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A Comprehensive Review of Thalassemia: From Genetic Mutations to Modern Therapeutic Approaches

Anjali Mishra, Mohd Arman Khan, Dr. Samatbek Turdaliev

Osh State University, Osh, Kyrgyzstan

Abstract: *Thalassemia is a type of inherited blood condition that makes it hard for the body to make enough hemoglobin, leading to anemia.*

Each year, about 100,000 babies are born with thalassemia. This condition is more common in people with Italian, Greek, Middle Eastern, Southern Asian, or African backgrounds. There are two main types of thalassemia, called alpha and beta, named after the parts of the protein that carry oxygen in red blood cells that are missing. Both types are passed down in the same way. If a parent has the changed thalassemia gene, they can pass it to their children. A child who gets one changed gene is a carrier, also known as having thalassemia trait. Most carriers are healthy and don't have symptoms. Doctors usually find thalassemia through blood tests, hemoglobin tests, and genetic tests. People with serious thalassemia need regular blood transfusions, medications like deferoxamine, deferasirox, or deferiprone, and sometimes a bone marrow transplant. Bone marrow transplant is the only sure way to cure thalassemia. This paper talks about the different types of thalassemia, what causes them, how they affect the body, possible problems, ways to prevent them, and how to treat them.[1].

Keywords*:* Thalassemia, Bone Marrow Transplant, hemoglobin, inherited disease

I. INTRODUCTION

Thalassemias represent a diverse group of inherited genetic disorders characterized by reduced synthesis of either the alpha or beta globin chains of hemoglobin (Hb). Hemoglobin, the oxygen-transporting molecule within red blood cells, is composed of two alpha and two beta globin chains. When the production of either chain is insufficient, red blood cells are malformed and unable to carry adequate oxygen, resulting in anemia that typically begins in early childhood and persists throughout life. Thalassemia is inherited, meaning that at least one parent must carry the defective gene. The condition arises due to either point mutations or deletions affecting essential regions of the globin genes.

Alpha thalassemia results from deletions in the alpha-globin gene, leading to reduced or absent production of alpha chains. The alpha-globin gene cluster contains four alleles, and the clinical severity correlates with the number of alleles deleted. Deletion of a single allele produces a clinically silent carrier state, whereas deletion of all four alleles leads to complete absence of alpha-globin synthesis, causing the formation of gamma-chain tetramers (Hb Bart's) during fetal life. This condition is incompatible with life and results in hydrops fetalis.

Beta thalassemia, on the other hand, is caused by point mutations in the beta-globin gene. It is classified into three forms based on the nature and zygosity of the mutation. A heterozygous mutation (β^+-thalassemia) leads to beta-thalassemia minor, which is usually mild and asymptomatic due to partial reduction of beta-chain production. Homozygous mutations (β^0-thalassemia) result in beta-thalassemia major, characterized by complete absence of beta-globin synthesis. Affected individuals present with severe anemia, jaundice, growth retardation, hepatosplenomegaly, and endocrine dysfunction, requiring lifelong blood transfusions. Beta-thalassemia intermedia represents an intermediate form, with moderate clinical manifestations that fall between the minor and major types.

One mutated gene: Individuals with a single defective beta-globin gene exhibit mild or no symptoms, a condition known as thalassemia minor or beta-thalassemia trait.

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Two mutated genes: When both beta-globin genes are mutated, the disease manifests with moderate to severe clinical features, referred to as thalassemia major or Cooley's anemia. Infants with this condition typically appear healthy at birth, but symptoms begin to develop around six months of age, as fetal hemoglobin (HbF) production declines and is replaced by adult hemoglobin (HbA).[2,14,15,16]

Epidemiology

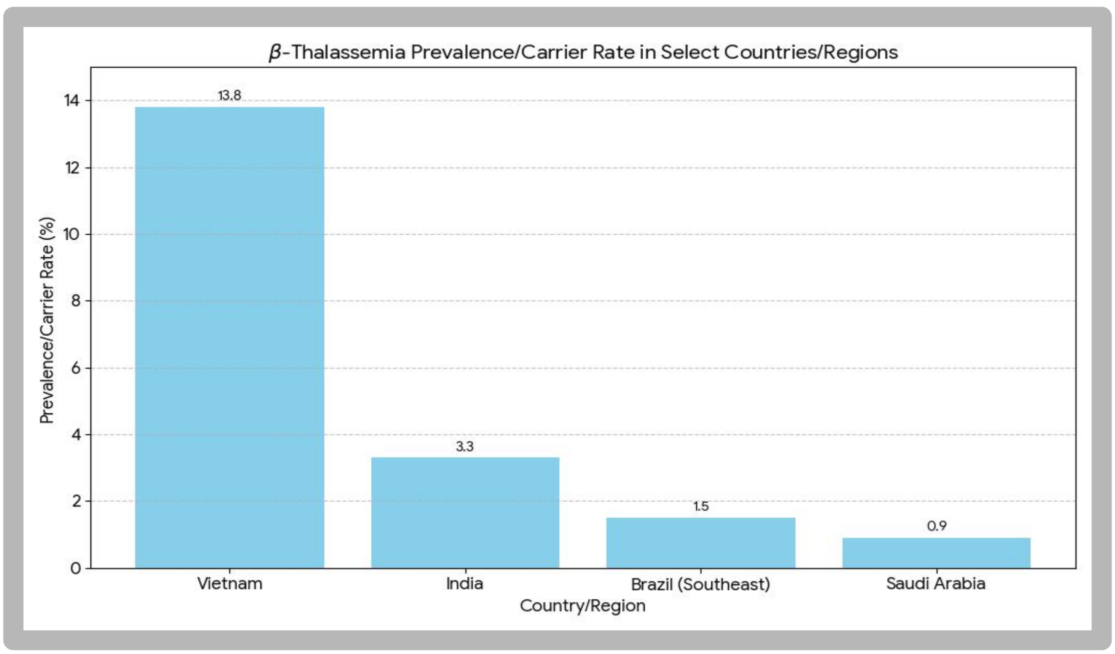
The data for a comparative graph must be based on a single comparable metric, such as overall carrier frequency or general population prevalence. Based on the provided text, the most comparable and directly stated statistics for the general population are:

Vietnam:β-thalassemia gene carrier rate is 13.8% of the total population.

India: The mean prevalence of β-thalassemia is 3.3% (with a range of 3% to 17%).

Brazil (Southeast):1% to 2% of the general population is heterozygous (carriers); 1.5% is used as an approximate average for the graph.

Saudi Arabia: The overall prevalence rate varied from **1 in 2011 to 1.6 in 2015** (per one thousand people). Using 1.3 per one thousand as an average, this converts to 0.13% (however, for better visualization with the other percentages, the overall prevalence rate of β-thalassemia is noted as 1 in 2011 to 1.6 in 2015, which is 0.1% to 0.16%. The text also states regional averages of 3% to 15% per one thousand people had β-thalassemia, which is 0.3% **to** 1.5% per one thousand people. For the graph, a common-sense mean of the two rates is used, which is 0.9%).[3]



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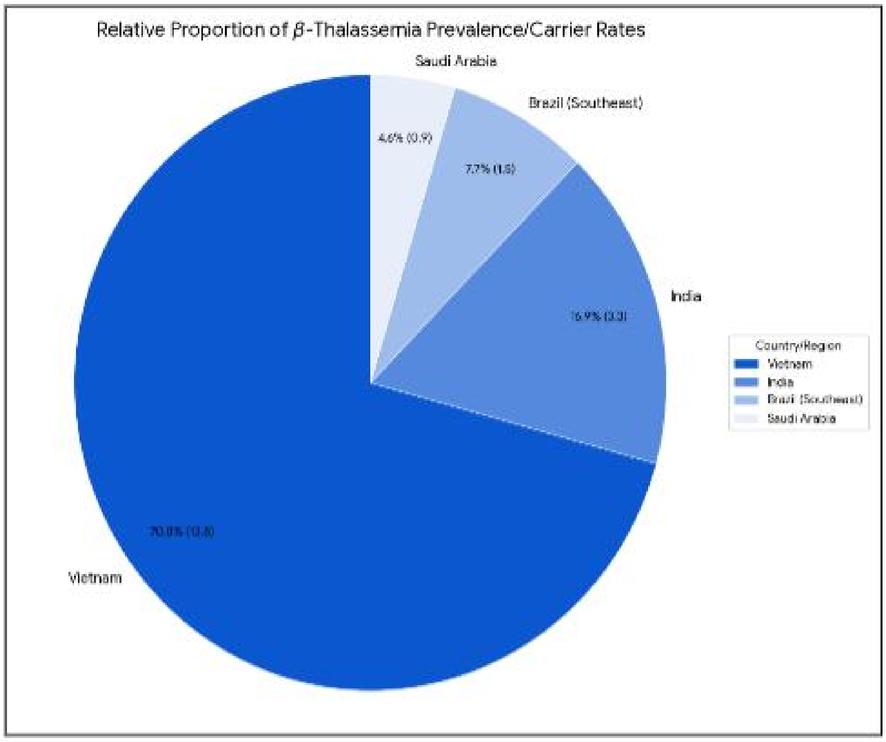
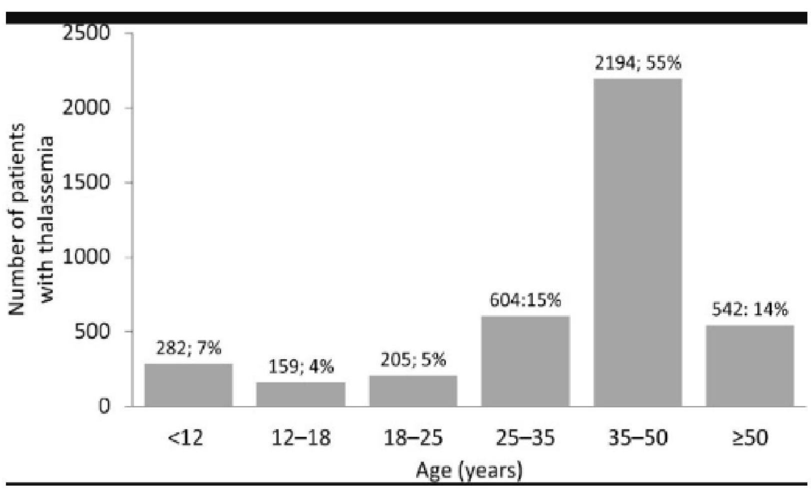


Distribution of age in thalassemia syndrome

As of December 31, 2017, the age distribution of the overall patient population (shown in Figure) was consistent across different geographic areas. Focusing only on the 3,149 patients with thalassaemia major (the most severe form), the age profile was similar: 60% were in the 35-50 years age group, and only 8% were over 50. The mean age for this group was 37.0 years, with ages ranging from 0.41 to 78.9 years. Patients with thalassaemia intermedia ($\text{n}=696$) showed a comparable pattern, but it was shifted to the right, which aligns with the known differences in the natural history of that condition.[18]



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Risk factors

Your risk of thalassemia is higher if you have:

- **Family history of thalassemia**: The condition can be passed from parents to children through changes in the hemoglobin genes.
- **Certain ancestry**: Thalassemia is more common in people from South Asia, Italy, Greece, the Middle East, or Africa.

Having these risk factors doesn't mean you will definitely get thalassemia, but it makes it more likely.[4]

Thalassemia Pathophysiology:

Understanding the Pathophysiology of Thalassemia

Thalassemia is a group of inherited blood disorders caused by mutations in the genes responsible for producing α or β globin chains, which are the building blocks of hemoglobin, the protein that carries oxygen in red blood cells.

The main problem in thalassemia is an imbalance in globin chain production. For example, in β-thalassemia, there is too little β-chain, causing α-chains to accumulate. These excess chains are unstable and harmful.

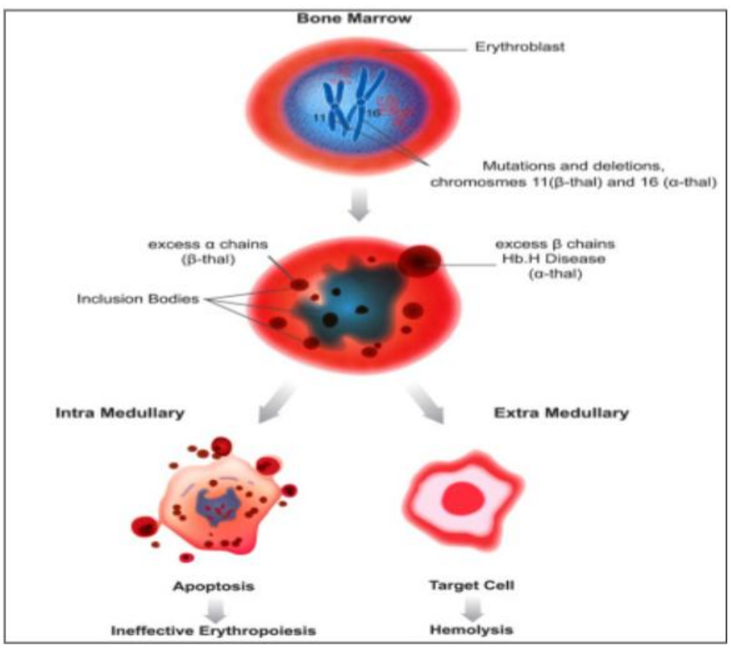
Key Mechanisms

1. Ineffective Red Blood Cell Production and HemolysisThe unmatched globin chains form toxic inclusions inside developing red blood cell precursors in the bone marrow.

These abnormal cells are damaged and destroyed before they can mature, a process called ineffective erythropoiesis, leading to chronic anemia.

The few red blood cells that survive and enter the bloodstream are often abnormal and fragile, causing them to break down easily (hemolysis), especially in the spleen.

2. Organ Damage and Complications To compensate for anemia, the body increases red blood cell production, which causes the bone marrow to expand (bone marrow hyperplasia). This can result in bone deformities and increase the risk of osteoporosis.



Patients who require frequent blood transfusions—or those whose intestines absorb extra iron—can develop iron overload (hemosiderosis).

Excess iron is toxic and accumulates in vital organs such as the heart and liver, causing long-term damage and becoming a major cause of complications and mortality in severe thalassemia.[5,6,7,8]

Major Complications of Thalassemia

Thalassemia can lead to a range of severe health problems primarily stemming from chronic anemia, the body's compensatory responses, and the necessity of frequent treatment.

Organ and System Damage

- **Iron Overload (Hemosiderosis):** This is a critical risk. Patients accumulate too much iron from both the underlying disease process and from frequent **blood transfusions**. Excess iron is highly toxic and deposits in major organs, causing irreversible damage to the **heart** (leading to congestive heart failure and irregular rhythms), the **liver**, and various endocrine **glands** that regulate hormones.
- **Infection Risk:** The body's immune defenses are weakened, raising the risk of infection. This risk becomes particularly high if the **spleen** has been surgically removed (a procedure called a **splenectomy**).

Skeletal and Growth Abnormalities

- **Bone Changes:** The body attempts to compensate for the anemia by dramatically increasing red blood cell production in the bone marrow. This intense activity causes the spongy marrow tissue to **expand**. This expansion leads to bones becoming thin, brittle, and prone to **fractures**. It can also cause characteristic **irregular bone structures**, especially in the face and skull.
- **Slowed Growth and Delayed Puberty:** Chronic anemia and the associated stress on the body can significantly **slow down a child's growth rate** and **delay the onset of puberty**.

Spleen-Related Issues

- **Enlarged Spleen (Splenomegaly):** The spleen works overtime to filter and destroy the large number of damaged or abnormal red blood cells produced in thalassemia. This overwork causes the organ to swell and enlarge. A significantly enlarged spleen can unfortunately worsen the anemia and may prematurely destroy healthy red blood cells from transfusions. If the spleen becomes too large or destructive, surgical removal (**splenectomy**) may be recommended.[4]

Thalassemia Diagnosis

Diagnosing thalassemia involves a combination of clinical assessment, blood tests, and increasingly, genetic analysis.

1. Clinical Evaluation

Thalassemia is often suspected in young children:Thalassemia Major: Usually appears before age two. Infants may show severe anemia, mild jaundice, and an enlarged liver and spleen (hepatosplenomegaly).
Thalassemia Intermedia: Symptoms appear later and are generally milder.
Thalassemia Minor (Carrier): Individuals often have no noticeable symptoms or may have only mild anemia.

2. Blood Test Findings

Red Blood Cell (RBC) Indices:All forms of thalassemia show microcytic anemia (small red blood cells).
Thalassemia Major: Very low hemoglobin (Hb < 7 g/dL), very low mean corpuscular volume (MCV 50–70 fL), and low mean corpuscular hemoglobin (MCH 12–20 pg).
Thalassemia Intermedia: Moderate reductions in Hb (7–10 g/dL), MCV (50–80 fL), and MCH (16–24 pg).
Thalassemia Minor: Mild reductions in MCV and MCH, with a characteristic increase in HbA2.
Peripheral Blood Smear:
Abnormal red blood cell shapes such as microcytosis, hypochromia, anisocytosis, and poikilocytosis are seen.

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Nucleated RBCs (immature red cells) are present in more severe forms and increase after splenectomy.
Carriers usually show milder changes without nucleated RBCs.

Hemoglobin Analysis:

Tests like electrophoresis, microchromatography, or HPLC determine the types and proportions of hemoglobin.
β^0-thalassemia homozygotes: HbA is absent; HbF makes up 92–95%.
β^+-thalassemia homozygotes or β^+/β^0 combinations: HbA is 10–30%, and HbF is 70–90%.
HbA2 levels are increased in carriers of β-thalassemia.
These tests can also detect other hemoglobin disorders such as HbS, HbC, or HbE.

3. Molecular Genetic Testing

Genetic testing is increasingly used because certain mutations are more common in specific populations.
Targeted Mutation Detection: PCR-based methods (like reverse dot blot or primer-specific amplification) identify common β-globin gene mutations specific to the patient's ethnic background.
Gene Sequencing: If common mutations are not detected, full sequencing of the β-globin gene can uncover rare or previously unknown mutations. [9,10,11,12]

Hematologic Findings

Red Blood Cell Indices in Beta-Thalassemia

Peripheral blood smear .Peripheral blood smear shows red blood cell changes like being small (microcytosis), pale (hypochromia), uneven in size (anisocytosis), oddly shaped (poikilocytosis), and sometimes having immature red cells (erythroblasts).
The number of immature cells depends on the level of anemia. In intermedia cases, the findings are similar. In minor cases, the red cells are small, pale, and sometimes have a target shape[13]

Red Blood Cell Indices	Normal [1]		β-Thalassemia Major	β-Thalassemia Intermedia	β-Thalassemia Minor [2]
	Male	Female			
Mean corpuscular volume (MCV, in fL)	89.1 ± 5.01	87.6 ± 5.5	50-70	50-70	55-78
Mean corpuscular hemoglobin (MCH, in pg)	30.9 ± 1.9	30.2 ± 2.1	12-20	Decreased	15-25
Hemoglobin (Hb, in g/dL)	15.9 ± 1.0	14.0 ± 0.9	<7	7-10	9.5-12.5

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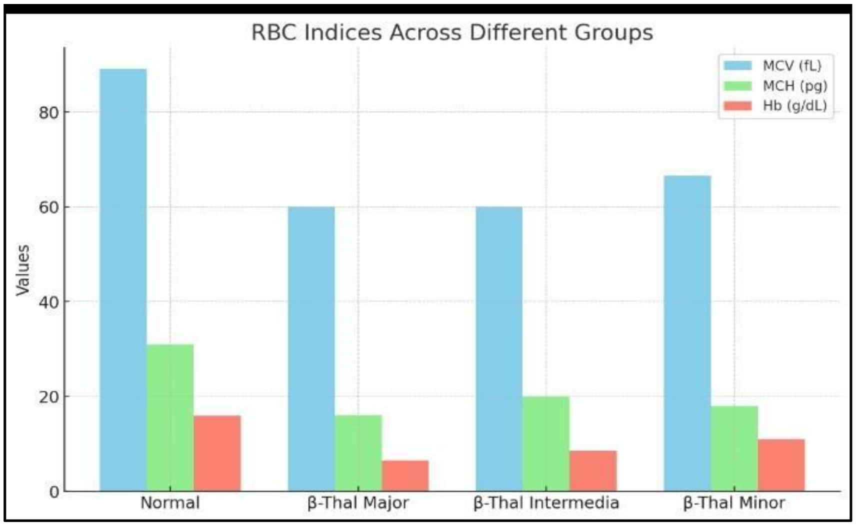

Qualitative and quantitative hemoglobin analysis

(using tests like cellulose acetate electrophoresis, DE-52 microchromatography, or HPLC) helps identify the type and amount of hemoglobin present.The most relevant types in ß-thalassemia are:

HbA

.Two alpha globin chains and two beta globin chains (α2β2)

HbF.

Two alpha globin chains and two gamma globin chains (α2γ2)

HbA2.

Two alpha globin chains and two delta globin chains (a282)

The hemoglobin pattern in ß-thalassemia varies depending on the type of ß-thalassemia.[13]

Hemoglobin Type	Normal [1]	β-Thalassemia Major [2]	β-Thalassemia Intermedia [2]	β-Thalassemia Minor [2]
HbA	96%-98%	0%-30% (typically near 0%)	10%-50%	>88%
HbF	<1%	Up to 95%	10%-50%	<5%
HbA_2	2%-3%	>5%	>4%	>4%

HbA = hemoglobin A; HbA_2 = hemoglobin A_2; HbF = hemoglobin F

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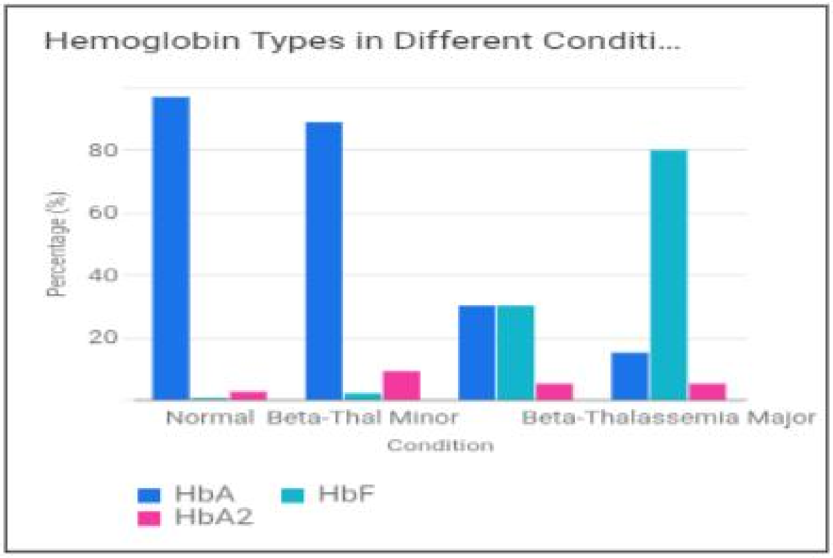

Treatment Goals

Managing thalassemia focuses on maintaining healthy hemoglobin levels, preventing complications, and improving quality of life.

1. Maintaining Hemoglobin Levels : Regular blood transfusions are essential for patients with severe forms to prevent symptoms like fatigue, weakness, and organ damage.
2. Preventing Iron Overload :Frequent transfusions can cause iron buildup, which may damage the heart, liver, and other organs.Iron chelation therapy removes excess iron and protects organ function.
3. Curative Options :Bone marrow or stem cell transplants can potentially cure thalassemia by replacing defective blood-forming cells with healthy ones.

These procedures are suitable only for selected patients and require careful evaluation.

4. Emerging Treatments :Gene therapy aims to correct the underlying genetic defect, offering hope for a more permanent solution in the future.[17]
5. Ongoing Care and Support :Lifestyle adjustments, regular monitoring for complications, and consultation with hematologists are crucial.

Psychological and social support is often overlooked but essential for improving quality of life, helping patients stay active in school or work, and coping with chronic illness.

Financial aid may be available through national disability programs, but it often does not cover recurring costs like hospital transportation or ongoing care needs.

Prevention

The prevention of thalassemia, an inherited blood disorder, is primarily achieved through public health measures focused on genetic screening and counseling to prevent the conception and birth of children with the severe forms of the disease.

The main strategies for thalassemia prevention are:Carrier Screening: Identifying individuals who carry the thalassemia gene (known as the thalassemia trait).

Genetic Counseling: Providing education to carriers, particularly carrier couples, about the 25% risk of having a child with a severe form (like Thalassemia Major) in each pregnancy.

Prenatal Diagnosis (PND): Testing the fetus during pregnancy to determine if it is affected, which allows the couple to make informed decisions

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II. CONCLUSION

Thalassemia represents a significant global public health concern, primarily affecting populations in Asia, the Mediterranean, and the Middle East. The disorder results from mutations in the globin genes that impair hemoglobin synthesis, leading to chronic anemia, ineffective erythropoiesis, and progressive organ damage due to iron overload. Advances in diagnostic methodologies — including molecular genetic testing and high-performance hemoglobin analysis — have enhanced the precision of diagnosis and facilitated early therapeutic interventions.

Current management focuses on maintaining adequate hemoglobin levels through regular transfusion regimens and mitigating transfusion-related iron toxicity via chelation therapy. Hematopoietic stem cell transplantation remains the only established curative treatment; however, its applicability is limited by donor availability, cost, and associated risks. Emerging modalities such as gene therapy offer promising avenues toward definitive management.

From a preventive standpoint, carrier screening, premarital and prenatal counseling, and molecular diagnostic programs are vital components in reducing the disease burden. Furthermore, comprehensive care should address not only hematologic and metabolic complications but also the psychosocial dimensions of chronic disease management. In conclusion, an integrated approach combining advanced diagnostics, effective therapy, genetic prevention, and social support is imperative to improve survival, quality of life, and ultimately to reduce the global prevalence of thalassemia.

REFERENCES

[1]. "Thalassemia: A Review" (Asian Journal of Pharmaceutical Research) — easier reading, broader view.

[2]. "Thalassemia – StatPearls" (free e-book/chapter) — provides etiology, laboratory/bedside evaluation, management options. Link: https://www.ncbi.nlm.nih.gov/books/NBK545151/

[3]. Global distribution of β-thalassemia mutations: an update mutation distribution & carrier frequencies across Mediterranean and Middle East populations. Useful for genetic heterogeneity and carrier ranges. ScienceDirect

[4]. Link:https://www.mayoclinic.org/diseases-conditions/thalassemia/symptoms-causes/syc-20354995

[5]. Schrier, S.L. Pathophysiology of thalassemia. Curr. Opin. Hematol. 2002, 9, 123-126. [Google Scholar] [Cross Ref]

[6]. Pearson, H.A. Pathophysiology of thalassemias. Ann. N. Y. Acad. Sci. 1974, 241, 274-279. [Google Scholar] [CrossRef]

[7]. Fertakis, A. Thalassemia: Pathophysiology, clinical and laboratory findings. In Radiology of Thalassemia, Springer: Berlin/Heidelberg, Germany, 1989; pp. 13-18. [Google Scholar]

[8]. Origa, R.; Galanello, R. Pathophysiology of beta thalassaemia. Pediatr. Endocrinol. Rev. 2011,8 , 263-270. [Google Scholar]

[9]. Vrettou C, Traeger-Synodinos J, Tzetis M, Malamis G, Kanavakis E: Rapid screening of multiple betaglobin gene mutations by real-time PCR on the LightCycler: application to carrier screening and prenatal diagnosis of thalassemia syndromes. Clin Chem. 2003, 49: 769-776.10.1373/49.5.769.Article CAS PubMed Google Scholar

[10]. Cao A, Galanello R, Rosatelli MC: Prenatal diagnosis and screening of the haemoglobinopathies. Baillieres Clin Haematol. 1998, 11: 215-238.10.1016/S0950-3536(98)80076-0.Article CASPubMedGoogle Scholar

[11]. Mavrou A, Kouvidi E, Antsaklis A, Souka A, Kitsiou Tzeli S, Kolialexi A: Identification of nucleated red blood cells in maternal circulation: a second step in screening for fetal aneuploidies and pregnancy complications. Prenat Diagn. 2007, 27: 150-153. 10.1002/pd.1640.Article CAS PubMed Google Scholar

[12]. Lo YM: Recent advances in fetal nucleic acids in maternal plasma. J Histochem Cytochem. 2005, 53: 293-296. 10.1369/jhc.4R6362.2005.

[13]. Beta-Thalassemia - GeneReviews® NCBI Bookshelf

[14]. He LN, Chen W, Yang Y, Xie YJ, Xiong ZY, Chen DY, Lu D, Liu NQ, Yang YH, Sun XF. Elevated Prevalence of Abnormal Glucose Metabolism and Other Endocrine Disorders in Patients with β-Thalassemia Major: A Meta-Analysis. Biomed Res Int. 2019;2019:6573497. [PMC free article] [PubMed]

[15]. Vichinsky E, Cohen A, Thompson AA, Giardina PJ, Lal A, Paley C, Cheng WY, McCormick N, Sasane M, Qiu Y, Kwiatkowski JL. Epidemiologic and clinical characteristics of nontransfusion-dependent thalassemia in the United States. Pediatr Blood Cancer. 2018 Jul;65(7):e27067. [PubMed]

[16]. Ahmadpanah M, Asadi Y, Haghighi M, Ghasemibasir H, Khanlarzadeh E, Brand S. In Patients with Minor Beta-Thalassemia, Cognitive Performance Is Related to Length of Education, But Not to Minor Beta-Thalassemia or Hemoglobin Levels. Iran J Psychiatry. 2019 Jan;14(1):47-53. [PMC free article] [PubMed]

[17]. Cooley's Anemia Foundation. Cooley's anemia foundation. resources on adoption of children with thalassemia (2022). Available at: https://www.thalassemia.org/adoption/ (Accessed January 2023).

[18]. Longo F, Corrieri P, Origa R, Barella S, Sanna PMG, Bitti PP, et al. Changing patterns of thalassaemia in Italy: a webthal perspective. Blood Transfus (2021) 19(3):261–8. doi: 10.2450/2020.0143-20 PubMed