thalassemia reports

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Review

Thalassemia: Pathophysiology, Diagnosis, and Advances in Treatment

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Abstract: Thalassemia represents a diverse group of inherited hematological disorders characterized by defective globin chain synthesis, leading to chronic anemia and associated complications. The complicated pathophysiology of beta-thalassemia involves genetic mutations or rarely deletions of the beta-globin gene on chromosome 11 whereas alpha-thalassemia involves deletions in the HBA1 and HBA2 genes or occasionally alterations to the DNA sequence in or around these genes. These mutation and deletion effects disrupt the balance of α/β-globin chain production, resulting in ineffective erythropoiesis, hemolysis, and a cascade of clinical manifestations including anemia, bone deformities, and iron overload. Advances in diagnostic techniques have enhanced our ability to detect and characterize these mutations, facilitating early and accurate diagnoses. Current management strategies encompass regular blood transfusions, the use of hydroxyurea to improve hemoglobin levels, and iron chelation therapy to prevent iron-related organ damage. Moreover, other therapeutics such as thalidomide for those not responding to hydroxyurea, Sirolimus for patients with immunodeficiencies, and use of vitamin E as an antioxidant have proven to be effective. Innovative therapies such as gene therapy and bone marrow transplantation offer promising curative potential, opening a new era in the treatment of thalassemia. This review focuses on pathophysiological mechanisms underlying thalassemia, explores the diagnostic methodologies, and highlights recent advancements in therapeutic approaches.

Keywords: thalassemia; hemoglobinopathies; pathophysiology; diagnosis; treatments

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1. Introduction

Thalassemia is a heterogeneous group of inherited anemia caused by mutations affecting the globin chain subunits of hemoglobin. This leads to inadequate hemoglobin production and the accumulation of insoluble unpaired chains that damage red blood cells, resulting in ineffective erythropoiesis and hemolytic anemia [1]. β-Thalassemia, a common form of thalassemia, is caused by mutations in the β-globin gene, disrupting β-globin production through various mechanisms, including transcription and translation interference [2]. Thalassemia patients often require lifelong blood transfusions, which can lead to iron overload and potential organ damage, particularly in the liver [3]. The disorder falls under hemoglobinopathies, affecting millions globally, with clinical manifestations reflecting genetic and molecular variations [4]. Management typically involves regular transfusions and iron chelation therapy to prevent iron overload, with novel therapies like gene therapy and bone marrow transplantation emerging as potential treatments [5]. Thalassemia's prevalence around the Mediterranean Sea and in regions such as South

Asia, the Middle East, and Africa highlights its global impact beyond its initial geographic association. This review aims to provide a comprehensive overview of thalassemia, encompassing its epidemiology, pathophysiology, clinical manifestations, diagnostic approaches, and current treatment modalities. Additionally, it will discuss recent advancements in research and emerging therapies that hold promise for improving patient outcomes.

2. Epidemiology of Thalassemia

Thalassemia represents a significant global health burden, with its prevalence varying widely across different regions and populations. While historically more prevalent in areas around the Mediterranean Sea, thalassemia is now recognized as a global health issue, affecting millions of individuals worldwide [6,7]. Understanding the epidemiology of thalassemia is essential for effective disease management and resource allocation. Thalassemia shows varying rates worldwide, with higher occurrences in regions such as the Middle East, Asia, and the Mediterranean compared to Europe and North America [8]. Epidemiological data on thalassemia are vital for policy planning and resource allocation, highlighting the need for precise information and patient registries, particularly in developing countries [9]. In 2021, there were 1,310,407 cases of thalassemia globally [10]. In Korea, studies have revealed an increasing trend in thalassemia prevalence, rising from 0.74 per 100,000 in 2006 to 2.76 per 100,000 in 2018. This trend highlights the importance of the early detection of comorbidities such as diabetes, hypertension, and cardiovascular diseases in thalassemia patients [11]. Additionally, research in Southern China has discovered new mutations and emphasized the importance of simple, feasible detection protocols for thalassemia, reflecting its high prevalence in the region [12]. These findings stress the necessity for accurate epidemiological data and comprehensive genetic screening to effectively manage and address the global challenges posed by thalassemia. The beta form of thalassemia is especially common among Mediterranean populations, which is why it was originally named based on this geographical link [13]. In Europe, the highest concentrations of the disease are found in Greece, coastal regions of Turkey, southern Spain, and parts of Italy, particularly southern Italy [14]. Other Mediterranean populations, including those in North Africa and West Asia, also have high rates of thalassemia. Additionally, South Asians are affected, with the Maldives having the highest concentration of carriers in the world (16–18% of the population) [15]. The disease is also present in populations in Africa, the Americas, Nepal, and India [16]. Thalassemias are particularly associated with people of Mediterranean origin, Arabs, and Asians [7].

Thalassemia prevalence varies geographically, with the highest rates observed in regions where consanguineous marriages are common, such as parts of South Asia, the Middle East, and Africa. Additionally, migration patterns have led to thalassemia becoming more prevalent in other parts of the world, including Europe, North America, and Australia [6]. Research indicated the prevalence of thalassemia in Southern China to be 19.48% [17]. A study estimated thalassemia prevalence of 9.8% among hill tribe children in Thailand. Various forms of thalassemia have been found, including the α-thalassemia 1 trait [18]. Epidemiological profiles of thalassemia in Gulf Cooperation Council countries indicated a prevalence of 0.25% to 43.3% across age groups [19].

Thalassemia affects individuals of all ages, races, and ethnicities. However, certain demographic groups, such as those with Mediterranean, South Asian [20], or African ancestry, have a higher risk of carrying thalassemia gene mutations. Thalassemia exhibits demographic variations across different regions and ethnicities. Research indicates high prevalence in the Mediterranean, the Middle East, the Arabian Peninsula, Turkey, Iran, India, Burma, and Southeast Asia [21]. In North America, individuals with homozygous β-thalassemia are primarily of Greek and Italian descent, with an increasing mean age due to improved treatments and the immigration of non-Mediterranean ethnic groups [22]. In India, the economic burden of transfusion-dependent thalassemia is substantial, with treatment costs consuming a significant portion of family income, highlighting the financial challenges faced by affected individuals [23]. Furthermore, studies in the Wasit Governorate

and Bhopal underscore the importance of understanding the socio-demographic profiles, clinical characteristics, and morbidity patterns of thalassemia patients in different regions to develop effective management strategies [24,25].

Communities with a high prevalence of thalassemia often have cultural and social practices that increase the risk of inherited genetic disorders. Consanguineous marriages, where individuals marry close relatives, can result in an increased frequency of thalassemia gene mutations within families and communities. People with a family history in regions where the disease is common are most at risk. For instance, in India, some groups have carrier rates as high as 17% [26]. Thalassemia major can lead to serious health issues. These include a higher chance of diabetes, low HDL cholesterol (good cholesterol), and hormone problems, all of which can increase the risk of heart disease [27]. People with thalassemia are also more likely to develop certain cancers, especially blood cancers and abdominal cancers. This risk is even higher for those who receive blood transfusions [28]. Interestingly, some studies suggest thalassemia patients might be less likely to get COVID-19, particularly in countries with a high number of thalassemia cases [29].

3. Hemoglobin Structural Biochemistry

Hemoglobin is a tetrameric protein consisting of four subunits (Table 1), each composed of one polypeptide chain and one heme group [30,31] (Figure 1). The heme group, iron protoporphyrin IX, is crucial for hemoglobin's oxygen-binding capability. Each polypeptide chain in hemoglobin is linked to a heme group, where the ferrous ion (Fe^{2+}) in the heme is coordinated to the nitrogen atom of a histidine residue within the polypeptide chain. Additionally, the porphyrin ring of the heme is stabilized by interactions with a phenylalanine residue from the polypeptide chain.

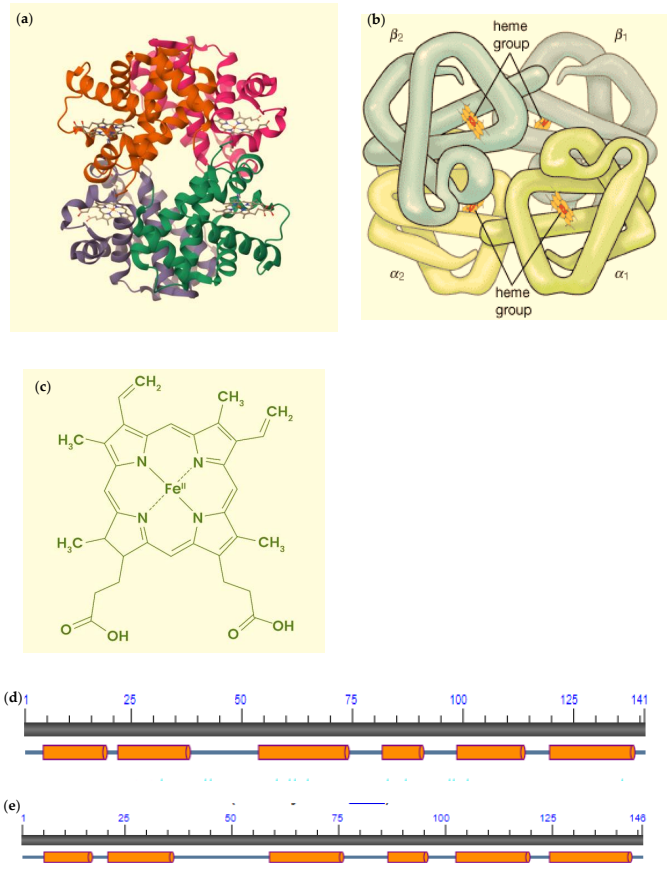

Figure 1. Structure of hemoglobin: (**a**) 3D structure of hemoglobin, (**b**) 2D structure of hemoglobin showing α2β2 subunits of hemoglobin, (**c**) structure of hemoglobin showing binding of Fe^{2+}, (**d**) Alpha Subunit showing number of amino acids, (**e**) Beta Subunit showing number of amino acids.

The polypeptide chains in adult hemoglobin are of two types: alpha (α) and beta (β). Each α chain consists of 141 amino acids, while each β chain comprises 146 amino acids (Figure 1). The alpha chains are identical across all forms of human hemoglobin, including embryonic and adult types. However, the non-alpha chains vary; they include the beta chain in normal adult hemoglobin (HbA, α2β2), the gamma (γ) chain in fetal hemoglobin (HbF, α2γ2), and the delta (δ) chain in HbA2 (α2δ2).

Hemoglobin's primary function is to transport oxygen from the lungs to tissues. This is achieved through cooperative binding and release of oxygen molecules, a process illustrated by the oxygen equilibrium curve (OEC), which shows hemoglobin's oxygen saturation (SO_2) at various partial pressures of oxygen (pO_2). The cooperative nature of this binding is key to hemoglobin's efficiency in oxygen transport and release [31].

4. Genetic Aspects and Inheritance Patterns

Thalassemia is inherited in an autosomal recessive manner, meaning that individuals must inherit two abnormal copies of the gene (one from each parent) to develop the disease [13] (Figure 2). Carriers of a single abnormal gene copy (heterozygotes) are generally asymptomatic but can pass the mutated gene on to their children (Figure 2). Thalassemia, a group of inherited anemias, follows an autosomal recessive inheritance pattern. To manifest the disease, individuals must inherit two abnormal gene copies, one from each parent [1]. Heterozygotes, who carry a single abnormal gene copy, are typically asymptomatic but can pass the mutated gene to their offspring, potentially leading to thalassemia in the next generation [2]. The genetic basis of thalassemia involves mutations that affect the expression of globin genes, particularly the β-globin gene, resulting in reduced or absent synthesis of β-globin chains [32]. The clinical impact of thalassemia is significant, with severe cases requiring lifelong transfusion support and iron chelation therapy [33]. Family members and caregivers of individuals with thalassemia also face substantial challenges, including emotional, social, financial, and physical burdens associated with the disease and its treatment [4].

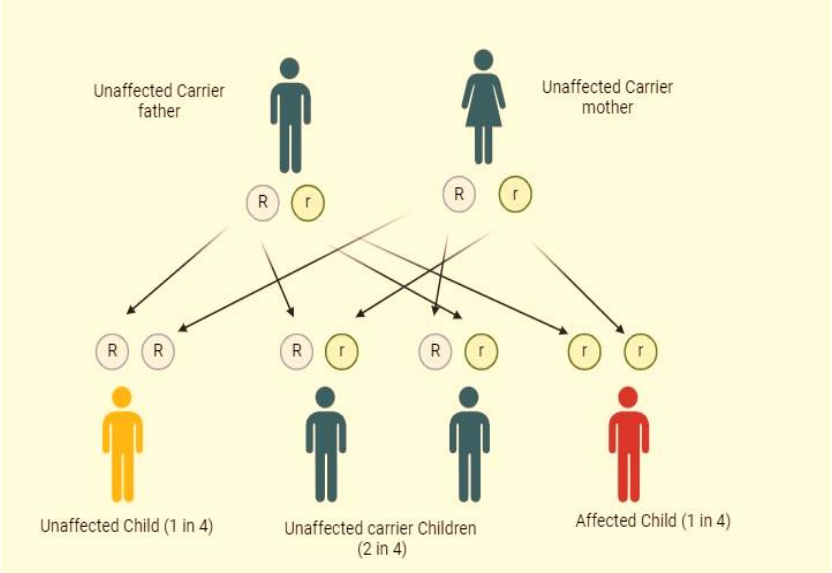

Figure 2. Inherited pattern of thalassemia.

5. Pathophysiology

The defects in the production of hemoglobin, the oxygen-carrying protein found in red blood cells, result from mutations in the genes responsible for producing the alpha- or beta-globin chains of hemoglobin. The pathophysiology of thalassemia involves a disruption in the balance of globin chain synthesis, leading to an imbalance in the alpha- and beta-globin chains and subsequent abnormalities in red blood cell formation and function [34]

(Table 1). Thalassemia is a group of genetic blood disorders characterized by the reduced synthesis of normal hemoglobin chains, leading to hypochromic microcytic anemias [35]. In homozygous thalassemia, such as beta-thalassemia, excess alpha chains accumulate, forming intracytoplasmic erythrocytic inclusions and resulting in anemia, bone marrow hyperplasia, osteoporosis, hemosiderosis, and organ failure [36]. The pathogenesis involves the accumulation of unmatched globin chains, like alpha-globin in beta-thalassemia, causing hemolysis and ineffective erythropoiesis, possibly due to accelerated apoptosis from alpha-globin deposition in erythroid precursors [35]. This imbalance in globin chain synthesis in beta-thalassemia leads to erythroid maturation issues, red cell destruction, and a heterogeneous cell population in the blood, with iron overload being a major cause of tissue damage and mortality [37]. Thalassemia is marked by reduced globin chain synthesis, resulting in premature cell destruction, ineffective erythropoiesis, hemolysis, and varying degrees of anemia [38].

6. Genetic Basis of Thalassemia

6.1. Alpha-Thalassemia

Alpha-thalassemia results from mutations or deletions in the genes encoding alpha-globin chains, primarily HBA1 and HBA2, located on chromosome 16. The severity of the condition depends on the number of affected alpha-globin genes. Loss of one or two alpha-globin genes leads to the alpha-thalassemia trait or alpha-thalassemia minor, respectively, while the loss of three or four genes results in more severe forms, including Hb H disease and hydrops fetalis. Alpha-thalassemia is an inherited blood disorder caused by genetic mutations in the HBA1 and/or HBA2 genes [39]. People with alpha-thalassemia produce less hemoglobin than normal, leading to mild to severe anemia [40]. There are four types of alpha-thalassemia, ranging from a trait (deletion of one to two alpha-globin genes) to alpha-thalassemia major (all four alpha genes deleted), resulting in severe transfusion-dependent anemia [41]. Understanding these genetic variations is essential for accurate diagnoses and potential therapeutic approaches [42].

6.2. Beta-Thalassemia

Beta-thalassemia is caused by mutations or deletions in the beta-globin gene (HBB) located on chromosome 11. These mutations impair the production of beta-globin chains, leading to decreased synthesis of normal hemoglobin (HbA). Depending on the severity of the mutation, beta-thalassemia can be classified as beta-thalassemia minor (trait), beta-thalassemia intermedia, or beta-thalassemia major. Beta-thalassemia results from mutations in the β-globin gene, leading to reduced or absent β-globin chain synthesis [43]. These mutations can be nucleotide substitutions, frameshift insertions/deletions, or gross deletions within the β-globin gene, causing an imbalance in the α/β-globin chain ratio. Consequently, ineffective erythropoiesis, chronic anemia, and iron overload may occur [39]. Severity varies based on residual globin production, with over 200 reported mutations affecting β-globin gene expression [44]. Understanding these molecular changes is crucial for accurate diagnoses and effective management. Ongoing research explores innovative cell and gene therapy strategies to potentially cure this monogenic disorder [41].

6.3. Mechanism of Abnormal Hemoglobin Production

Mutations in the globin genes are the primary drivers of abnormal hemoglobin production in thalassemia. These mutations can lead to either quantitative (thalassemias) or qualitative (hemoglobinopathies) defects in hemoglobin synthesis [4,45,46]. They may impact different stages of β-globin gene transcription, pre-mRNA processing, and mRNA translation, or result in structural abnormalities in the β chains, as seen in variants like HbE, HbS, and HbC [47]. In thalassemia, ineffective erythropoiesis (IE) plays a pivotal role. The imbalance in α-globin production due to mutations leads to oxidative stress and membrane damage in red blood cells, further complicating abnormal hemoglobin production [48,49]. Studies indicate that various forms of thalassemia, such as α-thalassemia and

β-thalassemia, manifest accelerated erythroblast expansion, limited differentiation, and varying degrees of erythroid maturation arrest. These factors collectively contribute to the defective hemoglobin production observed in these conditions.

Alpha-thalassemia disrupts normal hemoglobin production by causing a deficiency in alpha-globin chain synthesis [50]. This imbalance in globin chains leads to an excess of gamma chains in fetal life, forming Hb Bart's, and an excess of beta chains in adult life, forming HbH [46]. The abnormal hemoglobin production in alpha-thalassemia damages erythroid precursors, causing ineffective erythropoiesis and intramedullary hemolysis [51]. Additionally, structural hemoglobinopathies such as HbS, HbE, and HbC contribute to abnormal hemoglobin production, presenting region- and ethnicity-specific challenges [52]. Molecular tests are vital for identifying alpha-globin gene defects, with deletional and non-deletional alpha-thalassemias being detected through specific sequencing techniques [53]. Understanding the mechanisms behind abnormal hemoglobin production in alpha-thalassemia is crucial for accurate diagnoses and management of this inherited disorder.

Beta-thalassemia results from mutations in the beta-globin gene, causing reduced beta-globin production and an imbalance in globin chains, leading to ineffective erythropoiesis and anemia [45,54] (Table 1). This imbalance increases oxidative stress and damages red blood cell membranes due to excessive alpha-globin production [55]. Additionally, dysregulated iron metabolism, influenced by factors such as hepcidin, erythroferrone, and matriptase-2, is crucial in the disease's pathophysiology [46]. Mutations targeting the beta-globin gene's coding regions can result in beta-thalassemia major, characterized by a complete halt in beta chain synthesis, often requiring transfusion therapy [56]. Understanding these mechanisms has spurred the development of potential therapeutic strategies targeting iron metabolism, fetal hemoglobin production, erythroid maturation, and red blood cell membrane stability in beta-thalassemia patients.

Table 1. Summary of pathophysiology in thalassemia.

Aspect	Description	References
Hemoglobin Structure	Heterotetramer of two α- and two non-α-globin chains, each carrying a heme molecule with iron. Maximal oxygen-carrying capacity.	[13,57]
Types of Hemoglobin	HbA: α and β chains (adult hemoglobin). HbA2: α and δ chains (minor adult hemoglobin). HbF: α and γ chains (fetal hemoglobin).	[58,59]
Genetic Regulation	α-Globin cluster on chromosome 16 (HBA1 and HBA2), β-globin cluster on chromosome 11 (γ-, δ-, β-globin genes).	[43,60]
Normal Physiology	Balanced production of α- and non-α-globin chains ensures proper hemoglobin formation.	[61]
Thalassemia Pathophysiology	Disrupted equilibrium in globin chain production causes excess unpaired chains—α-thalassemia: excess β chains, β-thalassemia: excess α chains. Excess unpaired chains lead to ineffective erythropoiesis, apoptosis of red cell precursors, and anemia.	[62]
Consequences of Chain Imbalance	β-Thalassemia: Excess α chains cause oxidative damage, apoptosis of red cell precursors, hemolysis, and spleen enlargement. α-Thalassemia: Excess non-α chains form Hb Bart's (γ4) in utero and HbH (β4) after birth, both poor oxygen carriers.	[13,63,64]
Erythropoiesis and Anemia Response	Kidneys increase erythropoietin (EPO) secretion, exacerbating ineffective erythropoiesis and leading to bone marrow expansion and bone fragility. Suppressed hepcidin production increases iron absorption, contributing to iron overload.	[65,66]
Mutation Types	β0 mutations: No β-globin production, β+. β+ [67]+ mutations: Reduced β-globin production. Over 200 known β gene mutations, over 100 α-thalassemia varieties.	[13]
Iron Overload and Treatment	Excess iron leads to non-transferrin-bound iron (NTBI), generating reactive oxygen species and damaging organs. Daily iron chelation therapy is required to prevent lethal complications. Non-transfusion-dependent β-thalassemia (NTDT) forms have slower iron overload development, with complications appearing in the second and third decades of life.	[67,68]

6.4. Transcription Factors and Thalassemia

Transcription factors play a crucial role in both alpha- and beta-thalassemia. In beta-thalassemia, transcription factors such as NRF2 and BACH1 collaborate with antioxidant

enzymes to protect erythrocytes from oxidative damage, thereby increasing their lifespan [69]. Additionally, the erythroid transcription factor Krüppel-like factor 1 (KLF1) is a key regulator of erythropoiesis, and mutations affecting KLF1 are associated with increased fetal hemoglobin (HbF) levels, which can mitigate the severity of beta-thalassemia [70]. In alpha-thalassemia, the role of dysregulated transcription factors is less understood, highlighting the need for further research to identify potential therapeutic targets [44]. A study examines the impact of single-nucleotide polymorphisms (SNPs) in the TATA boxes of the human β-globin gene promoter, which are associated with varying severities of β-thalassemia. The TATA-binding protein (TBP), a key transcription factor, recognizes and binds to these TATA boxes to initiate RNA polymerase II transcription, leading to a reduction in normal β-globin RNA synthesis in patients with β-thalassemia [71]. A study of four factors (alpha-IRP, alpha-CP1, alpha-CP2, and NF-E1) identified DNA binding sites for factors interacting with the alpha-globin gene promoter, suggesting their role in regulating gene expression during erythroleukemia cell differentiation [72]. Mutations in the human KLF1 gene have been linked to increased fetal hemoglobin (HbF) and hemoglobin A2 (HbA2) levels, which are important features of β-thalassemia, suggesting that KLF1 mutations selectively occur in the presence of β-thalassemia, enhancing HbF production and thus reducing the clinical severity of the disease [73]. In β-thalassemia major, elevated regulatory T cells correlated with iron overload, while a link between these cells and specific regulatory genes was found, suggesting a complex immune response to chronic anemia [74]. Therefore, understanding the involvement of transcription factors in both alpha- and beta-thalassemia is essential for developing targeted therapies and improving patient outcomes.

6.5. Clinical Manifestations

Thalassemia encompasses a spectrum of clinical presentations, ranging from asymptomatic carriers to severe, life-threatening disease. The severity and manifestations of thalassemia depend on various factors, including the type of thalassemia, the number of affected globin genes, and individual genetic modifiers. Thalassemia displays a broad array of clinical signs that vary depending on the specific type and severity of the condition. In cases of homozygous thalassemia, such as beta-thalassemia, an excess of alpha chains leads to symptoms including anemia, bone marrow overactivity, osteoporosis, hemosiderosis, and organ failure [44]. The disrupted synthesis of globin chains in beta-thalassemias results in physical damage, hindrance of cell division, oxidative harm, and an accumulation of iron, culminating in tissue damage and illness [75]. Alpha-thalassemia spans from asymptomatic to severe anemia requiring transfusions, with conditions like Hemoglobin H disease and Hemoglobin Bart's hydrops fetalis, the latter typically proving fatal in the womb [40,76]. Identifying at-risk couples through screening and implementing innovative therapies are essential strategies for effectively managing the diverse clinical presentations of thalassemia.

7. Symptoms and Signs

7.1. Thalassemia Minor

Thalassemia minor, or the thalassemia trait, is characterized by a decreased number of red blood cells and lower hemoglobin levels compared to normal, resulting in mild anemia. Symptoms typically include fatigue, weakness, and paleness, while individuals may also exhibit physical abnormalities affecting the eyes, skin, ears, mental faculties, and bones/joints [77,78]. Those with thalassemia minor often have reduced hemoglobin levels, averaging 9.45 g/dL in younger age groups and 11.58 g/dL in older age groups [79]. Furthermore, they may be prone to various infections such as those affecting the eyes, gastrointestinal system, lungs, skin, urinary tract, and ears [80]. Raising awareness about the risks associated with consanguineous marriages is crucial for preventing the transmission of thalassemia within families [81].

7.2. Intermedia

Thalassemia intermedia exhibits a diverse range of clinical symptoms, including persistent anemia, enlargement of the spleen, the presence of masses outside the bone marrow, excess iron accumulation, jaundice, and growth irregularities [82,83]. Patients may present with characteristics such as short stature, microcytic hypochromic anemia, elevated levels of unconjugated bilirubin, and spleen enlargement [84]. Moreover, individuals with thalassemia intermedia might suffer from joint discomfort, pronounced paleness, the protrusion of the forehead and cheekbones, and the formation of tophaceous deposits. They may also face complications such as leg ulcers, tendencies toward blood clotting disorders, and skeletal anomalies [85,86]. An accurate diagnosis relies heavily on genetic analyses due to the condition's significant clinical diversity stemming from genetic variations. Mutations like HBB +1G>A have been linked to the clinical features of thalassemia intermedia, underscoring the necessity of understanding the molecular underpinnings and the relationship between genotype and phenotype across different ethnic backgrounds.

7.3. Thalassemia Major

Thalassemia major, a genetic condition marked by abnormal hemoglobin production, presents a spectrum of symptoms and indications. Typically, affected children and infants exhibit severe anemia, stunted growth, and abdominal swelling. Musculoskeletal abnormalities are also common, including long bone thinning with a "sun-ray" appearance, skull alterations resulting in a "hair-on-end" appearance, and enlarged maxillary sinuses often leading to a maxillary overbite [87,88]. Additionally, individuals with thalassemia major may encounter psychosocial hurdles due to the lifelong nature of the ailment, affecting their mental health and social interactions [76]. A diagnosis entails hematologic evaluations, hemoglobin electrophoresis, and a DNA analysis, while treatment frequently involves blood transfusions, iron chelation therapy, and, in severe instances, bone marrow transplants [89,90]. A comprehensive understanding of the diverse range of symptoms and indicators linked to thalassemia major is pivotal for prompt diagnoses and efficient management of this inherited disorder.

7.4. Other Manifestations

Thalassemia is characterized by a low hemoglobin level and reduced red blood cell count, leading to decreased oxygen-carrying capacity and tissue hypoxia. The destruction of red blood cells is due to the abnormal hemoglobin, resulting in increased levels of bilirubin and breakdown products, leading to jaundice and gallstones. Enlargement of the spleen is due to increased red blood cell destruction and erythropoiesis, leading to abdominal discomfort and early satiety. Chronic anemia and nutritional deficiencies can impair growth and development in children with thalassemia. The expansion of bone marrow due to increased erythropoiesis can lead to skeletal deformities, such as frontal bossing, prominent cheekbones, and pathologic fractures. Iron overload and chronic anemia can affect hormone production and lead to endocrine disorders such as hypogonadism, hypothyroidism, and diabetes mellitus. The accumulation of iron in organs such as the heart, liver, and endocrine glands can lead to organ damage and dysfunction, contributing to complications such as heart failure, liver cirrhosis, and endocrine disorders. Patients with thalassemia are at increased risk of infections due to impaired immune function, splenomegaly, and frequent hospitalizations.

8. Screening and Diagnostic Criteria

Diagnosing thalassemia involves a combination of clinical evaluation, laboratory tests, and a genetic analysis to confirm the presence of the disease and determine its severity. Given the heterogeneity of thalassemia phenotypes and the overlap of symptoms with other types of anemia, an accurate diagnosis is essential for appropriate management and treatment planning. Thalassemia screening and diagnostic protocols encompass a range of methods and guidelines. Programs such as the NHS Sickle Cell and Thalassemia

Screening Program advocate for antenatal and newborn screening, particularly in areas with high prevalence [91]. Evaluating thalassemia can be challenging due to the overlap of its signs and symptoms with other hematologic disorders. Physicians typically suspect thalassemia based on common features such as anemia, jaundice, hepatosplenomegaly, and growth retardation, which are not exclusive to thalassemia [40,92–94]. Differentiating thalassemia from other conditions requires a comprehensive approach, including genetic testing, hemoglobin electrophoresis, and specific hematologic parameter assessments like the MCV/RBC ratio and HbA2 levels [95]. Furthermore, studies have shown that markers of erythropoiesis, such as GDF-15 and EPO, are significantly elevated in thalassemia patients, suggesting their potential as diagnostic indicators and therapeutic targets [94]. Thus, a multidisciplinary approach that combines clinical evaluation with advanced diagnostic tools is essential for the accurate diagnosis and management of thalassemia.

8.1. Laboratory Tests

A Complete Blood Count (CBC) is an essential screening tool that aids in detecting microcytic hypochromic anemia, a common feature of thalassemia and other blood disorders [96]. Parameters such as red blood cell distribution width (RDW) and mean corpuscular volume (MCV) are crucial for distinguishing thalassemia from other types of anemia [97]. The CBC provides valuable insights into the blood's quantitative and qualitative composition, offering essential information on cell components such as white blood cells, red blood cells, and platelets [98]. Automated hematology analyzers have significantly improved the accuracy and efficiency of CBC results, although challenges like unreliable results due to interfering substances or abnormal cells still require careful consideration [99]. The CBC remains a cornerstone in diagnosing and monitoring various diseases, highlighting its importance in clinical practice [100].

8.2. Hemoglobin Electrophoresis

Hemoglobin electrophoresis is a vital diagnostic tool that separates different hemoglobin types based on their charge, aiding in the detection of abnormal patterns associated with conditions like thalassemia. Thalassemia typically presents with elevated fetal hemoglobin (HbF) levels and reduced adult hemoglobin (HbA) levels, resulting in distinctive patterns on hemoglobin electrophoresis [101,102]. Moreover, abnormal hemoglobin variants, such as hemoglobin C (Hb C), can affect the accuracy of glycosylated hemoglobin (A1C) tests, underscoring the need to consider these variants in diagnostic evaluations [54]. Electrophoresis is crucial for the separation and characterization of charged molecules like hemoglobin, providing valuable insights into various hematological disorders and guiding clinical decision-making [103,104].

8.3. High-Performance Liquid Chromatography (HPLC)

High-performance liquid chromatography (HPLC) is a method used to separate compounds or molecules based on their chemical properties. Ion-exchange chromatography is the most effective and commonly used technique for hemoglobin analyses. While HPLC can be performed manually, fully automated systems have become available, with some specifically designed for hemoglobin analyses. In regions with a low prevalence of hemoglobin disorders, systems capable of switching between a glycated hemoglobin analysis for diabetes and a variant hemoglobin analysis for thalassemia may be more practical. HPLC is especially useful for diagnosing the β-thalassemia trait because it allows for an accurate quantification of HbA2. Precise control of analytical conditions, including the column temperature, flow rate, and buffer conditions, is crucial for achieving accurate results [105].

8.4. Genetic Testing

Molecular genetic testing is crucial for confirming thalassemia diagnoses and identifying specific gene mutations, particularly in the alpha- and beta-globin genes, as highlighted by various studies [106,107]. Techniques such as the polymerase chain reaction (PCR)

and DNA sequencing are instrumental in detecting these mutations, providing essential information on disease severity and inheritance patterns [108]. These advanced molecular diagnostic tools have significantly enhanced the sensitivity and specificity of genetic testing, enabling the precise identification of mutation carriers, which is vital for accurate diagnoses and genetic counseling [109]. By leveraging nucleic acid-based approaches, healthcare professionals can confirm the presence of thalassemia, predict disease likelihood, monitor disease progression, and personalize treatment strategies based on genetic variations. Additionally, molecular genetic testing is invaluable for prenatal diagnoses, allowing the early detection of severe hemoglobinopathies and thalassemia in fetuses, thus enabling early intervention and management strategies [105].

9. Treatment and Management

The management of thalassemia aims to alleviate symptoms, prevent complications, and improve the quality of life for affected individuals. Treatment strategies vary depending on the type and severity of thalassemia and may include supportive measures, pharmacological interventions, and, in severe cases, bone marrow transplantation or gene therapy.

9.1. Blood Transfusion Therapy

Individuals with thalassemia major or severe thalassemia intermedia often require regular blood transfusions to maintain adequate hemoglobin levels and prevent complications associated with chronic anemia. Thalassemia patients, especially those with transfusion-dependent β-thalassemia (TDT), require regular blood transfusions to effectively manage their condition. These transfusions aim to alleviate symptoms of anemia, address complications from ineffective erythropoiesis, and maintain or increase hematocrit levels [110]. For TDT patients, chronic transfusions are often paired with iron chelation therapy to control iron overload, a frequent complication of thalassemia treatment [111]. To optimize transfusion therapy, it is crucial to prepare leucodepleted packed red blood cells (P-RBCs) using specific methods to reduce transfusion-related complications and enhance patients' quality of life [112]. Additionally, monitoring adherence to iron chelation therapy is essential, as poor adherence can negatively impact treatment outcomes and quality of life [113]. In a study of 328 pediatrics patients with β-thalassemia, 61% had low pretransfusion hemoglobin levels (<9.0 g/dL) despite receiving high transfusion volumes (>200 mL/kg/year). Among these patients, 83% had β-thalassemia major and 16% had hemoglobin E β-thalassemia. Hemoglobin E β-thalassemia patients had significantly lower pretransfusion hemoglobin levels compared to those with β-thalassemia major, though both groups required similar high transfusion volumes. Hepatomegaly and splenomegaly were more prevalent in hemoglobin E β-thalassemia and linked to lower pretransfusion hemoglobin levels. Additionally, patients with hepatitis C and those who were underweight had higher transfusion requirements [114].

Blood transfusion therapy in thalassemia, although life-saving, has several limitations and controversies. One major challenge is the lack of well-defined criteria for initiating transfusions or setting hemoglobin targets for patients with E thalassemia, leading to uncertainty in clinical decision-making [115]. Additionally, patients with thalassemia intermedia who begin transfusions as adults face a high risk of red cell alloimmunization and serious hemolytic transfusion reactions [115]. Furthermore, inadequate iron chelation therapy significantly contributes to preventable morbidity and mortality in transfusion-dependent thalassemia due to factors such as poor adherence, variable pharmacokinetics, and difficulties in monitoring treatment response [116]. To optimize patient outcomes, regular assessment of adherence, adverse effects, and iron burden with appropriate treatment adjustments is crucial. Collaboration between hematology and transfusion medicine specialists is essential to enhance patient care and establish evidence-based guidelines for the improved management of thalassemia patients [115].

9.2. Use of Luspatercept in Thalassemic Patients in TDT and NTDT

Luspatercept has shown promising results in thalassemic patients with TDT by reducing transfusion burden and improving erythropoiesis. Studies have indicated that luspatercept significantly increases HbF levels, with responders showing a greater HbF increase compared to non-responders [117]. Additionally, in NTDT patients, luspatercept has demonstrated efficacy in raising hemoglobin levels and improving NTDT-related symptoms, providing a novel approach for managing anemia in this population [118–120]. The drug acts as an erythroid maturation agent, promoting the differentiation and maturation of late-stage erythroid precursors, ultimately leading to clinical benefits in patients unable to receive adequate blood transfusions [121]. These findings highlight the potential of luspatercept as a valuable therapeutic option for both TDT and NTDT patients, offering improvements in hemoglobin levels, transfusion burden, and overall quality of life.

When comparing the response to luspatercept between transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) patient subgroups, both groups benefit significantly but in different ways. TDT patients experience a substantial reduction in transfusion requirements and improved iron overload management, while NTDT patients see a marked improvement in hemoglobin levels and anemia-related symptoms, leading to enhanced quality of life. The BEYOND study demonstrated that luspatercept treatment resulted in durable improvements in NTDT-related symptoms and hemoglobin levels for NTDT patients [118]. Similarly, in TDT patients, luspatercept provided clinically meaningful outcomes, including reductions in transfusion burden and improvements in hemoglobin levels, supporting its use as a preferred treatment for anemia associated with lower-risk myelodysplastic syndromes [122]. Both patient subgroups showed increased HbF levels, with TDT patients benefiting more directly from reduced transfusion frequency, while NTDT patients experienced significant improvements in anemia symptoms and quality of life.

9.3. Pharmacological Treatments

Hydroxyurea has proven to be effective in ameliorating the clinical severity of hemoglobinopathies by reducing phosphatidylserine expression on erythrocytes, contributing to its therapeutic benefits [123]. Research indicates that patients with transfusion-dependent major β-thalassemia who received hydroxyurea experienced longer intervals between transfusions, elevated hemoglobin levels, and decreased ferritin levels, highlighting its potential as an alternative to blood transfusions and iron chelation therapies [124]. Studies on β-thalassemia patients demonstrated that hydroxyurea reduced the necessity for blood transfusions, with 11.5% showing excellent response and 65.5% showing good response to the treatment [125] (Table 2). Additionally, in pediatric patients with transfusion-dependent β-thalassemia major, hydroxyurea significantly reduced the need for packed RBC transfusions, enhanced hemoglobin levels, and lowered serum ferritin levels compared to standard treatments [126]. However, a study assessing the impact of hydroxyurea on the physical health problems of β-thalassemia patients did not show significant improvement, indicating a need for further research to optimize treatment outcomes [127]. A study on 532 patients with TDT unresponsive to hydroxyurea showed that thalidomide significantly increased hemoglobin levels, with 76.7% of patients responding well, many achieving transfusion independence within 6 months, and other positive outcomes such as reductions in serum ferritin, lactate dehydrogenase levels, and liver and spleen size over 30 months [128]. A study on Sirolimus, an mTOR inhibitor, showed that it positively impacted the activity and number of memory CD4+ and CD8+ T cells releasing IFN-γ in response to antigenic stimuli, suggesting potential immune function benefits for β-thalassemia patients susceptible to immune deficiencies [129]. Research on early-start deferiprone therapy in infants and young children with TDT demonstrated that deferiprone significantly reduced iron overload, with a lower proportion of patients reaching the serum ferritin threshold compared to a placebo (39% vs. 66%) at 12 months; was well tolerated; and effectively increased transferrin saturation levels [130]. In a 3-month open-label ran-

domized controlled trial, vitamin E and N-acetyl cysteine (NAC) were assessed for their effects on oxidative stress in TDT patients, showing that vitamin E significantly decreased total oxidative stress (TOS), both supplements decreased total antioxidant capacity (TAC), hemoglobin levels remained unchanged, and mild adverse events were reported without needing treatment discontinuation, suggesting that vitamin E is safe and effective for improving oxidative stress in TDT patients [131] (Table 2). A study on silymarin, a flavonolignan, in patients with β-thalassemia major found that combined treatment with desferrioxamine and silymarin significantly reduced serum ferritin, iron, total iron-binding capacity, hepcidin, and soluble transferrin receptor levels; improved liver function; and effectively reduced iron overload, indicating its potential as a standalone treatment for iron burden reduction [132]. A double-blind clinical trial on beta-thalassemia intermedia patients found that curcumin intake significantly increased serum zinc and the zinc/copper ratio, decreased serum copper and ferritin levels, and showed potential protective effects against copper toxicity, suggesting curcumin's potential as a complementary treatment for regulating zinc homeostasis in these patients [133].

Table 2. Thalassemia treatment, Effectiveness, Limitations, and Controversies.

Treatment	Effectiveness	Limitations and Controversies
Hydroxyurea	Reduces phosphatidylserine expression, extends transfusion intervals, elevates hemoglobin, decreases ferritin levels [123,124]	Significant variability in patient response (11.5% excellent, 65.5% good response) [125]. Limited impact on physical health problems, indicating need for further research [127]
Thalidomide	Increases hemoglobin levels, 76.7% of patients achieve transfusion independence [128]	Long-term safety and potential side effects require careful consideration and further investigation
Sirolimus	Positively impacts immune function, increases activity and number of memory T cells [129]	Long-term impact on immune deficiencies associated with thalassemia remains unclear, necessitating more extensive clinical trials
Deferiprone	Reduces iron overload, well tolerated, increases transferrin saturation levels [130]	Long-term safety and efficacy compared to other iron chelation therapies require further study
Vitamin E and N-acetyl cysteine (NAC)	Improves oxidative stress markers, decreases total oxidative stress [131]	Long-term benefits and potential side effects need more thorough investigation to confirm safety and effectiveness
Silymarin	Reduces serum ferritin and iron, improves liver function in combination with desferrioxamine [132]	Standalone efficacy as an iron burden treatment requires additional research
Curcumin	Regulates zinc homeostasis, reduces copper toxicity [133]	More comprehensive studies needed to confirm findings and determine optimal dosage and long-term safety

9.4. Bone Marrow and Stem Cell Transplantation

Bone marrow and stem cell transplantation play a vital role in treating thalassemia, especially beta-thalassemia major, offering a potential cure [134]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the definitive curative treatment for transfusion-dependent thalassemia major, with advancements in conditioning regimens and donor sources enhancing patient outcomes and quality of life [134]. Research has shown that expanding the donor pool to include haploidentical related donors, along with innovative pharmacologic approaches, has significantly improved the safety and efficacy of HSCT in thalassemia patients, achieving high survival rates and reducing graft failures [135]. Additionally, studies on co-transplanting mesenchymal stem cells (MSCs) with hematopoietic stem cells (HSCs) in thalassemia major patients indicate that while MSC co-transplantation does not significantly change transplantation outcomes, it also does not notably improve liver fibrosis alleviation [136,137]. A study on allogeneic HSCT in 567 transfusion-dependent thalassemia patients found no significant survival advantage

between bone marrow and peripheral blood grafts, but peripheral blood had a significantly lower rejection incidence, suggesting it as a viable alternative to bone marrow for HSCT [138]. Over a decade, stem cell transplantations in 69 children using bone marrow, peripheral blood, or cord blood showed varied success rates by disease, with 79.4% of thalassemia cases cured, and lower graft-versus-host disease incidence than in Western countries, and demonstrated that these transplantation methods are effective treatments for various hematologic and malignant disorders in children [139]. A retrospective study by the European Group for Blood and Marrow Transplantation (EBMT) on 1493 patients with transfusion-dependent thalassemia major found that allogeneic HSCT achieved high 2-year overall survival (88%) and event-free survival (81%) rates, with the best outcomes observed in patients under 18, particularly those with HLA-identical sibling donors, highlighting HSCT as a highly effective curative option globally [140]. A prospective randomized study on class III beta-thalassemia major patients undergoing HSCT found no significant differences in overall survival (OS), thalassemia-free survival (TFS), transplant-related mortality (TRM), graft rejection, acute graft-versus-host disease (GvHD), or chronic GvHD between those who received the co-transplantation of bone marrow-derived MSCs with HSCs and those who received only HSCs over a 5-year follow-up period [136].

Bone marrow and stem cell transplantation have been pivotal in the treatment of thalassemia, offering a potentially curative approach to the disease [135]. However, significant limitations and controversies surround this treatment modality. Graft rejection, graft-versus-host disease (GVHD), and opportunistic infections are major concerns for thalassemia patients undergoing bone marrow transplantation [141]. Additionally, the availability of suitable donors and the medical condition of the patient can limit the widespread application of allogeneic hematopoietic stem cell transplantation, particularly when using haploidentical related donors [135]. Despite advancements aimed at improving outcomes and reducing complications, high rates of graft failure and GVHD remain challenges, especially when alternative donors are required [142].

9.5. Gene Therapy

Gene therapy has emerged as a promising curative treatment for thalassemia by correcting the genetic defect in hematopoietic stem cells, offering the potential for transfusion independence. Clinical trials using lentiviral vectors to introduce functional beta-globin genes and editing technologies like CRISPR/Cas9 to enhance fetal hemoglobin production have shown encouraging results [143–146]. Some patients have achieved transfusion independence and improved quality of life post-gene therapy. However, challenges remain in optimizing safety and efficacy, including the risk of secondary hematological malignancies and the high cost of this innovative treatment approach [147]. A study assessed the safety and efficacy of gene therapy for 22 patients with transfusion-dependent β-thalassemia using autologous CD34+ cells transduced with the LentiGlobin BB305 vector, encoding a modified β-globin gene (HbAT87Q). Over a median follow-up of 26 months, all but one patient stopped red cell transfusions [143,148]. In a phase 3 study of betibeglogene autotemcel (beti-cel) gene therapy for transfusion-dependent β-thalassemia patients with a non-β0/β0 genotype, 91% achieved transfusion independence, with an average hemoglobin level of 11.7 g/dL during treatment, and those maintaining independence at 12 months post-treatment had a median gene therapy-derived hemoglobin level of 8.7 g/dL, demonstrating promising efficacy and a generally favorable safety profile [149]. In a study using CRISPR-Cas9 to target the BCL11A erythroid enhancer in CD34+ hematopoietic stem and progenitor cells from healthy donors, successful allele modification in approximately 80% of cells was achieved with no off-target effects observed. Following myeloablation and transplantation, two patients—one with transfusion-dependent β-thalassemia (TDT) and the other with sickle cell disease (SCD)—demonstrated sustained high levels of allelic editing, demonstrated increased fetal hemoglobin production, achieved transfusion independence, and in the SCD patient, achieved the elimination of vaso-occlusive episodes more than a year post-treatment [150]. In an ongoing phase 1/2 trial, gene editing targeting the +58 BCL11A

erythroid enhancer has shown promising results in treating TDT, with two children achieving successful engraftment, sustained transfusion independence, substantial hemoglobin increases, and robust persistence of editing in bone marrow cells, without observed adverse effects related to the therapy [151]. Research on gene therapy using autologous CD34+ cells transduced with the lentiviral vector BB305 encoding anti-sickling βA-T87Q-globin for SCD and TDT demonstrated successful outcomes, including sustained clinical remission and transfusion independence without adverse events related to therapy, highlighting its potential as a long-term treatment option [152].

Gene therapy offers a promising, potentially curative, treatment for thalassemia by correcting genetic defects, but it comes with significant disadvantages. It is highly expensive due to advanced technology and complex manufacturing processes, limiting accessibility, particularly in low- and middle-income countries. Not all patients are eligible, as suitability depends on specific genetic mutations and overall health. Accessibility is further constrained by the need for specialized centers and ongoing monitoring, highlighting the need for further research to improve the therapy's affordability, safety, and applicability.

10. Targeting Signaling Pathways

The JAK-STAT pathway is vital in the pathogenesis and treatment of several conditions, including thalassemia. Research indicates that inhibiting JAK2 can effectively reduce splenomegaly in thalassemia by suppressing extramedullary erythropoiesis, potentially offering an alternative to splenectomy [153]. Methotrexate, a JAK/STAT pathway inhibitor, shows potential for treating conditions like thalassemia by suppressing STAT activation, offering a cost-effective alternative to JAK inhibitors like ruxolitinib [154]. Erythroid cells from cord blood and β-thalassemia showed higher levels of a cAMP linked to fetal hemoglobin production compared to adult bone marrow [155]. Signaling pathways are crucial in the pathophysiology of thalassemia, especially β-thalassemia. Pathways such as the MAPK pathway [156], cAMP signaling [155], JAK/STAT, MAPK, PI3K [157], and those involving inositides like PLC and PI3K play significant roles in regulating erythropoiesis and hemoglobin production. The dysregulation of these pathways can cause abnormal hematopoiesis, ineffective erythropoiesis, and iron overload in thalassemia patients. Research indicates that changes in gene expression, including ARRB1, GNAI2, and DUSP5, can affect the MAPK pathway and contribute to abnormal hematopoiesis in β-thalassemia [156]. Additionally, the suppression of hepcidin, influenced by pathways such as STAT and SMAD, can result in iron overload in thalassemia patients. Understanding and targeting these signaling pathways could lead to new therapeutic strategies for managing thalassemia [158].

11. Supportive Care

Proper nutrition is critical for individuals with thalassemia to support optimal growth and development, as underscored by multiple studies [33,159–162]. Patients with thalassemia frequently experience complications such as bone deformities, endocrine issues, and psychosocial challenges, highlighting the necessity for comprehensive management involving specialists in hematology, endocrinology, cardiology, and psychology. Nutritional deficiencies, particularly iron and folate, significantly contribute to the pathophysiology of thalassemia, affecting body composition, vitamin levels, and overall health [161,163]. The early detection of nutritional disorders, coupled with multidisciplinary care, can mitigate growth delays and comorbidities, thereby enhancing the quality of life for individuals with thalassemia.

12. Advances in Research and Future Directions

Advances in molecular genetics have led to a better understanding of the underlying genetic mutations responsible for thalassemia, facilitating more accurate diagnoses and personalized treatment approaches [164,165]. Research has focused on optimizing transfusion protocols to minimize iron overload and transfusion-related complications in

thalassemia patients, including the use of extended red blood cell phenotyping and novel blood conservation techniques [166,167]. Newer iron chelators with improved efficacy, safety profiles, and patient convenience have been developed, offering additional options for managing iron overload in thalassemia patients [168]. Several pharmacological agents targeting different aspects of thalassemia pathophysiology, such as fetal hemoglobin induction, erythropoiesis stimulation, and iron metabolism modulation, are under investigation in preclinical and clinical studies. Gene therapy approaches, including gene addition, gene editing, and gene regulation strategies, hold promise for correcting the underlying genetic defect in thalassemia and achieving long-term therapeutic benefits [169]. Advances in genomic medicine and precision therapeutics offer opportunities for tailored treatment approaches based on individual genetic profiles, disease severity, and treatment responses. Ongoing research in stem cell biology and regenerative medicine aims to develop novel stem cell-based therapies, including induced pluripotent stem cell (iPSC) technology and gene-edited stem cell transplantation, for the treatment of thalassemia. Strategies to mitigate immune responses, such as immune tolerance induction and immunomodulatory therapies, are being explored to enhance the safety and efficacy of gene therapy and stem cell transplantation in thalassemia patients [170,171].

13. Impact of Thalassemia on Quality of Life and Health Economics of Patient

Thalassemia has a profound impact on patients' quality of life (QoL) and presents significant health and economic challenges. Research highlights that various factors, such as treatment methods and access to social support, are critical in shaping health-related quality of life (HRQoL) outcomes. Patients with thalassemia consistently report lower HRQoL compared to the general population, with chronic pain and the burden of ongoing treatment being major contributors [172]. In Yemen, studies have shown that while social and emotional functioning tend to score higher, physical health is severely compromised by iron overload and difficulties in adhering to treatment protocols ("Factors Affecting Quality of Life Among Thalassemia Patients") [173]. Similarly, pediatric patients in Egypt demonstrated reduced HRQoL, highlighting the pressing need for specialized psychosocial support [174]. The financial burden of managing thalassemia, including the costs of regular blood transfusions and iron chelation therapy, places a significant strain on healthcare systems [175]. Emerging management strategies like hematopoietic stem cell transplantation and gene therapy offer promising improvements in both QoL and long-term healthcare cost reductions [172]. However, despite advancements that have extended survival rates, comprehensive care and continuous support are essential to further improve QoL and alleviate the economic pressures on healthcare systems.

14. Limitations/Restrictions of the Research

Recent developments in gene-editing technologies, such as CRISPR-Cas9, have revolutionized the potential for curative treatments in thalassemia patients [150]. Researchers have been able to enhance fetal hemoglobin production by targeting specific mutations within the beta-globin gene, significantly reducing the need for blood transfusions in some patients [176]. Research has demonstrated promising results, with patients achieving long-term transfusion independence and improved quality of life [177]. However, challenges remain in scaling these therapies for widespread use, particularly in regions with limited healthcare resources. Ethical considerations, long-term safety, and cost barriers are key factors that need to be addressed as gene-editing therapies move towards clinical implementation. Further research into more accessible gene-editing techniques and alternative therapies is critical to providing equitable treatment options for thalassemia patients worldwide.

15. Conclusions

Thalassemia represents a complex and multifaceted genetic disorder with significant implications for individuals, families, and healthcare systems worldwide. Despite ad-

vancements in understanding its pathophysiology, diagnosis, and treatment, thalassemia continues to present challenges that require a concerted effort from healthcare providers, policymakers, researchers, and advocacy organizations to address them effectively. From early detection through universal screening programs to comprehensive multidisciplinary care and innovative therapeutic approaches, the management of thalassemia encompasses a continuum of interventions aimed at improving patient outcomes, enhancing quality of life, and ultimately finding a cure for this chronic condition. While progress has been made in areas such as gene therapy, iron chelation therapy, and supportive care, there is still much work to be done to ensure equitable access to healthcare services, reduce the burden of disease, and support the psychosocial well-being of individuals living with thalassemia and their families.

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