary Hypertension
Platelet Activation Markers	Increased levels of P-selectin and platelet factor	Positive correlation with severity of PH
Hypercoagulable State Markers	Increased levels of D-dimer, fibrinogen, prothrombin fragments 1 and 2	Positive correlation with severity of PH
Antithrombin III	Decreased levels in b thalassemia patients (may contribute to hypercoagulable state	
Protein C	Decreased levels in b thalassemia patients	Lower levels increase thrombotic risk
Fibrinogen	Increased levels in b thalassemia patients	Increased levels increase thrombotic risk
Pulmonary Hypertension Markers	Increased levels of markers	Positive correlation with mean pulmonary artery pressure

Significant observations from Study 1

- The elevated P-Selectin levels could be attributed to increased platelet aggregation. Increased protein C levels can potentially be caused by low vitamin K or increased turnover rate, but this is still being investigated.
- The higher counts of WBCs in splenectomized patients could contribute to the higher thrombotic incidence in these thalassemic patients.
- Interestingly, pulmonary hypertension and mean pulmonary arterial pressure have a strong connection with hypercoagulability and platelet activation. Also, P-selectin and MPAP have a strong correlation, indicating that the connection may be significant in hypercoagulability.

Clinical Study 2

Sci Rep. 2018; 8: 13033.
Published online 2018 Aug 29. doi: 10.1038/s41598-018-31386-6
PMCID: PMC6115342
PMID: 30158562

Journal Article

Microparticles from β-thalassaemia/HbE patients induce endothelial cell dysfunction

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Patients and blood samples

This study was performed in accordance with the Helsinki declaration and was approved by the Mahidol University Institutional Review Board (MU-IRB), approval number 2014/013.0502. Written informed consent was obtained from all individual participants included in the study. Peripheral blood samples were collected from 32 β-thalassaemia/HbE patients (21 non-splenectomy and 11 splenectomy) and 16 normal subjects at ages ranging from 23 to 45 years old. All subjects had no evidence of concurrent infection, history of vaso-occlusive episode or atherosclerotic vascular disease. Patients under treatments with aspirin, antibiotics, anti-depressants, beta-blockers and anti-platelets were excluded, and none had been hospitalised or transfused within 4 weeks. All blood samples were collected at room temperature (RT) and processed within 2–3 h.

Images adapted from Kheansaard, W. *et al.* (2018a) *Microparticles from β-thalassaemia/HBE patients induce endothelial cell dysfunction, Scientific reports.* Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6115342/.

Clinical Study 2 Results

Correlation between MPs origin and endothelial cell activation markers.

	PMPs	RBCMPs	ECMPs
Unprimed HUVECs			
ICAM-1	$r_s = 0.904$, $P < 0.001$	n.s.	n.s.
VCAM-1	$r_s = 0.922$, $P < 0.001$	n.s.	n.s.
E-selectin	$r_s = 0.821$, $P < 0.001$	n.s.	n.s.
Tissue factor	n.s.	n.s.	n.s.
IL-6	n.s.	n.s.	n.s.
IL-8	n.s.	n.s.	n.s.
LPS-primed HUVECs			
ICAM-1	$r_s = 0.809$, $P < 0.001$	n.s.	n.s.
VCAM-1	n.s.	n.s.	n.s.
E-selectin	$r_s = 0.911$, $P < 0.001$	n.s.	n.s.
Tissue factor	$r_s = 0.907$, $P < 0.001$	n.s.	$r_s = 0.734$, $P < 0.001$
IL-6	$r_s = 0.907$, $P < 0.001$	n.s.	n.s.
IL-8	n.s.	n.s.	n.s.

Image adapted from Kheansaard, W. *et al.* (2018a) *Microparticles from β-thalassaemia/HBE patients induce endothelial cell dysfunction*, *Scientific reports*. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6115342/.

Microparticles (MPs)	MPs are small membrane-bound vesicles released from β-thalassaemia/HbE red blood cells. They include exosomes and microvesicles, carrying proteins, lipids, and genetic material, influencing cell signaling.
Type of Microparticles	Includes exosomes, microvesicles, and Platelet microparticles (PMPs) released from β-thalassaemia/HbE red blood cells.
Endothelial dysfunction	MPs derived from β-thalassaemia/HbE patients induce dysfunction in endothelial cells, impairing vasodilation and promoting inflammation.
Inflammatory response	MPs trigger endothelial cells to release pro-inflammatory cytokines and chemokines, contributing to vascular inflammation
Oxidative stress	MPs cause increased production of reactive oxygen species (ROS) in endothelial cells, leading to oxidative stress and cell damage.
Cell adhesion molecules (CAMs) expression	MPs promote upregulation of adhesion molecules such as ICAM-1 and VCAM-1 on endothelial cells, facilitating leukocyte adhesion and inflammation.
Trends	Increased levels of MPs and PMPs correlate with severity of beta thalassemia and endothelial dysfunction
Pro-coagulant activity	MPs enhance the expression of tissue factor (TF) and promote endothelial cell activation, leading to increased thrombotic potential.

Significant observations from Study 2

- MPs originating from both β-thalassaemia/HbE and normal subjects increased the effect of MPs on pro-inflammatory cytokine secretion, expression of adhesion molecules and also TF and further recruitment of monocyte adhesion to endothelial cells.
- PMPs also play a significant role in addition to a splenectomy. There is a significant positive correlation between the release of PMPs in splenectomized patients, so this could play a role in understanding why splenectomized patients have a higher rate of thrombosis.

Clinical Study 3

Front Mol Biosci. 2022; 9: 1108896.
PMCID: PMC9868635
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PMID: 36699704

Hemorheological profiles and chronic inflammation markers in transfusion-dependent and non-transfusion- dependent thalassemia

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Adapted from Caprari, P. *et al.* (2023a) *Hemorheological profiles and chronic inflammation markers in transfusion-dependent and non-transfusion-dependent thalassemia, Frontiers in molecular biosciences.* Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9868635/).

Hemorheological profiles and chronic inflammation markers in transfusion-dependent and non-transfusion- dependent thalassemia results

IL-6	Lower levels found in transfusion-dependent thalassemia patients
IL-8	Lower levels found in non-transfusion dependent patients and thalassemia patients
IL-10	Lower levels found in transfusion-dependent thalassemia patients
Leptin	Lower levels found in non-transfusion dependent patients and thalassemia patients
VEGF	Increased levels found in all patients but decreased in patients that took aspirin.
L-Selectin	Increased levels found in transfusion-dependent thalassemia intermedia
CD163	Increased levels found in transfusion-dependent thalassemia intermedia

Significant Observations from Study 3

- Both transfusions and splenectomy seem to influence thromboembolic events due to a state of hypercoagulability.
- The decreased levels of IL-6, IL-10, and IL-8 is only significant in transfusion-dependent patients, which showcases that multiple transfusions may be responsible for increased iron absorption, increasing thrombotic risks.
- For context, endothelial activation results from ICAM-1, VCAM-1, and VEGF. The higher numbers in the patients show that these factors play a role in the hypercoagulable state despite the severity and treatment.
- The increased levels of E-selectin and angiopoietin-1 only in Thalassemia Major and TDTI shows that these factors may be related to transfusion frequency in causing hypercoagulability.

Management of Thromboembolism in Thalassemia Patients

- Antiplatelet therapy can be used to prevent thromboembolism in these patients, such as warfarin and aspirin with caution.
- Vitamin E- prevents iron-related toxicity
- Penicillin- utilized for splenectomized patients
- Thalassemia-related thrombosis risk scoring system
- Ensuring that patients are receiving transfusions at the correct rate to prevent spleen complications

Adapted from Mavra Vasilopoulou, Highlights•Thromboembolic complications have opened a new chapter in β-thalassemia.•Several factors participate in the pathophysiology of thalassemic hypercoagulability.•Transfusion naivety and splenectomy are independent risk factors for thrombosis.•Guid and AbstractB-thalassemia is one of the most common recessive monogenic disorders (2022b) *The thrombotic spectrum of ß-Thalassemia, Thrombosis Update*. Available at: https://www.sciencedirect.com/science/article/pii/S2666572722000062#:~:text=Taher%20et%20al.%2C%20under%20the,and%20can%20be%20used%20for.

Table 1. Thalassemia-related thrombosis risk scoring system (TRT-RSS)

Risk factor at time of assessment	Score
Age >35	2.5
Hemoglobin level [a,b] <9 g/dL	2.5
Serum ferritin level [b] ≥1000 µg/L	2.0
Not regularly transfused [c]	3.5
Splenectomized	6.5
TRT-RSS Total Score minimum	0.0
TRT-RSS Total Score maximum	17.0
TRT-RSS risk categories	
Low risk	<9.5
Intermediate risk	9.5-13.5
High risk	>13.5

Conclusion

- Thalassemia is a dangerous hemolytic condition that affects many people. One of the most serious complications is thrombosis, leading to a hypercoagulable state in these patients.
- The exact mechanisms that cause this state in thalassemia patients are still being further investigated.
- According to the most recent research, the complications that contribute to VTE include increased platelet aggregation, increased endothelial activation, and the release of microparticles.
- Antiplatelet therapies, such as aspirin and direct oral anticoagulants (DOACs), can help to treat VTE in these patients.
- Further understanding the complications in thalassemia patients that lead to VTE can help determine further treatment and prevention mechanisms, which can help save lives in the future.

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