Research Article

Volume 5, Issue 1

JCMCRI

Journal of Clinical & Medical Case Reports, Images

Received: October 15, 2025 Published: January 12, 2026

DOI: 10.55920/3064-8025/1153

The Impact of Thalassemia Major on the Endocrine System: A Focus on Growth and Puberty

Hussein Naji Abdullah Alshammari[1], Kareem Abed Mobasher[1], Shatha Sahib Asal[2], Younis Abdulridha Alkhafaji[3], Mohammed Jasim khulaif[2], Miaad Adnan Abdul Salam[2], Maythum Ali Shallan[1], Rawaa Awad Kadhum[2] and Rania Abd ElMohsen Abo El Nour[2,4]

[1]College of Medicine, Al-Mustaqbal University, 51001 Babylon, Iraq

[2]Anaesthesia Techniques Department, College of Health and Medical Techniques, Al-Mustaqbal University, 51001, Babylon, Iraq

[3]Kidney dialysis techniques Department, College of Health and Medical technique, Al-Mustaqbal University, Babylon 51001, Iraq

[4]Community Health Nursing Department, Beni-Suef Health Technical Institute, Ministry of Health, Beni-Suef 62511, Egypt

Abstract

Growth impairment and pubertal dysfunction constitute the most prevalent endocrinopathies associated with homozygous thalassemia, contributing significantly to morbidity in 70–80% of children and adolescents worldwide. This review elucidates the pathophysiology of these endocrine complications, examining the evolution from historical presentations to the altered natural history resulting from optimized transfusion and chelation regimens. Furthermore, the discussion addresses the clinical manifestations, diagnostic criteria, and management strategies for growth retardation, delayed sexual maturation, and pubertal aberrations, including the therapeutic utility of growth hormone and sex steroids. Finally, the article highlights contemporary and emerging strategies for surveillance and early intervention, aiming to preserve fertility potential and maintain bone mineral density in affected cohorts.

Keywords: Endocrinopathies, Thalassemia; Thermal Intensity; Growth Hormone.

Introduction

The thalassemias constitute a heterogeneous group of hereditary hematological disorders defined by the defective synthesis of specific globin chains and the consequent precipitation of unpaired chains. beta-thalassemia represents the predominant genetic etiology of severe thalassemia major, particularly within populations across the Mediterranean basin, the Indian subcontinent, and Southeast Asia. While chronic blood transfusion regimens effectively mitigate mortality associated with severe anemia and extend survival into adulthood [1], they invariably precipitate progressive systemic iron overload. This secondary hemosiderosis arises from the cumulative effect of trans fusional iron loading and enhanced gastrointestinal absorption driven by ineffective erythropoiesis. In the absence of effective chelation therapy, iron toxicity results in significant morbidity, including growth retardation, pubertal delays, and multi-organ dysfunction. Notably, mortality attributable to cardiac failure is highly prevalent in the second decade of life among non-chelated patients [2]. However, the implementation of regular transfusion protocols aimed at maintaining pre-transfusion hemoglobin levels >10 g/dL, combined with subcutaneous desferoxamine infusion, has markedly enhanced survival rates and quality of life [3–5]. Consequently, the clinical management paradigm has evolved to address long-term psychosocial determinants of health, including educational attainment, career progression, and reproductive well-being.

Nevertheless, persistent growth attenuation, pubertal dysfunction, and the psychosocial sequelae inherent to chronic pathology continue to constitute significant barriers to achieving optimal adult quality of life. In this context, hematopoietic stem cell transplantation (HSCT) has emerged as a curative modality. This intervention has demonstrated efficacy in establishing thalassemia-free survival in a substantial patient cohort, presenting a viable alternative to lifelong transfusion-chelation dependence [6].

Growth impairment and delayed or absent puberty are prevalent complications associated with transfusion-dependent thalassemia. While physiological growth velocity is typically preserved during the first decade of life, growth deceleration characteristically manifests during the second decade [7–10]. Borgna Pignatti et al. reported that among 250 Italian adolescents undergoing desferoxamine chelation for 7–10 years, 62% of males and 35% of females aged >14 years exhibited stature >2 standard deviations (SD) below the population mean, with concurrent anomalies in sexual development [11]. A follow-up survey by the same investigators seven years later indicated that 29% of females and 52% of males remained short. Similarly, studies involving 405 Greek patients with thalassemia major documented growth retardation in 21.7% of males and 13% of females, with incidence peaking in the 15–20-year age group [12]. Analogous epidemiological patterns have been observed in smaller cohorts of Iraqi and Turkish patients. In adolescents exhibiting growth failure, concomitant hypogonadism is frequent, often resulting in an attenuated or absent pubertal growth spurt [13]. Consequently, to delineate the impact of variable therapeutic protocols on linear growth kinetics and final adult height in beta-thalassemia major.

De Sanctis et al. conducted a stratified analysis of growth kinetics across three patient cohorts: (1) those receiving low pre-transfusion hemoglobin support with delayed chelation (initiated >14 years); (2) those on hypertransfusion regimens with intermediate chelation onset (6–7 years); and (3) a group receiving hypertransfusion with early chelation (initiated >2 years). Paradoxically, the growth velocity in children of both sexes receiving aggressive early intervention (high transfusion and early chelation) was significantly attenuated compared to the other two cohorts. Regarding final adult stature, 50%

***Corresponding Author:** *Hussein Naji Abdullah Alshammari, F.I.C.M.S Hematology, College of Medicine, Al-Mustaqbal University, 51001 Babylon, Iraq. E-Mail: drhusseinnaji61@gmail.com.

Citation: Hussein Naji Abdullah Alshammari*, The Impact of Thalassemia Major on the Endocrine System: A Focus on Growth and Puberty Jour of Clin & Med Case Rep, Imag 2026; 5(1): 1153.

of males and 36% of females in the first two groups fell below the 10th percentile, with no statistically significant divergence observed between them [14]. In contrast, superior auxological outcomes and pubertal maturation were documented by centers in Sicily, where only 5% of patients exhibited short stature [15], and by investigators in Toronto [16].

De Sanctis et al. [17] reported that peak height velocity (PHV) during puberty fell below the 10th percentile in 66% of males and 70% of females managed with low pre-transfusion hemoglobin levels and chelation initiation between 14 and 15 years of age. Notably, in the cohort receiving hypertransfusion with chelation onset at 6–7 years, 100% of males and 46% of females exhibited a PHV below the 10th percentile. However, the study design did not clearly differentiate whether this blunted growth velocity resulted from delayed pubertal onset or a primary failure of the pubertal growth spurt in the presence of spontaneous or induced maturation. In a separate unchelated transfusion-dependent cohort, attenuated growth spurts were universally observed in females with spontaneous or induced puberty, while 33% of males exhibited minimal linear growth during testosterone replacement therapy.

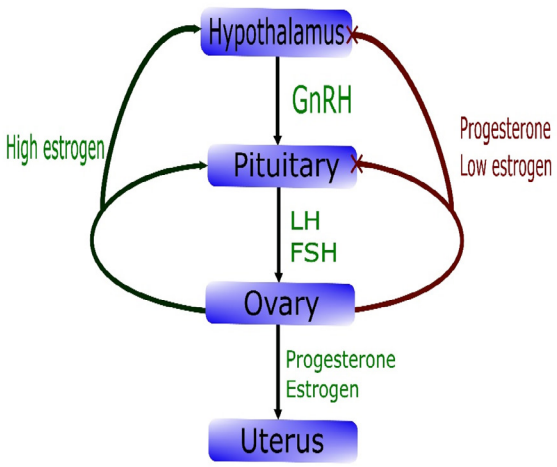
We recently evaluated auxological and pubertal parameters in a cohort of 28 patients aged >16 years. Although puberty was established (spontaneously or via induction) in all subjects, a significant pubertal growth spurt was detectable in only 46% of the cohort. Statistical analysis revealed no significant discrepancy in the upper-to-lower segment (U/L) ratio between responders and non-responders (1.09 pm 0.03 vs. 1.07 pm 0.06); conversely, serum ferritin levels were significantly elevated in patients.

Patient and Methods

Puberty and pubertal growth spurt in children with beta-thalassemia

Delayed pubertal onset represents a critical determinant of growth retardation in adolescents with thalassemia major. In an Italian cohort of 250 adolescents (aged 12–18 years) treated with chelation therapy for 7–10 years, a complete absence of secondary sexual characteristics was documented in 38% of females and 67% of males (Figure 1) [18]. A longitudinal follow-up conducted seven years later by the same investigators indicated that pubertal prognosis had improved particularly in females attributable to time and optimized iron chelation regimens; notably, this subsequent analysis established a deleterious correlation between elevated serum ferritin levels and sexual maturation [19-20].

Figure 1: *Puberty and pubertal growth spurt in children with beta-thalassemia.*



High prevalence rates of pubertal dysfunction have been consistently corroborated by other investigations. In our recent survey, spontaneous puberty was observed in only 13 of 41 subjects (32%) over the age of 14 years. These findings align with a recent Australian report in which abnormal sexual maturation and hypogonadism were identified in 36% of males and 67% of females [21]. Furthermore, a large multicenter Italian study involving 1,861 patients reported pubertal failure in 51% of males and 47% of females aged >15 years [22].

Patients exhibiting delayed puberty demonstrate significantly elevated serum ferritin concentrations compared to those with normative pubertal development, implicating iron overload in the pathogenesis of the disorder. Clinically, pubertal delay and hypogonadism result from iron-induced cytotoxicity within the hypothalamic pituitary gonadal (HPG) axis. The predominant etiology is hypogonadotropic hypogonadism arising from central dysfunction; however, primary gonadal failure is occasionally documented, evidenced by elevated follicle-stimulating hormone (FSH) levels and an absent testosterone response to human chorionic gonadotropin (hCG) stimulation. Pathophysiologically, this central defect manifests as diminished spontaneous pulsatile gonadotropin secretion and a blunted pituitary response to gonadotropin-releasing hormone (GnRH) [23-24].

Histological analysis confirms that iron distribution within the pituitary is heterogeneous, with demonstrated preferential siderosis of gonadotropic cells [25]. Even in eumenorrheic patients, diminished gonadotropin reserve suggests a high longitudinal risk for secondary amenorrhea. Nevertheless, therapeutic intervention alters this trajectory; Bronspiegel-Weintrob et al. reported that initiating desferoxamine chelation prior to age 10 resulted in normal sexual maturation in 90% of patients, compared to only 38% in those treated later. Corroborating data from Sicily and Britain confirm that early, compliant chelation regimens significantly optimize reproductive outcomes in contemporary cohorts [26].

Growth failure caused by Desferoxamine

The advent of subcutaneous desferoxamine (DFO) chelation has demonstrated efficacy in mitigating the systemic sequelae of tissue hemosiderosis, thereby preserving growth potential, pubertal development, and organ integrity. Conversely, contemporary evidence indicates that aggressive DFO dosing in pediatric patients with low somatic iron burden may paradoxically induce skeletal dysplasia and linear growth retardation [27].In a retrospective longitudinal analysis of auxological patterns in children aged 1–6 years, De Sanctis et al. observed that patients initiating chelation proximal to their inaugural transfusion exhibited a marked deceleration in growth velocity, declining from the 50th percentile at baseline to below the 5th percentile following six years of therapy [28]. In contradistinction, cohorts commencing subcutaneous or intramuscular DFO after age three maintained stable height percentiles over an equivalent duration. The clinical phenotype of DFO-induced toxicity is characterized by truncal shortening (platyspondyly), genu valgum, metaphyseal flaring, and articular rigidity. Radiographic manifestations of skeletal dysplasia typically emerge after a 2–4 year latency period in infants receiving high-dose regimens, though susceptibility persists in older children (>3 years) exposed to excessive therapeutic doses relative to iron burden [29–30].

Radiographically, the associated skeletal dysplasia is characterized by physeal thickening, metaphyseal flaring and cupping, subchondral sclerosis, and the presence of discrete metaphyseal radiolucencies. Concomitant findings include generalized osteoporosis and accentuation of the trabecular pattern in long bones with the distal radius and ulna representing the predominant sites of involvement. Although

these morphological features mimic the radiographic stigmata of rickets and scurvy, vitamin C and D deficiencies have been excluded as primary etiologies. Instead, the pathophysiology is attributed to the inadvertent chelation of essential trace metals by desferoxamine. The drug exhibits affinity constants (Ka) of $10^{31}$for iron, compared to 10^{14} for copper and zinc [30].

While zinc deficiency contributes to growth attenuation and hypogonadism [31] and supplementation improves linear growth in non-chelated cohorts [32], zinc depletion alone does not fully explain the observed dysplastic changes, despite documented reductions in leukocyte and hair zinc levels. Conversely, copper deficiency is known to precipitate skeletal anomalies that more closely resemble the specific lesions reported in these patients [33]. Despite the theoretical risks of chelation, serum copper levels have consistently been documented within reference ranges in affected cohorts, arguing against copper depletion as the primary etiology. Consequently, the precise pathogenesis of desferoxamine-induced skeletal dysplasia remains elusive. Current hypotheses posit a direct cytotoxic effect on collagen synthesis, mediated by the drug's antiproliferative properties and its inhibition of ribonucleotide reductase, which fundamentally alters cellular differentiation [34].

To optimize the therapeutic window balancing iron excretion efficacy against skeletal toxicity strict adherence to a "Therapeutic Index" is mandated. This index, defined as the quotient of the mean daily desferoxamine dose (mg/kg) and current serum ferritin concentration (mug/L), should be maintained below a threshold of 0.025 [35]. Furthermore, current clinical consensus recommends delaying the initiation of chelation therapy until after 2 to 3 years of age and strictly capping desferoxamine dosages at 50 mg/kg/day.

Growth hormone-releasing hormone (GHRH), growth hormone (GH), and insulin-like growth factor 1 (IGF-1) axis - patients with thalassemia major

While growth failure in transfusion-dependent thalassemia is a well-documented phenomenon, its precise etiology remains elusive. Although factors such as delayed puberty, the absence of a pubertal growth spurt, platyspondyly, and desferrioxamine toxicity are established contributors, the specific influence of the GHRH-GH-IGF-I axis remains unclear. Interpretations of the existing literature are confounded by methodological limitations, including small sample sizes and significant heterogeneity regarding treatment protocols and patient age over the last two decades. Notably, while growth hormone (GH) reserves are generally reported as intact in thalassemic children even those exhibiting short stature our investigation revealed an impaired GH response to insulin induced hypoglycemia in 12% (5 of 41) of patients with growth retardation, nearly all of whom were older than nine years.

Conversely, recent data indicates a significant prevalence of growth hormone (GH) deficiency among thalassemic populations, with reported rates of 24% and 50% in American and British cohorts, respectively. Pintor et al. observed that 95% of patients aged 10 to 23 exhibited impaired GH responses to clonidine and insulin-induced hypoglycemia, alongside a blunted response to growth hormone-releasing hormone (GHRH). However, conflicting reports suggest that the GH response to GHRH may remain intact in growth-retarded patients. In cases of delayed puberty, GHRH responsiveness is frequently compromised but has been shown to normalize following spontaneous puberty or the administration of sex steroids or gonadotropins; this reversibility suggests a functional alteration in GH secretion rather than an absolute defect. Although data regarding spontaneous GH secretion remains sparse and contradictory, an abnormal GH reserve is unlikely to be the primary etiology of short stature in the majority of patients. Nevertheless, as patient survival extends, the probability of GH deficiency or neurosecretory dysfunction rises, necessitating vigilance. Accurate diagnostic evaluation requires that clinicians first address potential confounders by normalizing thyroid status and employing sex steroid priming to rule out transient impairments caused by delayed puberty.

It is well established that IGF-I levels are reduced in transfusion-dependent thalassemia. The presence of low IGF-I alongside preserved GH reserves suggests a defect downstream of hormone secretion, specifically pointing toward GH insensitivity. Since hepatic GH binding appears intact in these patients, the defect is likely located at the post-receptor level. This view is corroborated by Werther et al., who reported that patients exhibited a subnormal IGF-I elevation following high-dose exogenous GH administration, suggesting that GH treatment may be ineffective [36]. In contrast to these mechanistic hypotheses, our study found no correlation between serum IGF-I levels and growth status in Iraqi children. The lack of difference between growth-retarded and normal-stature patients implies that the etiology of growth failure in this population may be independent of the GH-IGF-I axis.

Setting of the study

The study was conducted over approximately one year. During this period, all patients clinically suspected of having thalassemia who met the study's inclusion criteria were enrolled.

The study instruments and sampling

Given the autosomal recessive inheritance of thalassemia, the identification of carriers is clinically imperative and achievable through hematological screening. Heterozygotes for either alpha or beta thalassemia typically exhibit microcytic hypochromic indices, with or without identifying anemia; consequently, a differential diagnosis is required to exclude iron deficiency anemia. Following the assessment of iron biomarkers, such as ferritin or zinc protoporphyrin, clinical history and ethnicity provide critical context for the diagnostic approach. Ultimately, carrier identification relies on red blood cell indices and morphology, followed by the separation and quantification of hemoglobin fractions. The diagnostic algorithm for this process is outlined in (Table 1).

"In certain high-prevalence regions, carrier identification strategies employ a primary prescreening based on red cell indices, reserving the separation and measurement of Hb fractions for individuals exhibiting reduced mean corpuscular volume (MCV) and/or mean corpuscular hemoglobin (MCH). However, the selection of a screening protocol is heavily contingent upon disease frequency, population and genetic heterogeneity, resource availability, and specific sociocultural or religious determinants. In multi-ethnic populations, preselection relying solely on MCV and MCH cutoffs is inadvisable. To ensure the detection of significant normocytic traits, hemoglobin fraction analysis should be performed concurrently with the complete blood count [37].

Furthermore, the timing of screening is a critical determinant of its utility; newborn screening is generally discouraged for control programs as it occurs too late to facilitate primary prevention. Consequently, screening initiatives globally are predominantly targeted at the premarital or early antenatal stages and are stratified into either mandatory or voluntary frameworks. notably, in several high-prevalence Islamic regions including Iraq, Saudi Arabia, and the Palestinian territories hemoglobinopathy screening has recently been instated as a mandatory prerequisite for the issuance of marriage licenses.

Table 1: *Diagnostic Phase of thalassemia.*

Diagnostic Phase	Test / Assessment	Key Parameters / Thresholds	Findings / Patterns	Interpretation / Next Step
Clinical Evaluation	Medical and family history	History of anemia or hemoglobinopathy	Positive family history	Supports inherited anemia
Primary Hematological Tests	Complete blood count (CBC)	MCV < 80 fL; MCH < 27 pg	Microcytic, hypochromic indices	Suspect thalassemia or iron deficiency
Primary Hematological Tests	Peripheral blood smear / RBC staining	—	Microcytosis, hypochromia, target cells, ± Hb H inclusion bodies	Suggests thalassemia
Differential Assessment	Other causes of anemia	Normal indices or atypical features	Inconsistent with thalassemia	Evaluate alternative diagnoses
Iron Status Assessment	Serum ferritin	≤ 12 ng/mL	Low iron stores	Consider iron deficiency anemia
Iron Therapy Trial	Iron supplementation	3 months	No hematologic improvement	Proceed to hemoglobin analysis
Iron Status Assessment	Serum ferritin	> 12 ng/mL	Normal iron stores	Proceed directly to hemoglobin analysis
Hemoglobin Analysis	Hb electrophoresis / HPLC	HbA_2 ≥ 4%; HbF 0–1.5%	Elevated HbA_2	β-thalassemia trait
Hemoglobin Analysis	Hb electrophoresis / HPLC	HbA_2 < 4%; HbF < 1%	Normal HbA_2 and HbF	α-thalassemia trait or related disorders
Hemoglobin Analysis	Hb electrophoresis / HPLC	HbA_2 ≥ 4%; HbF 5–50%	Elevated HbA_2 and HbF	β-thalassemia intermedia
Hemoglobin Analysis	Hb electrophoresis / HPLC	Hb H 5–25%; HbA_2 < 4%; ± Hb CS	Presence of Hb H ± Constant Spring	Hemoglobin H disease
Hemoglobin Analysis	Hb electrophoresis / HPLC	Other normal or abnormal Hb variants	Variant hemoglobin detected	Hb E, Hb S, Hb C disorders, others
Genetic Confirmation	DNA analysis	α-globin gene mutations	Pathogenic variants identified	Confirm α-thalassemia
Genetic Confirmation	DNA analysis	β-globin gene mutations	Pathogenic variants identified	Confirm β-thalassemia or related disorders

Results and Discussion

Alpha-thalassemia: symptomatic forms

Hemoglobin H Disease (HbH), classified within the spectrum of Non-Transfusion-Dependent thalassemias (NTDT), Hemoglobin H (HbH) disease manifests when the synthesis of alpha-globin chains is suppressed to approximately 25% of physiological levels. This deficit promotes the formation of unstable beta-globin homotetramers (beta_4), designated as HbH (Table 2).

Beta-thalassemia carriers

Currently, the genetic landscape of beta-thalassemia is defined by over 200 distinct point mutations and deletions within the β-globin gene, varying significantly in severity. These mutations result in a broad spectrum of clinical and hematological phenotypes, even among heterozygous carriers. While the identification of thalassemia major and intermedia requires distinct diagnostic criteria, the primary focus for asymptomatic carriers lies in the analysis of red blood cell (RBC) counts and derived erythrocyte indices. The assessment of RBC indices is the cornerstone of laboratory screening, particularly in resource-limited settings. This is typically performed using automated electronic cell counters, which necessitate rigorous daily calibration to ensure precision (Table 3).

Note: The "Discriminant factor (DF *)" formula provided in the text (MCV, times (RDW^\Hb,times 100) appears to be a variation of the standard Green & King Index. The standard medical formula includes MCV^2 to achieve the diagnostic cut-off of 65.MCV: Mean Corpuscular Volume (fL)

MCH: Mean Corpuscular Hemoglobin (pg)

RBC: Red Blood Cell Count (10^12/L)

RDW: Red Cell Distribution Width (%)

Hb: Hemoglobin (g/dL)

Table 2: *Condition of alpha-thalassemia.*

Condition	Hemoglobin H-Disease	Hb Bart's Hydrops Fetalis
Genotype	3-Gene Deletion (alpha) Only 1 functional alpha-gene remains.	4-Gene Deletion No functional alpha-genes remain.
Classification	Non-Transfusion-Dependent thalassemia (NTDT)	Incompatible with life (without intra-uterine intervention).
Primary Hemoglobin Variant	HbH (beta_4): 3% – 30% HbA: Reduced but present.	Hb Bart's (gamma_4): Predominant Hb Portland: Trace amounts HbA / HbF: Absent
Clinical Presentation	Moderate Anemia (Microcytic/Normocytic) Chronic Hemolysis (High Bilirubin) Splenomegaly	Severe fetal anemia Generalized edema (Hydrops) Intrauterine death or death shortly after birth.
Diagnostic Findings	HbH Inclusions: "Golf ball" appearance in RBCs (using Brilliant Cresyl Blue stain).	Absence of alpha-chains: Total lack of functional hemoglobin synthesis.

Table 3: *Beta-thalassemia carriers.*

Index Name	Formula	Cut-off Value	Indication for β-Thalassemia Trait	Indication for Iron Deficiency Anemia (IDA)
Mentzer Index (MI)	Frac MCV, RBC	13	< 13	> 13
Srivastava Index (SI)	Frac MCH, RBC	3.8	< 3.8	> 3.8
Shine and Lal Index (SLI)	Frac MCV^2 \times MCH,100	1530	< 1530	> 1530
RDW Index (RDWI)	Frac MCV \times RDW, RBC	220	< 220	> 220
Green & King Index (Discriminant Factor *)	Frac MCV^2 \times RDW, Hb \times 100	65	< 65	> 65

Limitations of Discriminant Indices and Iron Status Due to the documented overlap in sensitivity and specificity among various discriminant formulas, relying on a single mathematical cutoff to differentiate thalassemia from iron deficiency is clinically insufficient; the application of dual thresholds is therefore recommended to minimize diagnostic error. Furthermore, establishing the patient's iron status is a prerequisite for accurate diagnosis. In cases of confirmed iron deficiency, a definitive diagnosis regarding thalassemia must be deferred until hematological parameters are re-evaluated following a course of therapeutic iron supplementation.

Peripheral blood smear analysis in thalassemia carriers typically reveals a distinct pattern of morphological alterations. The predominant features include microcytosis, hypochromia, and anisopoikilocytosis. Secondary findings may include the presence of basophilic stippling and codocytes (target cells), though these are less frequently observed.

The quantification of Hemoglobin A2 (HbA_2) constitutes the gold standard for identifying beta-thalassemia carriers. Among the available methodological approaches, microchromatography, cation-exchange High Performance Liquid Chromatography (HPLC), and capillary electrophoresis are preferred for their superior accuracy, efficiency, and operational simplicity. The interpretation of HbA2 levels is categorized as follows:

- Physiological Reference Range: 2.4% to 3.2% in healthy adults
- Beta-Thalassemia Carrier Range: Typically elevated between 3.6% and 7%.
- Borderline Interval: Values falling between 3.2% and 3.6% are considered equivocal. This range necessitates comprehensive diagnostic workup, particularly in pediatric populations or couples undergoing reproductive risk assessment. Concurrently, adult Hemoglobin F (HbF) levels are physiologically maintained below 1.5% of total hemoglobin.

HbE carrier

Molecular Basis and PathophysiologyHemoglobin E (HbE) is a structural hemoglobin variant resulting from a missense mutation in the beta-globin gene, specifically the substitution of glutamic acid with lysine at codon 26 (beta-26Glu rightarrow Lys). Crucially, this point mutation creates a cryptic splice site within the pre-mRNA transcript. This leads to aberrant splicing and a consequent quantitative reduction in betaˆE-globin chain synthesis. Therefore, HbE is classified phenotypically as a "thalassemic hemoglobinopathy," exhibiting features of both a structural variant and a biosynthetic defect (beta-halassemia). Epidemiology and Genotypic Interactions the HbE allele demonstrate high prevalence in Southeast Asia, with a notable concentration in Iraq (Table 4). The identification of carriers is clinically paramount due to the potential for complex compound heterozygosity. Co-inheritance of the HbE allele with alpha-thalassemia or beta-thalassemia mutations can result in a broad clinical spectrum, ranging from mild thalassemia intermedia to severe, transfusion-dependent phenotypes indistinguishable from thalassemia major. Hematologi-

cal and Morphological Profile Heterozygous carriers (HbE trait) are typically asymptomatic. Their hematological profile exhibits only marginal alterations; total hemoglobin levels are slightly decreased, and the Mean Corpuscular Volume (MCV) typically presents as mild microcytosis or low-normal values (84 pm 85fL). Peripheral blood morphology mirrors that of beta-thalassemia carriers, characterized predominantly by the presence of target cells (codocytes). Diagnostic quantification definitive diagnosis requires quantitative hemoglobin analysis. In cases of simple HbE trait, HbE typically constitutes 25–30% of the total hemoglobin (Table 5). However, it is established that these percentages fluctuate significantly in the presence of concurrent alpha- or beta-thalassemia traits, complicating the diagnostic picture.

Table 4: *Characteristic of HbE carrier.*

Parameter	Characteristic	Notes
Molecular Defect	beta-globin gene mutation at Codon 26 (GAG-rightarrow and AAG; Glu-rightarrow Lys)	Activation of a cryptic splice site causes reduced synthesis (beta-thalassemia phenotype).
Clinical Presentation	Asymptomatic	Generally requires no treatment.
RBC Indices	**MCV:** 84 pm 5 fL. **Hb:** Slightly reduced	Less microcytic than typical beta-thalassemia trait.
RBC Morphology	Target Cells (Codocytes)	Similar appearance to mild beta-thalassemia.
Hemoglobin Analysis	**HbE:** 25 - 30% **HbA:** 70 - 75% **HbA2:** Normal	HbE percentage decreases if alpha-thalassemia is co-inherited.

Table 5: *Comparative analysis, HbE Trait vs. HbE-beta-Thalassemia.*

Feature	Heterozygous HbE Trait	HbE / β-Thalassemia
Genotype	Beta-A & beta-E	Beta-A & beta-E OR beta+ and beta-E
Clinical Phenotype	Asymptomatic Clinically silent; normal life expectancy.	Variable Severity: Ranges from Thalassemia Intermedia to Thalassemia Major. Patients often present with hepatosplenomegaly, bone deformities, and growth retardation.
Anemia Severity	None to Mild Hb is usually normal or slightly reduced (>10 g/dL).	Moderate to Severe: Hb is often markedly reduced (3 - 8 g/dL), frequently requiring transfusion therapy.
RBC Indices	Mild Microcytosis MCV approx 84 fL (or slightly lower).	Severe Microcytosis & Hypochromia MCV typically < 65 fL with marked anisopoikilocytosis.
Peripheral Smear	Mild target cells; otherwise, unremarkable.	Marked anisocytosis, poikilocytosis, numerous target cells, nucleated RBCs, and basophilic stippling.
Hemoglobin Analysis (HPLC / Electrophoresis)	HbA Predominant HbA: approx 70% HbE: 25 - 30% HbF: Normal (<2%)	HbE & HbF Predominant HbE: 40 - 60% HbF: 30 - 60% HbA: Absent (in beta^0) or Low (in beta+)
Transfusion Status	Not Required.	Frequently transfusion-dependent (in severe cases) or transfusion-occasional.

Despite comprehensive hematological and familial evaluations, diagnostic ambiguity persists in a subset of clinical cases. These diagnostic challenges frequently arise from the presence of mild or silent mutations, or from complex epistatic interactions between alpha- and beta-globin loci which mask typical phenotypic expression [38-40]. Consequently, in such equivocal scenarios, definitive molecular characterization is deemed an essential prerequisite prior to the initiation of therapeutic management. In the context of prenatal diagnosis, DNA analysis derived from Chorionic Villus Sampling (CVS) constitutes the standard of care. The specific molecular methodologies employed mirror those utilized for postnatal mutation detection, selected according to institutional infrastructure and technical proficiency.

Conclusion

The foregoing analysis has examined thermal elevations induced by

the absorption of infrared laser radiation within transparent ocular tissues. The resulting thermal models elucidate the correlation between temperature profiles and optical absorption coefficients, thereby substantiating the thermodynamic viability of infrared laser vitrectomy and TKP. While distinct from clinical practicability and acknowledging the merits of alternative physical modalities, these findings hold substantial clinical relevance for the refinement of vitrectomy instrumentation and the advancement of safe, non-invasive techniques for modifying corneal curvature. Furthermore, this fundamental thermal analysis is applicable to other ocular media and highlights the critical need for precise quantification of their infrared optical properties. Ultimately, the data suggest a broad spectrum of therapeutic applications for infrared lasers, ranging from the management of pathological myopia and thermal inactivation of resistant corneal viral pathogens to novel approaches for extracapsular cataract extraction and the treatment of orbital neoplasia.

Recommendations and Future Research

Based on the thermal analysis and clinical potential discussed in the text, here are five academic recommendations and future research directions for Infrared Laser Applications in Ophthalmology.

1. High-resolution quantification of optical properties, prioritize the development of a comprehensive database of infrared optical properties (absorption coefficient, scattering coefficient, and anisotropy) for specific ocular tissues (cornea, aqueous humor, lens, vitreous) across a continuous spectrum of infrared wavelengths rather than discrete points. Conduct spectroscopic mapping of age-dependent changes in ocular media transparency. Research should quantify how the water content variations in the aging vitreous or sclerotic lens affect thermal relaxation times and laser energy absorption thresholds.
2. Integration of real-time thermal feedback mechanisms, while thermodynamic feasibility is established, clinical safety relies on preventing collateral thermal damage (e.g., endothelial damage during corneal reshaping) Develop "closed-loop" laser delivery systems that utilize non-contact real-time temperature monitoring. This would allow the system to dynamically adjust power density or pulse duration if the tissue temperature approaches the threshold for denaturation or necrosis. Investigate the integration of infrared thermography or optical coherence tomography (OCT)-based thermometry directly into surgical microscopes to provide surgeons with a heat-map overlay during procedures like Laser Thermal Keratoplasty (LTK).
3. Biomechanical Stability in Corneal Remodeling, the text mentions "altering corneal curvature" for myopia, but historically, thermal reshaping (like TKP) suffers from regression (the cornea returning to its original shape). Research must move beyond immediate thermal effects to long-term biomechanical stability. Recommendations should include combining thermal laser treatments with chemical stiffening agents to "lock in" the refractive change. Evaluate the efficacy of combined protocols using Infrared Laser remodeling followed by Corneal Collagen Cross-linking (CXL). Longitudinal studies are needed to determine if this hybrid approach prevents the regression of corneal curvature changes over 1–5 years periods.
4. Optimization of Pulse Structure for Pathogen Inactivation, the potential to treat "resistant viral infections" suggests a narrow therapeutic window where the virus is inactivated without harming the host corneal stroma. Move away from Continuous Wave (CW) lasers toward ultra-short pulsed laser systems for this application. The goal is to maximize the peak temperature of the target (pathogen) while keeping the total energy delivered low enough to protect the surrounding transparent media (thermal confinement). Define the Arrhenius damage integrals specifically for resistant viral strains (e.g., Herpes Simplex, Adenovirus) versus corneal keratocytes. Establish a safety ratio that defines the exact laser parameters required to achieve viral inactivation while maintaining stromal transparency.
5. Advanced Modeling for Intraocular Applications, develop complex 3D finite-element models (FEM) that account for fluid dynamics (convection) in the eye. Simple static models may overestimate heating because they ignore the natural cooling effect of aqueous humor circulation and choroidal blood flow. Simulate the thermodynamic impact of convection currents induced by laser heating in the vitreous cavity. Research should determine if laser-induced convection aids in the procedure (by moving debris) or poses a risk to the retinal pigment epithelium (RPE).

Conflict of Interest

The authors declare no conflict of interest

References

1. Chatterjee R, Bajoria R (2010) Critical appraisal of growth retardation and pubertal disturbances in thalassemia. Annals of the New York Academy of Sciences 1202(1): 100–114.
2. Carsote M, Vasiliu C, Trandafir AI, Albu SE, Dumitrascu MC, Popa A, Sandru F (2022) New entity—thalassemic endocrine disease: major beta-thalassemia and endocrine involvement. Diagnostics 12(8): 1921.
3. Ahmed S, Soliman A, De Sanctis V, Alyafei F, Alaaraj N, Hamed N, Yassin M (2022) A short review on growth and endocrine long-term complications in children and adolescents with β-thalassemia major: conventional treatment versus hematopoietic stem cell transplantation. Acta Bio Medica 93(4): e2022290.
4. Ghassemi F, Khamseh ME, Sadighnia N, Malek M, Hashemi-Madani N, Rahimian N, Faranoush M (2024) Guideline for the diagnosis and management of growth and puberty disorders in patients with transfusion-dependent thalassemia. Iranian Journal of Blood and Cancer 16(1): 43–52.
5. Venou TM, Barmpageorgopoulou F, Peppa M, Vlachaki E (2024) Endocrinopathies in beta thalassemia: a narrative review. Hormones 23(2): 205–216.
6. Tenuta M, Cangiano B, Rastrelli G, Carlomagno F, Sciarra F, Sansone A, Krausz C (2024) Iron overload disorders: growth and gonadal dysfunction in childhood and adolescence. Pediatric Blood & Cancer 71(7): e30995.
7. Tsilionis V, Moustakli E, Dafopoulos S, Zikopoulos A, Sotiriou S, Zachariou A, Dafopoulos K (2024) Reproductive health in women with major β-thalassemia: evaluating ovarian reserve and endocrine complications. Metabolites 14(12): 717.
8. Soliman A, Yassin M, Alyafei F, Alaaraj N, Hamed N, Osman S, Soliman N (2023) Nutritional studies in patients with β-thalassemia major: a short review. Acta Bio Medica 94(3): e2023187.
9. De Sanctis V, Daar S, Soliman AT, Tzoulis P, Di Maio S, Kattamis C (2023) Retrospective study on long-term effects of hormone replacement therapy and iron chelation therapy on glucose homeostasis and insulin secretion in female β-thalassemia major patients with acquired hypogonadotropic hypogonadism. Acta Bio Medica 94(4): e2023195.
10. Gagliardi I, Mungari R, Gamberini MR, Fortini M, Dassie F, Putti MC, Ambrosio MR (2022) GH/IGF-1 axis in a large cohort of β-thalassemia major adult patients: a cross-sectional study. Journal of Endocrinological Investigation 45(7): 1439–1445.
11. Casale M, Baldini MI, Del Monte P, Gigante A, Grandone A, Origa R, Forni GL (2022) Good clinical practice of the Italian Society of Thalassemia and Haemoglobinopathies for the management of endocrine complications in patients with haemoglobinopathies. Journal of Clinical Medicine 11(7): 1826.
12. Sahu UP, Kumari Y, Rani N, Hasan O, Mobin N, Soumya S, Kumar N Jr (2025) Functional abnormalities of the endocrine system in beta-thalassemia major patients: insights from a hospital-based observational study. Cureus 17(12).
13. Motta I, Mancarella M, Marcon A, Vicenzi M, Cappellini MD (2020) Management of age-associated medical complications in patients with β-thalassemia. Expert Review of Hematology 13(1): 85–94.
14. Bhat V, Dar MI, Digra SK, Sharma S (2025) Impact of pretransfusion hemoglobin and ferritin levels on growth and clinical parameters in children with transfusion-dependent thalassemia major. Journal of the Scientific Society 52(3): 283–289.
15. Di Maio S, Marzuillo P, Daar S, Kattamis C, Karimi M, Forough S, De Sanctis V (2023) A multicenter ICET-A study on age at menarche and menstrual cycles in patients with transfusion-dependent thalassemia who started early chelation therapy. Mediterranean Journal of Hematology and Infectious Diseases 15(1): e2023058.
16. de Kloet LC, Bense JE, van der Stoep MYEC, Louwerens M, von Asmuth EGJ, Lankester AC, Hannema SE (2022) Late endocrine effects after hematopoietic stem cell transplantation in children with nonmalignant diseases. Bone Marrow Transplantation 57(10): 1564–1572.
17. Ananvutisombat N, Tantiworawit A, Punnachet T, Hantrakun N, Piriyakhuntorn P, Rattanathammethee T, Charoenkwan P (2024) Prevalence and risk factors predisposing low bone mineral density in patients with thalassemia. Frontiers in Endocrinology 15: 1393865.
18. Abdelaziz GA, Elsafi OR, Abdelazeem M (2022) Psychosocial disturbances in thalassemia children. NeuroQuantology 20(18): 1041–1047.
19. Adiwinoto RD, Pranoto A, Prayogo AA, Soelistijo SA (2020) Low total testosterone levels in adult male thalassemia major patients: an overlooked complication of iron overload. EurAsian Journal of BioSciences 14(1).
20. Yavropoulou MP, Anastasilakis AD, Tzoulis P, Tourni S, Rigatou E, Kassi E, Makras P (2022) Approach to the management of β-thalassemia major associated osteoporosis: a long-standing relationship revisited. Acta Bio Medica 93(5): e2022305.
21. Ahmadi M, Rassouli M, Gheibizadeh M, Ebadi A, Asadizaker M (2025) Experiences of Iranian patients with thalassemia major regarding their palliative and supportive care needs: a qualitative content analysis. International Journal of Community Based Nursing and Midwifery 13(2): 113.
22. Rostami T, Mohammadifard MA, Ansari S, Kiumarsi A, Maleki N, Kasaeian A, Ghavamzadeh A (2020) Indicators of male fertility potential in adult patients with beta-thalassemia major. Fertility Research and Practice 6(1): 4.
23. Ansharullah BA, Sutanto H, Romadhon PZ (2025) Thalassemia and iron overload cardiomyopathy: pathophysiological insights, clinical implications, and management strategies. Current Problems in Cardiology 50(1): 102911.
24. Faranoush M, Faranoush P, Heydari I, Foroughi-Gilvaee MR, Azarkeivan A, Parsai Kia A, Rohani F (2023) Complications in patients with transfusion-dependent thalassemia: a descriptive cross-sectional study. Health Science Reports 6(10): e1624.
25. Abid F, Husnain M (2025) Micronutrient-endocrine interactions: molecular mechanisms underlying hormonal regulation. Insights of Pakistan, Iran and the Caucasus Studies 4(1): 82–98.
26. Bazi A, Poodineh Moghadam M, Baranipour J, Noori Sanchooli H, Soleimani Samarkhazan H, Aval OS, Aghaei M (2025) Vitamin D deficiency as a modulator of outcomes in transfusion-dependent thalassemia: a narrative review. Health Science Reports 8(10): e71383.
27. Di Paola A, Marrapodi MM, Di Martino M, Giliberti G, Di Feo G, Rana D, Roberti D (2024) Bone health impairment in patients with hemoglobinopathies. International Journal of Molecular Sciences 25(5): 2902.
28. Jobanputra R, Gandhi AU, Rajani A (2025) Clinical and investigative profile of beta thalassemia major patients visiting a tertiary care center in Gujarat, India. Journal of the Indian Medical Association 123(2): 13–18.
29. Zhou X, Huang L, Wu J, Qu Y, Jiang H, Zhang J, Lian Q (2022) Impaired bone marrow microenvironment and stem cells in transfusion-dependent beta-thalassemia. Biomedicine & Pharmacotherapy 146: 112548.
30. Kazakou P, Nicolaides NC, Chrousos GP (2023) Basic concepts and hormonal regulators of the stress system. Hormone Research in Paediatrics 96(1): 8–16.

31. Di Marcello F, Di Donato G, d'Angelo DM, Breda L, Chiarelli F (2022) Bone health in children with rheumatic disorders. International Journal of Molecular Sciences 23(10): 5725.
32. Basu D, Sinha R, Sahu S, Malla J, Chakravorty N, Ghosal PS (2022) Identification of severity and oxidative stress biomarkers in β-thalassemia patients. Advances in Redox Research 5: 100034.
33. Lal A, Viprakasit V, Vichinsky E, Lai Y, Lu MY, Kattamis A (2024) Disease burden and unmet needs in α-thalassemia due to hemoglobin H disease. American Journal of Hematology 99(11): 2164–2177.
34. Pinto VM, Forni GL (2020) Management of iron overload in beta-thalassemia patients. International Journal of Molecular Sciences 21(22): 8771.
35. Jabeen R, Ansari I, Durrani B, Salman MJ, Mazhar L, Ansari MUH, Ansari SH (2024) Perceptions and experiences of females with β-thalassemia major. Transfusion Clinique et Biologique 31(4): 244–252.
36. Tantawy AAG, Tadros MAR, Adly AAM, Ismail EAR, Ibrahim FA, Eldin NMS, Ebeid FSE (2023) Endothelin-1 gene polymorphism and vascular dysfunction in pediatric β-thalassemia major. Cytokine 161: 156048.
37. Chia RW, Atem NV, Lee JY, Cha J (2024) Microplastic and human health with focus on pediatric well-being. Clinical and Experimental Pediatrics 68(1): 1.
38. Rossi F, Tortora C, Paoletta M, Marrapodi MM, Argenziano M, Di Paola A, Iolascon G (2022) Osteoporosis in childhood cancer survivors. Cancers 14(18): 4349.
39. Giordano P, Urbano F, Lassandro G, Faienza MF (2021) Mechanisms of bone impairment in sickle bone disease. International Journal of Environmental Research and Public Health 18(4): 1832.
40. Arumsari DK, Cahyadi A, Andarsini MR, Efendi F, Wardhani ANK, Larasati MCS, Ugrasena IDG (2024) Psychosocial aspects in children with transfusion-dependent thalassemia. Vulnerable Children and Youth Studies 19(1): 124–139.