

New Insights into Pathophysiology, Hearing Loss, Efficiency, Height, Kidney Growth Complications, Treatment and Other Alternatives in β Thalassemia Patients

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ABSTRACT

Beta-thalassemia is a common autosomal recessive hemoglobin disorder and a significant global health concern, particularly in tropical regions. Southeast Asia accounts for approximately 50% of the world's thalassemia carriers. The disease results from mutations in the β -globin gene that disrupt hemoglobin synthesis, causing an imbalance in α and β -globin chain production. This imbalance contributes to ineffective erythropoiesis, chronic anemia, tissue hypoxia, compensatory hematopoietic expansion, and iron overload. This narrative literature review examined English language publications retrieved from PubMed, Google Scholar, and the Cochrane Library to explore the pathophysiology, clinical complications, and therapeutic approaches associated with β -thalassemia. β -thalassemia might be associated with impaired growth, hearing loss, renal dysfunction, and reduced bone mineral density. These complications can arise from disease-related mechanisms, iron overload, and treatment-related factors. Conventional management includes blood transfusion and iron chelation, while emerging therapies, such as luspatercept, can reduce transfusion requirements in eligible patients. Early detection and genetic counseling are also important components of disease prevention. Understanding the pathophysiology and clinical manifestations of β -thalassemia is essential for optimizing disease management. Appropriate monitoring, individualized treatment, and preventive strategies also can help reduce complications and improve patient outcomes.

Keyword : β -thalassemia; growth impairment; hearing loss; pathophysiology; renal complications

Introduction

β -Thalassemia is an autosomal recessive hemoglobin disorder characterized by reduced or absent synthesis of β -globin chains. This condition remains a significant clinical concern due to its varying severity, the need for long-term treatment, and the potential for complications affecting various organ systems. The disorder is caused by mutations in the HBB gene located on chromosome 11, which disrupt normal hemoglobin synthesis and result in an imbalance between α - and β -globin chains^{1,2}. Clinical manifestations vary depending on the underlying genetic abnormality and its effect on β -globin production, ranging from asymptomatic carrier status to severe, transfusion-dependent disease¹.

β -Thalassemia is generally classified into three clinical categories: β -thalassemia major, intermediate, and minor. Patients with β -thalassemia major typically experience severe anemia from an early age and often require regular blood transfusions. β -thalassemia intermediate exhibits a variable clinical course, and transfusion needs vary from person to person. In contrast, β -thalassemia minor is generally asymptomatic or causes only mild anemia^{1,2}. At the molecular level, reduced β -globin synthesis leads to the accumulation of unpaired α -globin chains, which contributes to oxidative stress, erythroid cell damage, and ineffective erythropoiesis. Chronic anemia and increased iron absorption, combined with iron overload resulting from transfusions in patients who receive regular transfusions, can further exacerbate complications associated with the disease^{2,3}.

In addition to hematologic abnormalities, β -thalassemia can be associated with complications involving growth, hearing, kidney function, and bone health. Growth disorders have been extensively studied in patients with β -thalassemia major, with potential contributing factors including chronic anemia, iron overload, and endocrine dysfunction^{4,5}. Hearing impairment has also been reported in patients with β -thalassemia, although its prevalence and associated factors vary across the available evidence⁶. Furthermore, renal complications can occur in association with iron overload and iron chelation therapy, highlighting the importance of monitoring kidney function during long-term management^{7,8}. These complications underscore the need to consider the broader clinical consequences of β -thalassemia, beyond merely anemia.

The management of β -thalassemia involves individually tailored treatment and long-term monitoring, with blood transfusions and iron chelation therapy remaining essential components of care for patients who require them. Advances in therapeutic development have introduced additional options beyond conventional transfusion and chelation strategies⁹. Luspatercept, for example, has been studied for its efficacy and safety in β -

thalassemia, particularly in reducing transfusion requirements in eligible patients¹⁰. Nevertheless, treatment decisions must take into account disease severity, transfusion dependence, iron overload, and the potential for organ complications. This narrative review aims to discuss the pathophysiology of β -thalassemia, with a specific focus on growth disorders, hearing loss, renal complications, and current therapeutic approaches. By integrating findings from the available literature, this review seeks to provide an overview of the mechanisms underlying these complications and their implications for clinical management.

Material and Methods

This narrative literature review was conducted to examine the pathophysiology, clinical complications, and therapeutic approaches associated with β -thalassemia. A search for relevant literature was conducted using three databases: PubMed, Google Scholar, and the Cochrane Library. The search focused on English-language publications discussing β -thalassemia, specifically its pathophysiology, growth disorders, hearing loss, renal complications, and treatment options. The keywords used included “ β -thalassemia,” “pathophysiology,” “growth disorders,” “hearing loss,” “renal complications,” and “treatment,” which were used separately or in combination to identify relevant publications. Publications were selected based on their relevance to the scope of this review. The findings were analyzed qualitatively and synthesized narratively to describe the underlying disease mechanisms, associated clinical complications, and available therapeutic approaches.

Results and Discussion

β -Thalassemia is a congenital hematologic disorder characterized by reduced or absent β -globin synthesis, resulting in chronic anemia and various complications that can affect multiple organ systems^{11,12}. Although anemia is the primary clinical manifestation, the impact of this disease extends beyond the hematopoietic system. Growth disorders, hearing loss, renal dysfunction, and skeletal abnormalities have been reported in affected patients, particularly those with more severe disease phenotypes^{13–15}. These complications can reflect the combined effects of ineffective erythropoiesis, chronic tissue hypoxia, iron overload, endocrine dysfunction, and long-term treatment. The course and severity of the disease vary depending on the underlying genetic abnormality, transfusion requirements, iron burden, treatment history, and individual clinical characteristics. Therefore, β -thalassemia should be understood not only as a disorder of hemoglobin synthesis but also as a chronic condition requiring comprehensive, multidisciplinary management^{16–19}.

Growth disorders are a major complication of β -thalassemia, particularly in patients

with β -thalassemia major. A systematic review and meta-analysis by Arab-Zozani et al. identified a significant burden of height-related complications among patients with β -thalassemia major, emphasizing that linear growth disorders remain a significant problem in this population⁴. Growth abnormalities might become apparent during childhood and adolescence, when normal development depends on an adequate oxygen supply, nutritional status, and coordinated endocrine function. Chronic anemia can impair tissue oxygenation, while increased erythropoietic activity reflects the body's attempt to compensate for inadequate hemoglobin production²⁰⁻²². In addition, iron overload can disrupt endocrine function when excess iron accumulates in organs involved in hormonal regulation. Dysfunction of the pituitary gland and other endocrine organs can interfere with growth hormone secretion and the regulation of growth-related pathways, thereby contributing to reduced height and delayed physical development^{23,24}.

Iron overload is particularly relevant in patients who require repeated blood transfusions. Although transfusion therapy increases oxygen-carrying capacity and helps control severe anemia, repeated transfusions introduce additional iron that the body cannot efficiently eliminate. Without adequate chelation therapy, iron can progressively accumulate in tissues and contribute to organ dysfunction^{25,26}. Increased intestinal iron absorption associated with ineffective erythropoiesis can further exacerbate the overall iron burden. These mechanisms illustrate the complexity of managing growth disorders in β -thalassemia: correcting anemia alone cannot fully restore normal growth if endocrine abnormalities or other chronic complications are already present²⁷⁻²⁹. Growth hormone therapy has been studied as a potential intervention in selected patients; however, its efficacy and safety require careful evaluation, and treatment must be based on confirmed clinical indications, not solely on short stature. Therefore, longitudinal monitoring of height, weight, growth velocity, pubertal development, and relevant endocrine parameters is essential³⁰⁻³². Measurement of serum ferritin can also aid in assessing iron overload, although ferritin results must be interpreted in conjunction with the clinical context and other relevant tests. Regular iron chelation therapy, when indicated, remains essential for controlling iron accumulation and reducing the risk of further complications^{33,34}.

Hearing loss is another clinical complication reported in patients with β -thalassemia. Tartaglione et al. reported a prevalence of hearing loss of approximately 32.3% in their systematic review, indicating that hearing impairment warrants greater attention in the long-term care of these patients⁶. Hearing loss can have significant consequences for communication, participation in education, psychosocial development, and quality of life,

especially if it occurs during childhood. However, the reported prevalence must be interpreted in relation to the population and diagnostic methods used in the underlying studies, as differences in patient characteristics and hearing assessment procedures can influence these estimates^{35–37}. Therefore, the presence of hearing loss should not be assumed to be uniform across all patients with β -thalassemia.

The mechanisms underlying hearing loss in β -thalassemia are likely multifactorial. Iron overload can contribute to oxidative stress and cellular damage, while chronic anemia can affect oxygen delivery to metabolically active tissues. In addition, certain iron chelating agents have been associated with adverse effects on hearing; therefore, exposure to such treatments is an important consideration during clinical evaluation^{6,38,39}. Nevertheless, the contributions of disease-related mechanisms and treatment-related effects can vary among patients, and the presence of an association does not necessarily indicate a causal relationship^{9,10}. Therefore, the relationship between hearing loss and age, disease duration, iron load, or exposure to iron-chelation therapy should be interpreted with caution and not generalized to all patients. These considerations support the use of appropriate audiological evaluations, particularly in patients with hearing symptoms or relevant treatment-related risk factors. Early detection can facilitate timely intervention and help minimize the functional consequences of hearing loss.

Renal complications are another significant issue in β -thalassemia, as renal abnormalities can develop before clear clinical signs of renal dysfunction become apparent. Renal involvement can be associated with chronic anemia, changes in renal hemodynamics, iron overload, and exposure to iron-chelating agents. Chronic anemia can affect oxygen delivery to the kidneys and adaptive renal blood flow, while iron-mediated oxidative stress can contribute to cellular damage. On the other hand, iron-chelation therapy is necessary to manage iron overload resulting from transfusions; however, in some cases, it can cause renal side effects. Therefore, striking a balance between controlling iron accumulation and minimizing treatment-related toxicity is a critical consideration in the long-term management of β -thalassemia^{40–43}.

Conventional assessment based on serum creatinine cannot fully detect kidney abnormalities in the early stages, especially when changes in kidney function are still subtle. Therefore, several biomarkers have been studied to identify potential kidney injury at an earlier stage⁴⁴. Neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl- β -D-glucosaminidase (NAG), and kidney injury molecule-1 (KIM-1) have been studied as potential indicators of tubular damage. Urinary cystatin C and β 2-microglobulin can provide

complementary information regarding kidney function and tubular abnormalities, depending on the biomarker and the clinical context. Changes in these markers can indicate renal alterations that warrant further investigation; however, this should not automatically be interpreted as evidence of a diagnosed chronic kidney disease^{45–47}. Their diagnostic and prognostic value depends on the study population, the testing methods used, and the clinical cutoffs applied. Further validation is needed before any individual biomarker can be considered a definitive predictor of renal complications in all patients with β -thalassemia.

These findings highlight the importance of integrating renal monitoring into routine care, particularly for patients undergoing long-term iron chelation therapy. Such monitoring can include conventional renal function tests, assessment of relevant urinary parameters, and additional biomarkers if clinically indicated. Renal test results should be interpreted in light of iron burden, transfusion history, chelation regimens, and other potential causes of kidney injury. Early identification of abnormalities can allow physicians to reevaluate treatment and investigate potentially modifiable contributing factors. However, renal protection requires an individually tailored approach because inadequate chelation therapy can lead to progressive iron accumulation, while excessive or poorly monitored treatment can increase the risk of side effects. Therefore, the goal is not merely to lower iron levels but to maintain the proper balance between treatment effectiveness and organ safety^{7,41,48,49}.

The clinical complications of β -thalassemia can be better understood through its underlying molecular and cellular pathophysiology. Mutations in the HBB gene reduce or halt β -globin synthesis, thereby disrupting the balance between α - and β -globin chains required for the formation of normal hemoglobin^{11,50}. The resulting excess unpaired α -globin chains accumulate within erythroid precursors, triggering oxidative stress, cellular damage, and premature destruction of developing red blood cells. This process contributes to ineffective erythropoiesis, in which erythroid precursors are produced but fail to mature effectively into functional circulating red blood cells. The resulting anemia stimulates compensatory erythropoiesis, which can lead to bone marrow enlargement and contribute to bone abnormalities in more severe cases of the disease^{51,51,52}.

Iron overload further exacerbates the disease burden. In addition to iron entering the body through repeated transfusions, ineffective erythropoiesis can impair hepcidin regulation and increase iron absorption in the intestine. When iron accumulates beyond the body's storage capacity, redox-active iron can trigger the formation of reactive oxygen species, causing oxidative damage to vulnerable tissues. Iron-related damage can affect the liver, heart, endocrine organs, and other tissues, depending on the distribution and severity

of iron accumulation^{7,8}. This mechanism also helps explain why the clinical consequences of β -thalassemia cannot be assessed based solely on hemoglobin concentration. A patient can experience improved hematologic control but still be at risk for iron-related organ damage, endocrine dysfunction, or other long-term complications. Therefore, comprehensive management must address both ineffective erythropoiesis and the consequences of chronic iron overload^{29,53}.

Bone abnormalities, including a decrease in bone mineral density, are another manifestation of a broader disease process. Bone health can be affected by bone marrow expansion, chronic anemia, iron-related endocrine dysfunction, and changes in bone formation and resorption. These factors can act simultaneously, making it difficult to attribute bone complications to a single mechanism^{54,55}. Although routine transfusion therapy can suppress excessive erythropoietic activity and help reduce bone marrow expansion, it does not always eliminate other factors contributing to bone health disorders, such as endocrine disorders and iron overload. Consequently, maintaining adequate hematologic control is important but might not be sufficient to prevent all skeletal complications. Assessments of growth, endocrine function, nutritional factors, and bone health should be considered according to the patient's clinical needs^{3,7,8}. This integrated approach is particularly important for patients with severe diseases requiring lifelong monitoring and treatment.

Advances in our understanding of ineffective erythropoiesis have also contributed to the development of therapeutic approaches beyond conventional transfusions and iron chelation. Luspatercept is an erythroid maturation agent that promotes late-stage erythroid maturation by modulating signaling within the transforming growth factor- β superfamily^{56,57}. Rather than directly correcting the underlying HBB mutation, this drug targets downstream processes involved in ineffective erythropoiesis. Clinical evidence has shown that luspatercept can reduce the need for transfusions in some eligible patients with transfusion-dependent β -thalassemia, making it an important additional treatment option. Reducing the need for transfusions can lower the rate at which excess iron from transfusions enters the body. However, this benefit should not be equated with the removal of existing excess iron, and patients can still require iron chelation and ongoing monitoring^{9,57,58}.

The potential benefits of luspatercept must also be weighed against its safety profile, eligibility criteria for treatment, and individual variability in response. Evidence from clinical studies and systematic reviews supports its efficacy in certain patients; however, the magnitude of benefit varies among individuals, and treatment decisions should be based on

available clinical evidence and patient-specific factors. Furthermore, a reduction in transfusion burden does not automatically prove that luspatercept prevents kidney dysfunction, hearing loss, growth impairment, or other organ complications. These findings require direct evaluation in appropriately designed studies. Therefore, luspatercept should be considered an adjunctive therapeutic option within an individually tailored management strategy, rather than a substitute for all established treatments. Transfusion therapy, iron chelation, and monitoring for organ complications remain essential when clinically indicated^{10,59,60}.

Overall, the reviewed literature indicates that β -thalassemia is a multisystem disorder in which impaired β -globin synthesis triggers a cascade of hematological and systemic complications. Growth impairment, hearing loss, renal abnormalities, and skeletal complications highlight the importance of considering the broader disease burden beyond anemia. Although these complications have distinct underlying mechanisms, they can share contributing factors, including iron overload, chronic anemia, endocrine dysfunction, and long-term treatment exposure. Their identification and management therefore require individualized assessment, appropriate monitoring, and multidisciplinary care. Therapeutic advances such as luspatercept offer additional treatment options for selected patients; however, they do not eliminate the need for established supportive care and continued clinical monitoring. Further research is needed to clarify the mechanisms underlying specific organ complications, validate biomarkers for early detection, and determine whether newer therapies can improve long-term clinical outcomes beyond reducing transfusion requirements.

Conclusion

β -Thalassemia is a multisystem disorder characterized by ineffective erythropoiesis, chronic anemia, and iron overload, which may contribute to growth impairment, hearing loss, renal dysfunction, and skeletal complications. These manifestations highlight the importance of comprehensive disease management beyond hematological control. Regular monitoring of growth, auditory function, renal parameters, and iron burden is essential for detecting complications and guiding individualized treatment. Although blood transfusion and iron chelation remain important components of disease management, emerging therapies such as luspatercept offer additional treatment options for eligible patients. Further research is needed to improve the early detection of organ complications, validate potential biomarkers, and clarify the long-term effects of emerging therapies on clinical outcomes.

Declaration of Generative AI in Scientific Writing

The authors affirm that the usage of generative artificial intelligence tools, including ChatGPT (OpenAI) and DeepL is intended solely for assist with language editing, including grammar correction, vocabulary refinement, and improvements in clarity and readability. These tools were not used for generating content, data analysis, or interpretation. The authors are fully responsible for the accuracy and integrity of the content as well as the conclusions presented in this study

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