GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

Check for updates

Thalassemia: A comprehensive review of the genetic disorder

Umesh S. Saware *, Supriya S. Barewar, Ravindra L. Bakal and Pooja R. Hatwar

Department of pharmacology, Shri Swami Samarth Institute of Pharmacy, At Parsodi, Dhamangaon Rly, Dist. Amravati (444709) Maharashtra, India.

GSC Biological and Pharmaceutical Sciences, 2025, 31(01), 116-130

Publication history: Received on 23 February 2025; revised on 08 April 2025; accepted on 11 April 2025

Article DOI: https://doi.org/10.30574/gscbps.2025.31.1.0145

Abstract

Thalassemia is a group of inherited blood disorders affecting haemoglobin production. It's the most common form of inherited anaemia worldwide. The two main types are alpha and beta thalassemia, caused by defects in alpha or beta globin chain synthesis. This leads to anaemia, impaired red blood cell production, and other complications. Beta thalassemia has three forms: carrier state, thalassemia intermedia, and thalassemia major, a severe anaemia requiring regular transfusions. Advances in genetics and haemoglobin structure understanding have improved diagnosis and treatment. Management involves carrier detection, genetic counselling, prenatal diagnosis, and transfusions. Haemoglobin electrophoresis and genetic testing help diagnose and confirm thalassemia subtypes. The severity of alpha and beta thalassemia varies, with some forms requiring only monitoring and others needing transfusions. Overall, thalassemia requires comprehensive management to prevent complications and improve quality of life.

Keywords: Alpha-Thalassemia; Beta- Thalassemia; Thalassemia Major; Gene Therapy; Iron Overload

1. Introduction

The most prevalent type of hereditary anaemia in the world, thalassemia is defined by the reduced or eliminated production of either the beta-like (beta-thalassemia) or alpha-like (alpha-thalassemia) globin chains, which are formed to form haemoglobin tetramers during foetal and postnatal life [1]. The production of globin chains has decreased genetically. Theoretically, the number of globin chain kinds is equal to the number of thalassemia types. The α and β-thalassemia's are the most clinically significant. All thalassemia is brought on by mutations in the cluster of globin genes. Both deletional and non-deletional mutations are among the many problems (more than 100 distinct mutations have been reported). There is typically a regional and ethnic distribution to mutations [2]. Reduced or non-existent haemoglobin (Hb) production and chronic anaemia of variable severity are the hallmarks of thalassemia, one of the most prevalent families of recessively inherited illnesses in the world. Red blood cells form, integrity, and half-life are all crucially influenced by haemoglobin (Hb), which is also in charge of binding and transporting carbon dioxide and oxygen. A variety of mutations lead to b-thalassemia, which is characterized by a quantitative decrease in structurally normal b-globin chains. Its pathophysiology is caused by a quantitative decrease in b-globin and a build-up of a-globin chains. Researchers and physicians have created novel therapy options because of advances in understanding b-thalassemia's underlying pathophysiology.

Natural selection has raised and preserved the gene frequencies of b-thalassemia heterozygotes in these dangerous tropical and sub-tropical areas, suggesting that they are immune to the severe effects of falciparum malaria [3]. When treating patients with blood disorders, haematologists constantly try to adhere to established standards for practice and use the finest care possible. Treatment, however, can never be carried out precisely. Diverse perspectives are present about the best approach; at times, several treatment philosophies produce similar outcomes, or therapies differ only in their failures. The haematologist also must deal with limitations because of the local economy. In the developed

* Corresponding author: Umesh S. Saware

world, both early presentation and patient comprehension of the disease process are increasingly prevalent. This in turn affects the outcome, the strictness of patient adherence to the treatment plan, and the manner which patients are handled. Alpha thalassemia, in its severe form, results in intrauterine death unless advanced measures are taken to save the foetus. The thalassemia's are a diverse group of genetic disorders of haemoglobin (Hgb) synthesis, with clinical pictures ranging from practically symptom free in thalassemia trait to the debilitating and life-shortening illness of beta-thalassemia major 1 the degree of iron overload, organ involvement, and the severity of the ensuing anaemia all have a direct impact on how symptomatic patients are managed. It goes without saying that not all patients can take advantage of the most recent advancements in care, given its prevalence in nations with struggling economies. Also, given the growing refugee crisis in the modern world, such issues may be intractable. Lastly, comorbidities and even death are higher in transfusion-dependent thalassemia, even in nations with highly developed healthcare systems [4].

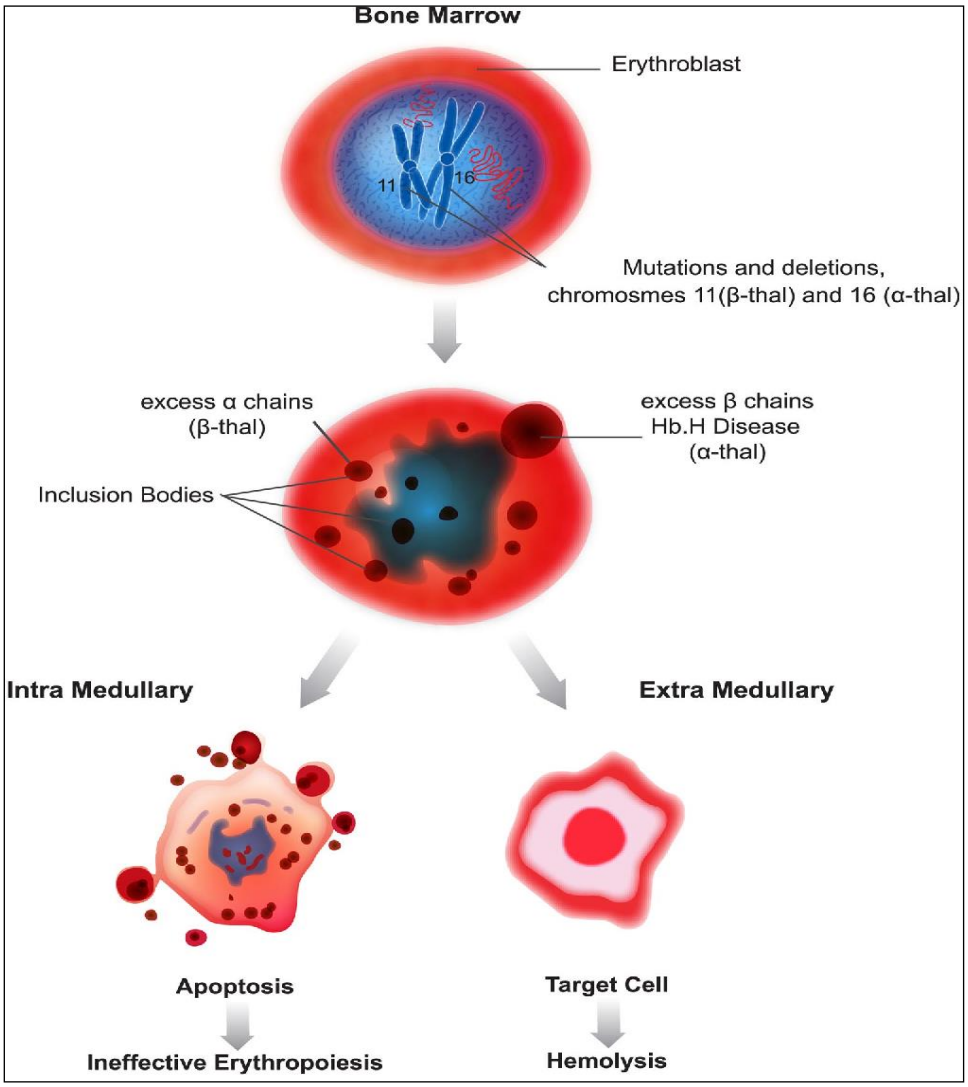

Figure 1 Mechanism of IE and hemolysis in thalassemia [9]

A globin gene condition known as thalassemia causes a decreased rate of synthesis of one or more globin chains, which in turn causes a decreased rate of synthesis of the haemoglobin or haemoglobins that the chain. Since all early occurrences were documented in children of Mediterranean descent, the word thalassemia is derived from the Greek words "thalas," which means sea, and "haimas" which means blood [5]. A genetic flaw that affects the process of haemoglobin formation causes thalassemia, and this genetic disease is passed down from parents to their offspring. Some children have thalassemia from birth, while others only show symptoms within the first two years of life. This depends on the degree and type of the disease. People who have a single gene defect, for example, might not exhibit symptoms. The ß-globin gene, located on chromosome 11, is susceptible to more than 200 distinct mutations (defects). Bitmap mutations, or altering just one letter of the genetic code, account for most of the mutations that cause ß-thalassemia [6]. Different types of thalassemia from different Indian states have been reported in numerous studies;

however, complete information, including regional variations is limited. To provide insights into the current management and prevention techniques for thalassemia, this study reviewed the prevalence of the condition in several groups and regions (Central, Northern, Southern, Eastern, and Western) throughout India [7]. Consanguinity and natural selection are responsible for the high prevalence of carriers with pathogenic globin gene variations. Natural selection favours heterozygotes, or people with one faulty gene that results in poor Hb synthesis, because they are protected from malaria. Despite producing fewer corpuscles and being less fit than normal individuals, heterozygotes are less vulnerable to Plasmodium falciparum attacks. In Greece, Sicily and Italy, where malaria is more common, mutations are also more common [8].

2. Classification of Thalassemia:

2.1. Alpha- Thalassemia

Excess beta globin chains are the result of inadequate or non-existent alpha globin chain production in alpha thalassemia. Two genes on each chromosome 16 regulate the synthesis of alpha globin chains. Typically, one or more of these genes are deleted, which results in less production. Alpha thalassemia silent carrier status, which is asymptomatic with normal hematologic findings, is caused by a single gene loss. Alpha thalassemia trait (minor) with microcytosis and typically minimal anaemia is caused by the loss of two genes. Significant amounts of haemoglobin H (HbH), which has four beta chains (beta4), are produced because of the three-gene deletion. Haemolysis, splenomegaly, and microcytic anaemia are the symptoms of alpha thalassemia intermedia, often known as HbH sickness. Significant amounts of haemoglobin Bart's (Hb Bart's), which has four gamma chains (gamma4), are produced because of the four-gene deletion. Hydrops fetalis is typically deadly in patients with alpha thalassemia major and Hb Bart's [10]. Gene frequencies for thalassemia range from 1% to 98% in the tropics and subtropics, making it the most prevalent hereditary haemoglobin (Hb) production problem worldwide. In G 95% of known cases of thalassemia, one or both globin genes from chromosome 16 are deleted, in contrast to thalassemia, where no deletional mutations are more common. Southern blot analysis was the accepted method for molecular characterisation of thalassemia till a few years ago. PCR-based testing, which is quicker, less costly, safer (no radiation is required), and simpler to interpret than Southern blot analysis, is now possible because to DNA sequence analysis of each deletion breakpoint. However, due to varying reagent and thermos cycling requirements, distinct assays are now needed for the various mutations [11]. Mild microcytic hypochromic anaemia is the typical symptom of alpha thalassemia minor, which is defined by two deletions in the alpha gene. The two gene deletions may be in the cis form, which is more frequently linked to Southeast Asian heritage, or the transform which is generally connected with African ancestry [12].

Table 1 Common forms of Alpha-thalassemia: [16]

Subtype	**Chromosome-16 mutation**	**Signs and symptoms**	**Hb and MCV**
Silent carrier (alpha thalassemia minima)	One of four gene Deletions	Normal Hb and haematocrit, asymptomatic	Normal
Trait (alpha-thalassemia minor)	Two of four gene deletions.	Microcytosis, possibly mild anaemia,Asymptomatic	Hb slightly subnormal. MCV < 80 μm3 (80 FL)
Deletional HbH disease (alpha-thalassemia intermedia)	Three of four gene deletions.	Mild to moderate anaemia, ineffectiveerythropoiesis, skeletal abnormalities	Hb = 6.9 to 10.7 g per dL (69 to 107 g per L); MCV = 46 to 76 μm3 (46 to 76 FL)
Alpha-thalassemia major with Hb Bart's disease	Four of four gene deletions	Nonimmune hydrops fetalis, usually fatal without treatment	Transfusion dependence if surviving

The term "alpha thalassemia syndrome" describes a collection of inherited anaemia's brought on by either insufficient or non-existent haemoglobin a-chain synthesis. These common gene mutations can affect up to 5% of the global population. The genotypic diversity in a-thalassemia leads to significant phenotypic variation. A fully asymptomatic

phenotype at one extreme of the spectrum is caused by a malfunctioning one of the four a gene [13]. Previously believed to be less of a global issue than β-thalassemia, the more severe types are mostly seen in China and Southeast Asia (SEA) [14]. Since the alpha-globin gene's expression level determines the phenotypic presentation of alpha-thalassemia, deletion of the globin gene has a greater effect than deletion of alpha1, unless compensatory expression -$\alpha^{3.7}$takes place, as in the case of those who express 1.8 times as much as normal people [15].

2.2. Beta-Thalassemia

Excess alpha chains are the result of inadequate or non-existent beta globin chain production in beta thalassemia. Each chromosome 11 has a single gene that regulates the synthesis of beta globin. Any of the more than 200-point mutations and (infrequently) deletions of the two genes can cause beta thalassemia. There are different levels of excess alpha globin to beta globin chain synthesis, which can range from almost normal to non-existent [10]. One of the most prevalent congenital haemolytic anaemia's, β-thalassemia, is primarily seen in South-East Asia and the Mediterranean region and is caused by a partial or whole loss of β-globin chain synthesis, which can lead to significant morbidity and mortality. The most severe form of Cooley's anaemia, called β-thalassemia major (β-TM), is characterized by inefficient erythropoiesis and extra medullary haematopoiesis (EMH) and requires numerous blood transfusions annually. During the first few years of life, untreated β-TM is lethal [17]. More than 200 disease-causing mutations have been found so far in beta-thalassemia, making them extremely diverse at the molecular level. A comprehensive, up-to-date list can be found at the Globin Gene Server. Most often, frame shift is caused by mutations that involve single nucleotide substitutions, deletions, or insertions of single nucleotides or short oligonucleotides. A consistent residual output of b chains from the affected b globin locus is caused by the coinheritance of homozygosity or compound heterozygosity for mild b-thalassemia alleles. Their diversity and the resulting variable degree of globin chain imbalance are the primary determinants for milder phenotypes. However, other genetic factors that can lessen the a/non-a chain imbalance and hence result in a lower degree of a chain precipitation also account for a large portion of the phenotypic diversity [18].

Table 2 Common form of Beta thalassemia: [16]

Subtype	**Chromosome 11 mutation**	**Signs and symptoms**
Beta-thalassemia minor	Single gene defect	Asymptomatic
Beta-thalassemia Intermediate.	Two defective genes (mild to moderate impairment in beta-globin production).	Symptoms like beta-thalassemia are major but with variable severity; may have mild to moderate anemia and may require intermittent or regular transfusions.
Beta-thalassemia Major	Two genes defective severe impairment in beta globin production.	Ineffective erythropoiesis, resulting in severe anemia, gallstones, skeletal abnormalities (due to bone marrow expansion), hepatosplenomegaly (causing abdominal distension), jaundice, and pallor; requires lifelong blood transfusions starting by six to 24 months of age.

2.2.1. Type of Beta- thalassemia

Thalassemia minor

Major, intermedia, and minor are the names of the three forms of β-thalassemia. A mutation in two genes causes β-thalassemia major, which results in either no β-globin synthesis or a significant reduction in it. The clinical profile of β-Thalassemia intermedia is characterized by transfusion independence and mild anaemia. Mutations in the 2 β genes cause a slight to moderate reduction in their synthesis, which is the genetic cause of it. The condition known as β-Thalassemia minor, or thalassemia trait, arises when a single gene is defective [19]. People who have beta thalassemia minor, also known as beta thalassemia trait or carrier, typically have moderate hypochromic microcytic anaemia but no other symptoms. The hallmark of beta thalassemia trait is an increased Hb A2 (usually greater than 3.5%), which is essential for diagnosis. Although they usually don't need therapy, patients should refrain from taking needless iron supplements. Pregnant women who experience significant anaemia should get supportive transfusion therapy as needed along with 1–5 mg/d of folic acid [12].

Beta-thalassemia intermediate

The clinical picture of thalassemia intermedia patients is notably varied. The main signs and symptoms include liver and spleen enlargement, pallor, jaundice, cholelithiasis, moderate to severe skeletal changes, leg ulcers, extra medullary masses of hyperplastic erythroid marrow, a propensity to develop osteopenia and osteoporosis, and thrombotic complications brought on by a hypercoagulable state due to the abnormal red blood cells lipid membrane composition (especially in splenectomised patients). Transfusions are either never needed or only needed in certain situations. The primary cause of iron overload is increased intestinal iron absorption brought on by inefficient erythropoiesis. The mechanism of beta-thalassemia's iron hyper absorption has recently been partially or completely clarified. Hepcidin, a little peptide released by the hepatocytes, fundamentally regulates iron absorption by preventing iron release from the reticuloendothelial system and intestinal iron absorption. The hepcidin-ferroprotein complex is absorbed and quickly broken down, which explains the impaired intestinal absorption of iron. Hepcidin binds ferroprotein, an iron transporter found on the surface of absorptive enterocytes, macrophages, and hepatocytes. Bone morphogenetic proteins (BMP) regulate hepcidin transcription by activating the SMAD protein complex, which translocate to the nucleus and promotes hepcidin transcription [20].

Beta-thalassemia major

Significant anaemia is the outcome of a genetic haemoglobin production defect called thalassemia major (TM). The extra iron obtained from the transfusions may gradually build up in several organs, particularly the heart, liver, and endocrine system [21]. Less than half of TM patients who have transfusions receive enough iron chelation treatment, and uncontrolled iron overload in their mid-20s claims the lives of almost 3,000 of them annually [22]. Both thalassemia major and thalassemia intermedia can develop in homozygotes for beta-thalassemia. People with thalassemia major typically seek medical care within the first two years of their condition and need frequent blood transfusions to stay alive. Those that show up later are diagnosed with thalassemia intermedia and do not need transfusion. Babies with thalassemia major suffer from poor growth and gradually turn pale. There may be issues with feeding, diarrhoea, irritability, frequent fever episodes, and splenomegaly-induced abdominal enlargement [20].

3. Pathophysiology

The underlying pathogenesis of the various forms of thalassemia is identical, even though clinical spectra differ based on the coinheritance of other genetic modifiers. Red blood cell (RBC) survival and Hb synthesis are reduced in this disorder due to an overabundance of undamaged globin chains that precipitate as inclusion bodies as unstable homotetramers. Due to their greater instability, homotetramers in thalassemia precipitate earlier in the RBC life span, resulting in severe haemolysis linked to extra medullary haemolysis and inefficient erythropoiesis (IE) as well as significant RBC destruction. (Fig. 1) IE causes enlarged marrow cavities in severe beta-thalassemia, which press on healthy bone and distort the skull, long bones, and face. Furthermore, erythroid activity multiplies in extramedullary hematopoietic locations, leading to hepatosplenomegaly, widespread lymphadenopathy, and occasionally extramedullary malignancies [9]. A relative excess of unbound alpha globin chains precipitates in erythroid precursors in the bone marrow due to the decreased number (ß+) or absence (ß0) of beta globin chains. This premature demise of the precursors causes inefficient erythropoiesis. The type of mutation at the beta globin gene on chromosome 11 determines the extent of globin chain reduction. In thalassemia major, peripheral haemolysis which causes anaemia occurs when insoluble alpha globin chains destroy the peripheral erythrocytes' membranes. This phenomenon is less common in thalassemia intermedia [5]. This deficiency in β-globin chains causes an excess of α-globin chains to precipitate, forming inclusion bodies that aid in haemolysis of red blood cells. Between the ages of three and six months, haematological changes start to appear [19]. Reduced synthesis of at least one globin polypeptide chain (beta, alpha, gamma, and delta) causes thalassemia, which leads to uneven haemoglobin synthesis. Thalassemia is inherited in an autosomal recessive manner [6].

Heterozygous thalassemia has been proposed as a protective result of selection pressure against malaria since the malarial parasite needs normal erythrocytes to finish its life cycle. Because of this, β-thalassaemia, sickle cell anaemia, and thalassemia E are mostly found in developing nations in the world's tropical and subtropical regions [24]. Through unchecked uptake mechanisms like calcium and zinc channels, non-transferrin-bound iron is excessively absorbed by the cells. This leads to the growth of labile iron pools, which are then accessible to take part in the production of free radicals. Iron-induced liver illness, endocrine problems, and, if left untreated, mortality from iron-induced cardiomyopathy are all consequences of tissue iron overload [1]. Haemoglobin is made up of four globin chains two alpha and two no alpha and a hammering that contains iron. The type of haemoglobin is determined by the makeup of the four globin chains. Two alpha and two gamma chains (alpha2 gamma2) make up foetal haemoglobin (HbF). There are two alpha and two beta chains (alpha2 beta2) in adult haemoglobin A (HbA), while haemoglobin A2 (HbA2) includes

two alpha and two delta chains (alpha2 delta2). About 80% of haemoglobin at birth is made up of HbF, while 20% is made up of HbA [10].

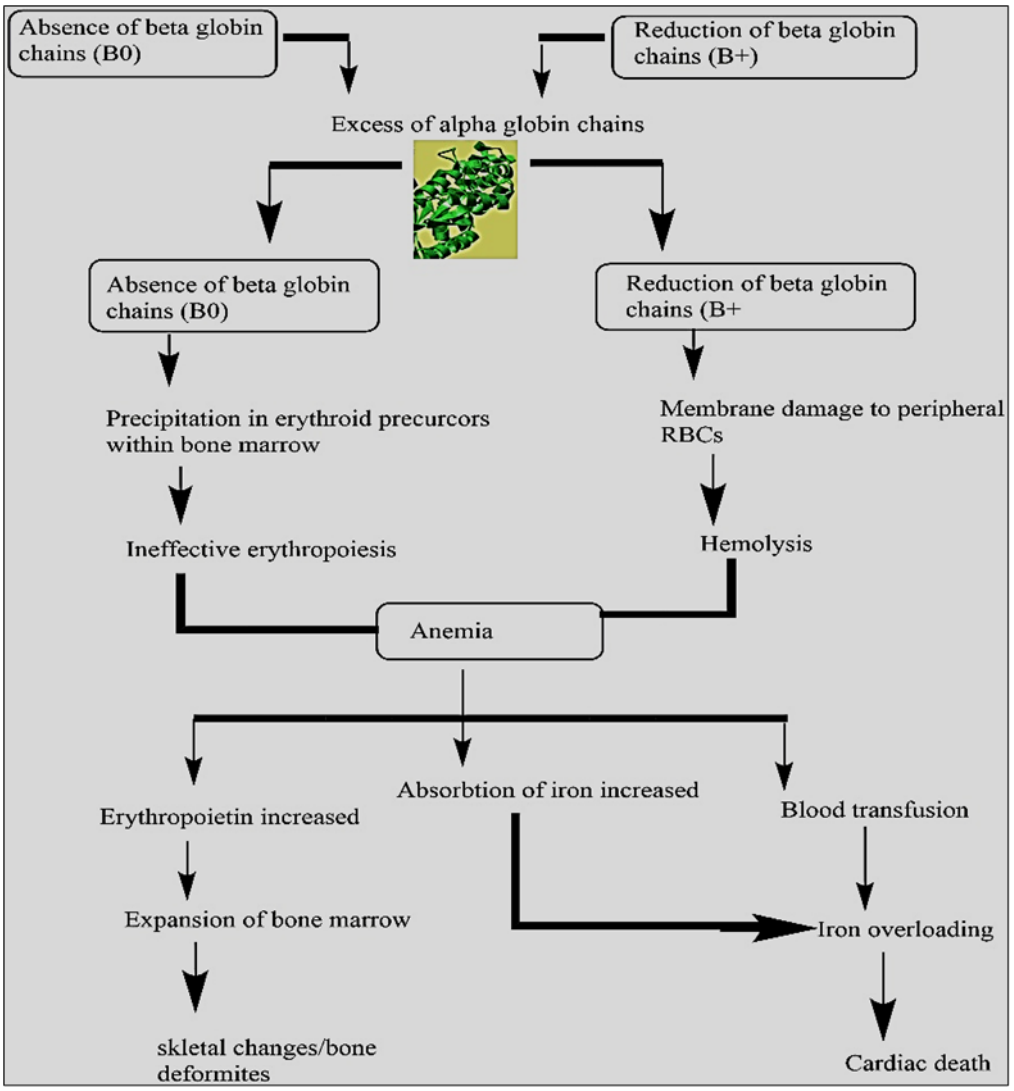

Figure 2 Pathophysiology of thalassemia [23]

4. Complications

Patients burden with thalassemia is caused by the disease's consequences or by the adverse effects of their treatment. Iron overload eventually develops in transfusion-dependent thalassemia patients, requiring iron chelation as a therapeutic strategy. The medical resource people in charge of long-term monitoring and care should be haematologists [25].

Patients with thalassemia syndrome may experience iron overload because of frequent blood transfusions, which can harm their liver, heart, and glands. Marrow hyperplasia can also result in bone abnormalities, particularly in the face and skull bones, which cause the bones to become thin and fragile [6].

10 individuals developed grade III mucositis, whereas twenty-five patients had grade I to II mucositis. With supportive care measures, all 15 patients who acquired mild to moderate Veno-occlusive disease were able to recover. The class 3 HR and the remaining patient group did not differ in their incidence of Veno-occlusive illness. CMV reactivation occurred in 15 individuals. Two were infected with CMV. Three patients got adenovirus cystitis, and 23 patients acquired BK-virus cystitis [26].

4.1. Iron overload

Overloaded iron manifests more slowly in the heart's tissues and in a variety of endocrine tissues, including the hepatic parenchyma. In healthy people, iron homeostasis is achieved by regulating iron concentration. Through the detachment of epithelial cells from the urinary system, colon, dermis, and other endodermal tissues, the body loses 1 mg of iron every day, along with 1 millilitre of transfused blood. Have 1 mg of iron, which causes tissues to accumulate 200 mg of iron. Because they lacked the body's iron excretory mechanisms, patients with severe thalassemia who received blood transfusions shown a notable capacity for iron deposition [23]. The intricate system of iron homeostasis keeps daily absorption and excretion at about 2 mg/day. Several chemicals carefully regulate this [27]. Given the prevalence of myocardial siderosis in thalassemia major and the advantages of customizing an iron-chelating treatment, myocardial iron testing is crucial for determining the risk of cardiac problems [28].

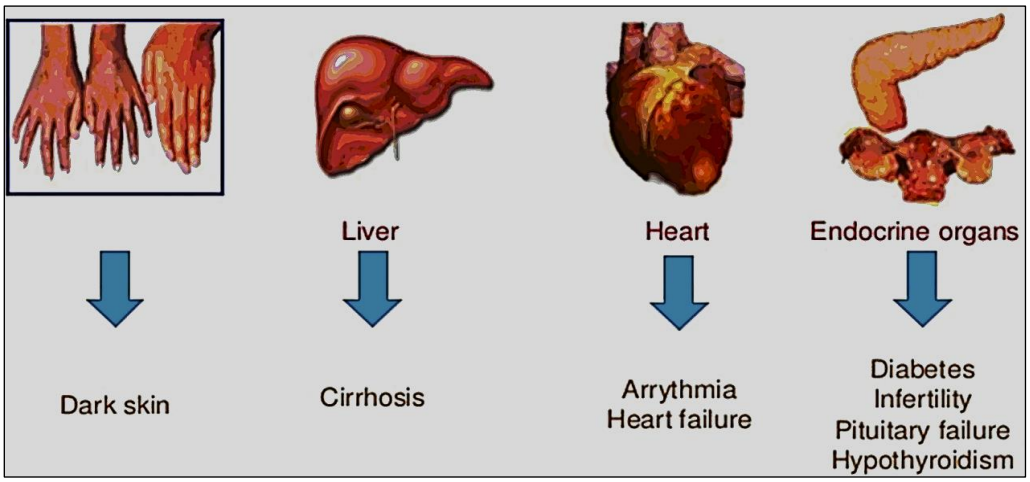

Figure 3 Features of iron overload [23]

4.2. Hepatitis

There is a significant risk of virus-related infection for thalassemia patients. For example, chronic exposure to blood and blood transfusion products might result in pathological hepatitis. The availability of immunizations can significantly lower the frequency of hepatitis B in thalassemia patients and donors, but the absence of a vaccine makes hepatitis C extremely difficult for these patients [23].

4.3. Osteoporosis

Nearly all thalassemia patients develop osteoporosis, which causes numerous fractures and bone discomfort. It also shows that as people age, the density of minerals in axial bone increases more quickly than in fringe bone. In patients with β-thalassemia, osteoporotic also results in iron toxicity, endocrine deficits, bone marrow enlargement, and possible chelator toxicity. It may be acceptable for hepatocytes to accumulate iron at a level of 7 mg/g (dry weight); however, frequent transfusions without iron chelation can cause liver fibrosis, which leads to iron overload that cannot be eliminated from the liver and raises the risk of liver cancer [23].

4.4. Abnormal thalassemia RBCs to the hypercoagulable state

It is still unclear how thalassemia causes the hypercoagulable condition. The genesis of the latter phenomenon, however, may be better understood by considering data from investigations of other forms of haemolytic anaemia, such as sickle cell disease (SCD) and paroxysmal nocturnal haemoglobinuria (PNH), in which thrombosis is also a significant clinical feature. According to our group's study of normal RBCs with those isolated from TM or TI patients, thalassemia RBCs might serve as a source of negatively charged phospholipids that can boost thrombin production as determined by the prothrombinase assay [29].

4.5. Complication of Deferoxamine Therapy

None of these patients experienced visual or auditory signs of neurotoxicity or pulmonary syndrome, which have been linked to intravenous administration of deferoxamine at doses of 10g per day or more, even though many patients reported some local irritation and swelling following subcutaneous infusions of the drug. There were no additional side effects from the deferoxamine treatment [30].

5. Diagnosis

5.1. Laboratory Diagnosis of Thalassemia

The diagnosis of thalassemia and aberrant haemoglobin in humans requires several laboratory tests. These tests are noteworthy because they include the use of an automatic haematology analyser to evaluate the features of red blood cells, the identification of Hb A2, and the investigation of Hb and Hb F. Capillaries, area electrophoresis, and high-performance liquid chromatography (HPLC)[25].

5.2. Qualitative and quantitative Hb analysis

Determines the kind and quantity of Hb present (by cellulose acetate electrophoresis and DE-52 micro chromatography or HPLC). The kind of beta-thalassemia determines the variation in the Hb pattern. Homozygotes with beta0 thalassemia have no HbA and 92–95% of their entire Hb is HbF. HbA levels range from 10 to 30% and HbF levels range from 70 to 90% in beta+ thalassemia homozygotes and beta+/beta genetic compounds. HbA2 is elevated in beta thalassemia minor and varies in beta thalassemia homozygotes. Other hemoglobinopathies that may interact with beta-thalassemia are also detected by Hb electrophoresis and HPLC [31].

5.3. Genetic Counselling

Alpha-thalassemia genetic counselling is especially important for couples with both alpha carriers because they have a 25% chance of having children with Hb Bart hydrops fetalis syndrome. Prenatal diagnosis is always recommended for this disorder because to its severity, lack of an effective therapy, and potential to prevent serious maternal toxic consequences during pregnancy. To address homozygous alpha-thalassemia, a few nations have implemented universal prenatal screening programs. Since HbH disease is typically moderate and compatible with a nearly normal postnatal life, prenatal diagnostics is not recommended for couples at risk of having children with this problem [32].

5.4. Molecular screening

Prenatal counselling for parents at risk of having an afflicted child, new-born screening for early diagnosis, and the correct diagnosis and management of anaemia are the three key contexts in which screening for thalassemia syndromes is crucial. Patients with thalassemia frequently take lengthy iron courses, sometimes parenterally, after being misdiagnosed as iron deficiency anaemia. Monitoring helps people with thalassemia intermedia avoid chronic complications and squeal, whereas appropriate screening would avoid needless iron consumption in carriers [33]. The primary issue with 3-thalassemia prenatal diagnosis to date is the disorder's notable molecular heterogeneity, which makes it challenging to arrange foetal testing in a practical manner [34].

5.5. Prenatal Diagnosis

Even though it offered at-risk couples a chance to have healthy sons, prenatal diagnosis based on foetal blood was not readily accepted. The method was difficult for the couples to accept because of the late gestational age at which the foetal diagnostic was performed, the possibility of a misdiagnosis because of a vague cut-off between some heterozygotes and afflicted foetuses, and the high chance of miscarriage because of the sampling procedures [35]. The finding that adult haemoglobin synthesis could be detected in foetuses at mid-trimester and that b-globin chain synthesis in the cord blood of b-thalassemia heterozygotes was significantly lower than normal first raised the prospect of prenatal diagnosis of inherited hemoglobinopathies. Later, the base-chain was discovered in the blood of foetuses. Following the establishment of foetal blood collection by placenta centesis globin chain synthesis on foetal blood was introduced as a prenatal diagnostic method [36].

6. Treatment

6.1. Blood Transfusion

Red cell transfusions are necessary to raise the Hb concentration in individuals with acute or chronic anaemia, hence increasing the blood's ability to carry oxygen.

The British Committee for Standards in Haematology is followed in the handling of transfusion patients and blood and blood components. The following are the main objectives of blood transfusion therapy: [19].

- Maintenance of red cell viability and function during storage to ensure sufficient transport of Oxygen.

- Use of donor erythrocytes with a normal recovery and half-life in the recipient.
- Achievement of appropriate Hb level.
- Avoidance of adverse reactions, including transmission of infectious agents.

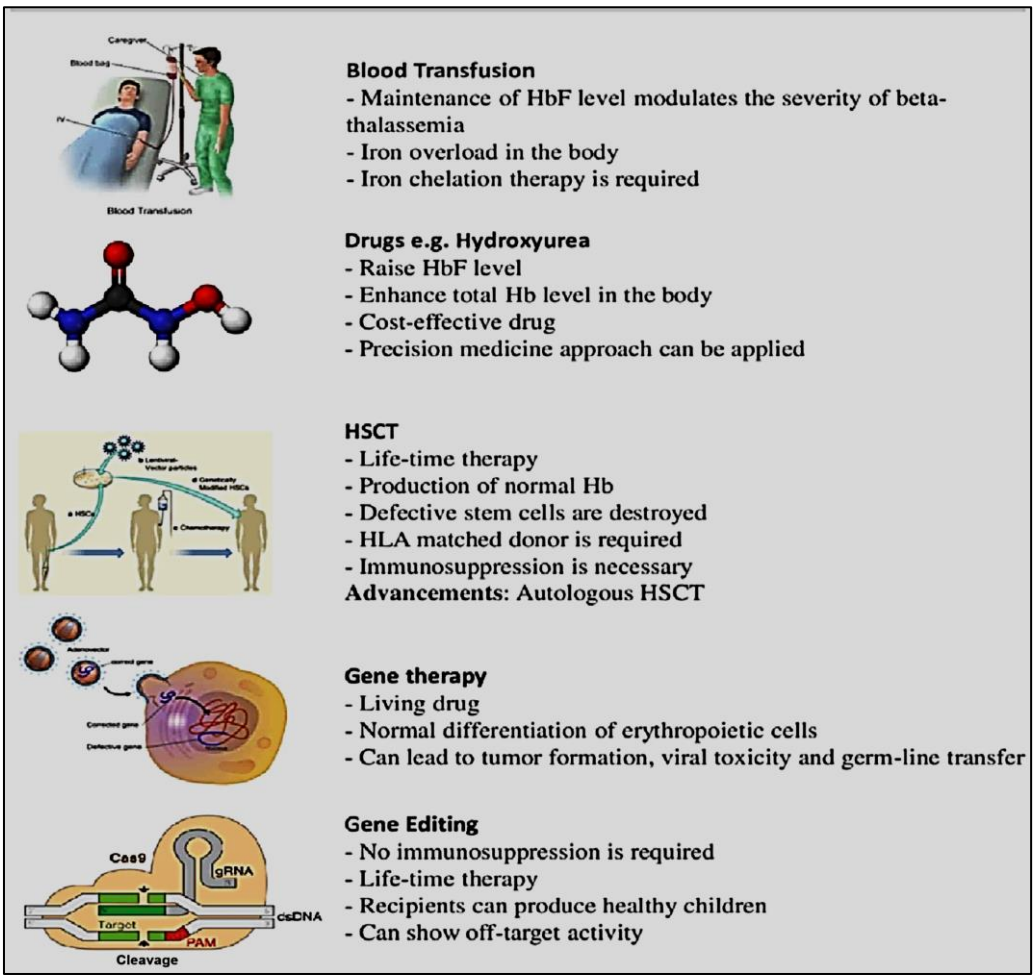

Figure 4 Therapies for curing thalassemia [8]

6.2. Iron Chelation therapy

Achieving neutral or negative iron balance, where iron excretion equals or surpasses the rate of new iron build up, is necessary for iron chelation therapy to be effective. Regular red blood cell (RBC) transfusions are the main source of iron intake for people with beta-thalassemia major. For children under the age of ten, an annual transfusion of 10 to 20 units of packed red blood cells is necessary to maintain a haemoglobin level of 9 to 10 g/dL [37]. Patients with trans fusional iron overload run the danger of iron deposition in critical organs including the liver and heart if they do not receive appropriate iron chelation therapy. The heart is more vulnerable to iron overload than the liver, and compared to the higher iron load that the liver can withstand before experiencing hepatic dysfunction, lower iron levels are enough to cause iron-related heart failure and mortality [38].The use of chelators for myelodysplastic syndrome and new chelator applications, such treating neurological diseases2 or infections based on iron sequestration, are outside the purview of this review. Deferoxamine, deferiprone, and deferasirox are the iron chelators [39].

6.2.1. Deferasirox

In November 2005, deferasirox, an oral iron chelator, was approved with the intention of enhancing patient compliance and quality of life. The effectiveness of once-daily oral deferasirox in regulating liver iron content (LIC) has been shown in numerous carefully monitored clinical trials. Deferasirox has a 12- to 16-hour half-life, is frequently prescribed seven days a week, is preferred by patients, and increases compliance. Consequently, deferasirox reduces labile plasma iron levels more effectively over an extended period than intermittent, subcutaneous DFO therapy [40]. In the deferasirox cohort, the mean dose was 21.6 ϱ 6.4 mg/kg/day, while in the crossover cohort, it was 23.2 ϱ 5.9 mg/kg/day. Many

patients got final doses of ʃ25 mg/kg/day; the percentage of patients getting 15 mg/kg/day decreased significantly over the course of the research [41].

6.2.2. Deferiprone

Although it is not authorized in the US or Canada, the oral chelator deferiprone (Ferriprox, Apopharma, and others) is used as the primary treatment for iron overload in various regions of the world, particularly southern Asia, and is authorized as a second-line agent in Europe. The FDA is still considering the medication. Over the past four years, several intriguing investigations have demonstrated the apparent benefit of deferiprone in accelerating the elimination of cardiac iron in patients with iron overload who do not yet have severe cardiac dysfunction. The nature of these investigations has been incremental [39]. No patient was using deferiprone at baseline. All patients were given a daily dose of 75 mg/kg of deferiprone during the experiment [42].

6.2.3. Deferoxamine

Deferoxamine's place in the arsenal against transfusion-induced iron overload is still developing. This medication has been used since the 1960s, and more than 30 years ago, deferoxamine therapy became widely used due to the development of practical subcutaneous pumps and strong evidence of its effectiveness. Some patients in the United States and Europe prefer deferoxamine over the current oral alternatives, and some patients have switched back to deferoxamine if deferasirox proved to be unsuccessful or unacceptable. Knowing how to employ deferoxamine in combination regimens is currently the biggest challenge. Numerous instances of the concurrent or overlapping usage of deferiprone and deferoxamine have been documented, as was previously mentioned for deferiprone [39].

Important properties for an ideal iron chelator: [43]

- High and specific affinity for Fe3+
- High chelating efficiency
- Slow rate of metabolism
- Tissue and cell penetration
- No iron redistribution
- Relatively non-toxic
- Achievement of negative iron balance
- Low cost
- Oral availability

6.3. Bone marrow transplantation

The sole cure for TM is bone marrow transplantation (BMT) from an HLA-identical sibling, which is a commonly used substitute for conventional transfusion and chelation therapy. The pre transplantation clinical parameters, particularly the degree of liver fibrosis, the presence of hepatomegaly, and the amount of iron build up, have historically been linked to the outcome of BMT. The disease-free survival rate for children without these risk factors is around 90%. Even in high-risk patients, treosulfan-based conditioning has increased overall and thalassemia-free survival. Due to an advanced stage of the disease, adults with β-thalassemia are more likely to have transplant-related damage, and current treatment procedures have a cure rate of about 65%. BMT from unrelated donors has been performed on a few of β-thalassemia patients. The outcomes are like those achieved when the donor is a compatible sibling, if the donor is chosen based on strict HLA compatibility criteria and the recipients have minimal iron overload. Haploidentical mother-to-child transplantation, whose outcomes seem promising, may also help affected persons without matched donors [44].

6.4. Prevention and treatment of iron overload

Regular transfusions always result in iron overload since the human body is unable to eliminate excess iron. However, proper iron chelation can avoid and, to some extent, reverse the most frequent problems associated with transfusional hemosiderosis, including growth retardation, cirrhosis, heart failure, and numerous endocrine disorders. There are now three different types of iron chelators. The first medication to clearly show the benefits of iron chelation therapy for eliminating excess iron from the body was desferrioxamine B, which has been used in clinical settings for almost 50 years [44].

6.5. Splenectomy

In thalassemia patients whose annual transfusion needs surpass 200 millilitres of packed cells per kilogram of body weight, splenectomy should considerably reduce red blood cell needs and iron build up. Transfusions that are timely

and frequent can prevent hypersplenism. This decade has seen many patients reach adolescence without needing a splenectomy. Due to the possibility of infection following a splenectomy [45]. In cases of severe TI, removing the spleen may be a helpful treatment approach that improves growth and development and raises Hb levels by 1-2 g/dL. Although there are many reasons to have a splenectomy for TI, the decision to remove the spleen should be considered carefully because individuals who have one are more likely to get thrombosis, infection, and PHT. According to TIF splenectomy guidelines, nontransfusion-dependent thalassemia patients under the age of five should not have splenectomy. Additionally, individuals should have splenectomy if their anaemia worsens and impairs their growth and development, or if their hypersplenism causes leucopoenia, thrombocytopenia, or severe anaemia [46].

6.6. Hematopoietic Stem Cell Transplantation

The development of allogeneic hematopoietic stem cell transplantation (HSCT) in thalassemia has been a key component. In thalassemia, the rationale behind HSCT is to replace the thalassemia HSC with inefficient erythropoiesis with an allogeneic one that can produce successful erythropoiesis. The complete hematopoietic system is replaced by this cellular replacement therapy, not just the faulty erythropoietic component. However, it is an effective method of achieving a clinically successful, long-lasting, and likely permanent repair of haemolytic anaemia, hence avoiding the need for transfusions and the related problems (such as iron overload) [47]. Our study presents the clinical results of a large cohort of 516 children and adults with thalassemia treated with HSCT or conventional therapy over 30 years in a single centre to help physicians and patients make decisions by giving them more information about the benefits and possible risks of HSCT. The study's primary goal was to compare the OS and TFS of 258 thalassemia patients receiving HSCT to an age-sex matched group of thalassemia patients who were not receiving transplants and were receiving standard treatment with iron chelation therapy and routine transfusions using a 1:1 case control design. The assessment of long-term HSCT results in a subgroup of adult patients and the effects of conditioning regimens based on treosulfan or busulfan were secondary objectives [48].

Bone marrow, peripheral blood, and cord blood can all provide stem cells for HSCT. Because bone marrow has a higher percentage of T lymphocytes than peripheral blood and is linked to a lower incidence of GVHD, particularly chronic GVHD, most transplant centres worldwide use bone marrow as a source of stem cells. According to several research, bone marrow stem cells have improved overall survival. According to the 2014 expert panel guidelines, bone marrow is a better source of stem cells than peripheral blood, and the incidence of graft failure has been comparable across all sources [49].

6.7. Gene Therapy

The safety and effectiveness of gene editing and gene insertion to restore Hb production in β-thalassemia are being studied in a number of clinical trials. Few products use gene-editing techniques to reawaken foetal haemoglobin (HbF), while the majority are gene addition-based methods. Lentiglobin BB305 (Zynteglo), manufactured by Bluebird Bio, was the first gene addition product authorized for TDT in Europe in July 2019. For the majority of the β0/β0 adults, the amount of integration [vector copy number (VCN)] was not enough to achieve transfusion independence [50].The primary goal of gene therapy is to restore the alpha/non-alpha globin ratio in red blood cells by increasing the synthesis of β- or ɣ-globin and decreasing the numbers of unattached α-globin chains. This prolongs the lifespan of red blood cells and produces functional haemoglobin-carrying erythrocytes by preventing RBC haemolysis and inefficient erythropoiesis. The anaemia is corrected as a result, and fewer transfusions are required [51].

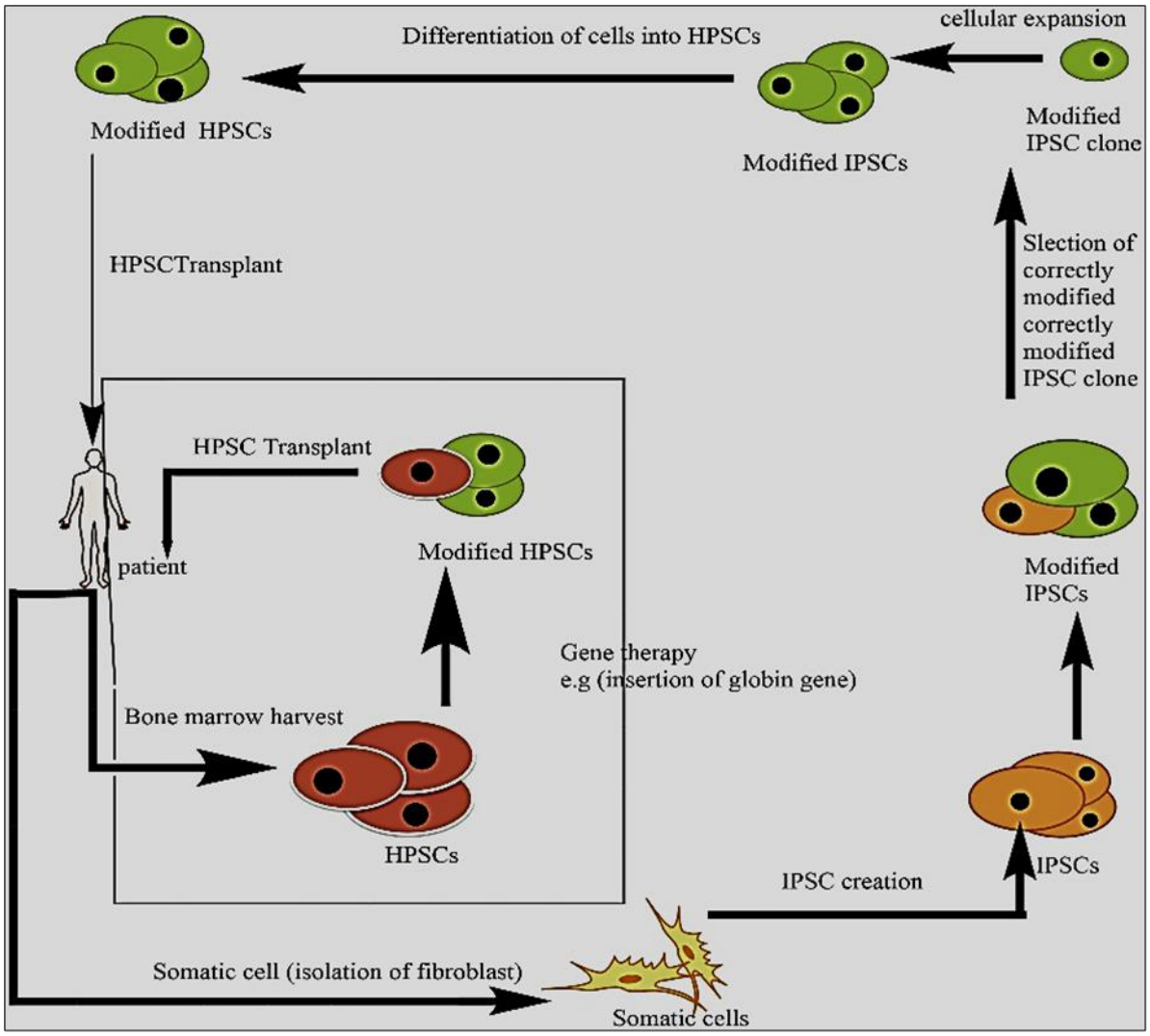

Figure 5 Gene therapy process. Induced pluripotent stem cells (iPSCs), Hematopoietic stem and progenitor cells (HSPCs) [23]

7. Conclusion

Thalassemia is a complex genetic disorder requiring comprehensive management to prevent complications and improve quality of life. Understanding the molecular basis and pathophysiology of the disorder has led to the development of novel therapeutic approaches. Blood transfusions, iron chelation therapy, and bone marrow transplantation are current treatment options. Gene therapy and hematopoietic stem cell transplantation hold promise for future treatment. Early diagnosis and prevention are crucial in reducing the burden of thalassemia. genetic counselling and prenatal diagnosis can help identify carriers and affected individuals, enabling timely interventions. Further research is necessary to improve treatment outcomes and develop more effective therapies for this debilitating disorder. By understanding the complexities of thalassemia, healthcare professionals can provide better care and support to affected individuals, ultimately improving their quality of life.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Galanello R, Origa R. Beta-thalassemia. Orphanet journal of rare diseases. 2010 ;5(11):1-5.

[2] Cao A, Galanello R. Beta-thalassemia. Genetics IN Medicine. 2010;12(2): 61–76.

[3] Cohen AR, Galanello R, Pennell DJ, Cunningham MJ, Vichinsky E. Thalassemia. ASH Education Program Book. 2004 :14-34.

[4] Aydinok Y. Thalassemia. Hematology. 2012; 17 (1): 28-31.

[5] Rachmilewitz EA, Giardina PJ. How I treat thalassemia. Blood, The Journal of the American Society of Hematology. 2011 ;118(13):3479-88.

[6] Muncie Jr HL, Campbell JS. Alpha and beta thalassemia. American family physician. 2009 Aug 15;80(4):339-44.

[7] Origa R. β-Thalassemia. Genetics in medicine. 2017 Jun;19(6):609-19.

[8] Sarnaik SA. Thalassemia and related hemoglobinopathies. The Indian Journal of Pediatrics. 2005 Apr;72(4):319-24.

[9] Cao A, Kan YW. The prevention of thalassemia. Cold Spring Harb Perspect Med. 2013 Feb 1;3(2):1-15.

[10] Galanello R, Cao A. Alpha-thalassemia. Genetics in medicine. 2011 Feb;13(2):83-8.

[11] Sayani FA, Kwiatkowski JL. Increasing prevalence of thalassemia in America: Implications for primary care. Annals of medicine. 2015 Oct 3;47(7):592-604.

[12] Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. Blood, The Journal of the American Society of Hematology. 1997 Feb 1;89(3):739-61.

[13] Danjou F, Anni F, Galanello R. Beta-thalassemia: from genotype to phenotype. haematologica. 2011 Nov;96(11):1573.

[14] Baird DC, Batten SH, Sparks SK. Alpha-and beta-thalassemia: rapid evidence review. American family physician. 2022 Mar;105(3):272-280.

[15] Karimi M, Cohan N, De Sanctis V, Mallat NS, Taher A. Guidelines for diagnosis and management of Beta-thalassemia intermedia. Pediatric hematology and oncology. 2014 Oct 1;31(7):583-596.

[16] Ali S, Mumtaz S, Shakir AH, Khan M, Tahir MH, Mumtaz S, Mughal AT, Hassan A, Kazmi AS, Sadia, Irfan M, Khan AM. Current status of beta--thalassemia and its treatment strategies. Mol Genet Genomic Med. 2021;9(1788):1-14.

[17] Mensah C, Sheth S. Optimal strategies for carrier screening and prenatal diagnosis of α-and β-thalassemia. Hematology. 2021 Dec 10;2021(1):607-613.

[18] Cristina Rosatelli M, Tuveri T, Teresa Scalas M, Battista Leoni G, Sardu R, Faa V, Meloni A, Alessandra Pischedda M, Demurtas M, Monni G, Cao A. Molecular screening and fetal diagnosis of β-thalassemia in the Italian population. Human genetics. 1992 Aug;89:585-589.

[19] Vichinsky EP. Clinical manifestations of α-thalassemia. Cold Spring Harbor perspectives in medicine. 2013 May 1;3(5):1-10.

[20] Singer ST. Variable Clinical Phenotypes of α-Thalassemia Syndromes. The Scientific World Journal. 2009;9(1):615-625.

[21] Jaing TH, Chang TY, Chen SH, Lin CW, Wen YC, Chiu CC. Molecular genetics of β-thalassemia: A narrative review. Medicine. 2021 Nov 12;100(45):1-9.

[22] Chong SS, Boehm CD, Higgs DR, Cutting GR. Single-tube multiplex-PCR screen for common deletional determinants of α-thalassemia. Blood, The Journal of the American Society of Hematology. 2000 Jan 1;95(1):360-362.

[23] El-Kalla S, Baysal E. α-thalassemia in the United Arab Emirates. Acta haematologica. 1998 Aug 5;100(1):49-53.

[24] Rivella S, Rachmilewitz E. Future alternative therapies for β-thalassemia. Expert review of hematology. 2009 Dec 1;2(6):685-97.

[25] Motta I, Bou-Fakhredin R, Taher AT, Cappellini MD. Beta thalassemia: new therapeutic options beyond transfusion and iron chelation. Drugs. 2020 Jul;80:1053-1063.

[26] Chauhan W, Shoaib S, Fatma R, Zaka-ur-Rab Z, Afzal M. Beta-thalassemia and the advent of new interventions beyond transfusion and iron chelation. British Journal of Clinical Pharmacology. 2022 Aug;88(8):3610-3626.

[27] Mahmoud HQ, Mhana RS, Mohammed AA. Therapeutic options and management approach on thalassemia an overview. International Journal of Medical Science and Dental Health. 2024;10(01):17-28.

[28] Qari MH, Wali Y, Albagshi MH, Alshahrani M, Alzahrani A, Alhijji IA, Almomen A, Aljefri A, Al Saeed HH, Abdullah S, Al Rustumani A. Regional consensus opinion for the management of Beta thalassemia major in the Arabian Gulf area. Orphanet journal of rare diseases. 2013 Dec;8(143):1-12.

[29] Hokland P, Daar S, Khair W, Sheth S, Taher AT, Torti L, Hantaweepant C, Rund D. Thalassaemia—A global view. British Journal of Haematology. 2023 Apr;201(2):199-214.

[30] Jha R, Jha S. Beta thalassemia-a review. Journal of pathology of Nepal. 2014 Sep 24;4(8):663-671.

[31] Meri MA, Al-Hakeem AH, Al-Abeadi RS. An overview on thalassemia: A review article. Medical Science Journal for Advance Research. 2022 Mar 1;3(1):26-32.

[32] Malay J, Salama RAA, Alam Qureshi GS, Ammar ARAA, Janardhan G, Safdar M, Elshamy HAH. Gene Therapy: A Revolutionary Step in Treating Thalassemia. Hematol Rep. 2024 Oct 21;16(4):656-668.

[33] Yadav SS, Panchal P, Menon KC. Prevalence and Management of β-Thalassemia in India. Hemoglobin. 2022 Jan;46(1):27-32.

[34] Amjad F, Fatima T, Fayyaz T, Khan MA, Qadeer MI. Novel genetic therapeutic approaches for modulating the severity of β-thalassemia. Biomedical Reports. 2020 Nov;13(5):48.

[35] Singh S, Sri CK, Bakane A. The Thalassemia Syndromes: New Insights. InThalassemia Syndromes-New Insights and Transfusion Modalities 2023 Sep 29;1-13

[36] Angelucci E. Hematopoietic stem cell transplantation in thalassemia. Hematology 2010, the American Society of Hematology Education Program Book. 2010 Dec 4;2010(1):456-462.

[37] Anurathapan U, Hongeng S, Pakakasama S, Songdej D, Sirachainan N, Pongphitcha P, Chuansumrit A, Charoenkwan P, Jetsrisuparb A, Sanpakit K, Rujkijyanont P. Hematopoietic stem cell transplantation for severe thalassemia patients from haploidentical donors using a novel conditioning regimen. Biology of Blood and Marrow Transplantation. 2020 Jun 1;26(6):1106-1112.

[38] Neufeld EJ. Update on iron chelators in thalassemia. Hematology 2010, the American Society of Hematology Education Program Book. 2010 Dec 4;2010(1):451-455.

[39] Pennell DJ, Porter JB, Piga A, Lai Y, El-Beshlawy A, Belhoul KM, Elalfy M, Yesilipek A, Kilinç Y, Lawniczek T, Habr D. A 1-year randomized controlled trial of deferasirox vs deferoxamine for myocardial iron removal in β-thalassemia major (CORDELIA). Blood, The Journal of the American Society of Hematology. 2014 Mar 6;123(10):1447-1454.

[40] Wood JC, Kang BP, Thompson A, Giardina P, Harmatz P, Glynos T, Paley C, Coates TD. The effect of deferasirox on cardiac iron in thalassemia major: impact of total body iron stores. Blood, The Journal of the American Society of Hematology. 2010 Jul 29;116(4):537-543.

[41] Brittenham GM, Griffith PM, Nienhuis AW, McLaren CE, Young NS, Tucker EE, Allen CJ, Farrell DE, Harris JW. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. New England Journal of Medicine. 1994 Sep 1;331(9):567-573.

[42]

[43] Pinto VM, Forni GL. Management of Iron Overload in Beta-Thalassemia Patients: Clinical Practice Update Based on Case Series. Int. J. Mol. Sci. 2020; 21(8771):1-20.

[44] Cappellini MD, Bejaoui M, Agaoglu L, Canatan D, Capra M, Cohen A, Drelichman G, Economou M, Fattoum S, Kattamis A, Kilinc Y. Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up. Blood, The Journal of the American Society of Hematology. 2011 Jul 28;118(4):884-893.

[45] Cohen AR, Glimm E, Porter JB. Effect of transfusional iron intake on response to chelation therapy in β-thalassemia major. Blood, The Journal of the American Society of Hematology. 2008 Jan 15;111(2):583-587.

[46] He T, Gatehouse PD, Kirk P, Mohiaddin RH, Pennell DJ, Firmin DN. Myocardial T measurement in iron-overloaded thalassemia: An ex vivo study to investigate optimal methods of quantification. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine. 2008 Aug;60(2):350-356.

[47] Wahidiyat PA, Liauw F, Sekarsari D, Putriasih SA, Berdoukas V, Pennell DJ. Evaluation of cardiac and hepatic iron overload in thalassemia major patients with T2* magnetic resonance imaging. Hematology. 2017 Sep 14;22(8):501-507.

[48] Carpenter JP, Roughton M, Pennell DJ, Myocardial Iron in Thalassemia (MINT) Investigators. International survey of T2* cardiovascular magnetic resonance in β-thalassemia major. Haematologica. 2013 Sep;98(9):1368-1374.

[49] Rosatelli MC, Saba L. Prenatal diagnosis of β-thalassemias and hemoglobinopathies. Mediterranean journal of hematology and infectious diseases. 2009 Nov 15;1(1):1-12.

[50] Tanner MA, Galanello R, Dessi C, Smith GC, Westwood MA, Agus A, Roughton M, Assomull R, Nair SV, Walker JM, Pennell DJ. A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. Circulation. 2007 Apr 10;115(14):1876-1884.

[51] Eldor A, Rachmilewitz EA. The hypercoagulable state in thalassemia. Blood, The Journal of the American Society of Hematology. 2002 Jan 1;99(1):36-43.

[52] Caocci G, Orofino MG, Vacca A, Piroddi A, Piras E, Addari MC, Caria R, Pilia MP, Origa R, Moi P, La Nasa G. Long-term survival of beta thalassemia major patients treated with hematopoietic stem cell transplantation compared with survival with conventional treatment. American journal of hematology. 2017 Dec;92(12):1303-1310.