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Review

Endocrine morbidity and growth impairment in β-thalassemia intermedia: Insights from 25 years of multinational studies

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Abstract. *Background:* β-thalassemia intermedia (β-TI) encompasses a spectrum of clinical severity. Although patients typically require fewer transfusions than those with β-thalassemia major, they remain vulnerable to iron overload from increased intestinal absorption and occasional transfusions. This iron accumulation, combined with chronic anemia, can impair growth and predispose to a wide range of endocrine disorders. *Objectives:* This review brings together validated evidence on growth and endocrine outcomes in β-TI, describing prevalence patterns across different regions, assessing differences related to transfusion practices, and evaluating the quality of available research. *Methods:* A structured search of PubMed, Scopus, and Google Scholar (inception–March 2025) identified studies that reported the prevalence of short stature, growth hormone deficiency (GHD), hypogonadism, delayed puberty, hypothyroidism, hypoparathyroidism, diabetes mellitus (DM), and impaired glucose tolerance (IGT) in patients with clinically or genetically confirmed β-TI. Studies enrolling at least 10 patients and using established clinical or laboratory criteria were included. Data extraction covered study design, sample characteristics, transfusion history, diagnostic definitions, and iron indices. Methodological quality was graded using modified MINORS and selected Cochrane criteria. *Results:* Eighteen eligible studies from the Middle East, Asia, the Mediterranean, and North America were reviewed. The prevalence of short stature ranged from 21% in non-transfused Qatari patients to 46% in Iranian non-transfused cohorts. Where endocrine testing was performed, GHD affected 26–31% of patients. Hypogonadism and delayed puberty were present in 5–25%, with higher rates in intermittently transfused groups and those with greater iron load. Hypothyroidism ranged from absent in some pediatric series to over 20% in older cohorts, with subclinical forms being more frequent. Hypoparathyroidism was uncommon (<2%: 4.4%). Abnormal glucose metabolism was reported in 2–25% of cases, correlating closely with hepatic iron content. Large multicenter datasets generally reported lower prevalence figures than smaller single-center studies, likely reflecting differences in monitoring and chelation access. *Conclusions:* Growth failure and endocrine disturbances are frequent in β-TI, regardless of transfusion dependence. Prevalence varies by geography, iron burden, and healthcare resources. These findings support the need for standardized endocrine surveillance and coordinated multicenter studies to inform earlier detection and targeted intervention strategies. (www.actabiomedica.it)

Key words: β-thalassemia intermedia, growth impairment, endocrine disorders, iron toxicity, global geographic disparities.

Introduction

Beta-thalassemias (β-thal) are hereditary blood disorders caused by reduced or absent synthesis of the β-globin chains of hemoglobin, leading to ineffective erythropoiesis. β-thal can be subdivided into two main types depending on the clinical features: Thalassemia Major (β-TM) patients, who are transfusion-dependent thalassemia (TDT), and Thalassemia Intermedia (TI) patients, who are non-transfusion-dependent thalassemia (NTDT) but may need transfusions occasionally or in specific clinical settings. β-thalassemia intermedia (β-TI) is a clinically variable condition that falls between the severe, transfusion-dependent β-thalassemia major and the asymptomatic carrier state. Ineffective erythropoiesis and peripheral hemolysis result in anaemia-related symptoms and clinical complications that cause a substantial burden, affect survival and impair quality of life. Over time, this persistent anemia can result in organ complications, including disturbances in endocrine function. A major contributor is iron overload, which arises mainly from excessive intestinal absorption and, in some cases, from occasional blood transfusions. Treatment options targeting β-TI and its complications are limited and include splenectomy, red blood cell (RBC) transfusions, iron chelation therapy, and hydroxyurea in some cases (1,2). Studies from Middle Eastern countries—particularly Iran, Egypt, Qatar, and Iraq—have documented that a considerable proportion of patients with TI present with growth failure, delayed puberty, or hypogonadism. These issues are strongly linked to elevated serum ferritin levels and lower hemoglobin, even among those not dependent on transfusions (3,7–11). Male patients appear especially at risk, with growth problems becoming more pronounced during adolescence (3–5). The spectrum of endocrine involvement in β-TI is wide. It includes hypogonadism, thyroid dysfunction, glucose intolerance, diabetes mellitus, and, less frequently, hypoparathyroidism or adrenal insufficiency (5–15). Thyroid disease, for example, has been observed in 14–23% of patients in Iranian and Iraqi cohorts, with many cases remaining undetected due to a lack of systematic screening (8–11). Similarly, glucose metabolism disorders affect up to 16% of adolescents and young adults with β-TI, often related to pancreatic iron deposition and liver impairment from chronic iron overload, regardless of transfusion status (2,12,13). Despite how common these complications are, routine endocrine follow-up is still inconsistent worldwide. In resource-limited healthcare systems, screening often occurs only after symptoms emerge, delaying diagnosis and worsening long-term outcomes—particularly in areas such as fertility, osteoporosis and adult height (1,3). Marked geographical variation also exists in how frequently these complications are reported, reflecting differences in healthcare resources. Countries with well-established thalassemia programs—such as Italy, Cyprus, and certain regions of Iran—provide regular follow-up, access to iron chelation, and proactive endocrine care. By contrast, in parts of Africa and Asia, late diagnosis and limited treatment availability contribute to higher rates of complications (15–19). This review brings together prevalence data on growth and endocrine complications in β-TI from diverse regions, relying exclusively on validated, peer-reviewed studies. By underscoring the impact of transfusion practices, iron burden, and healthcare access, it highlights the gaps in current monitoring strategies and emphasizes the need for coordinated, prospective multicenter research—especially across low- and middle-income countries (3,7,11–18).

Objectives

This review aimed to bring together and critically evaluate the available evidence on growth and endocrine complications in patients with β-TI across different regions and healthcare systems. The specific goals were to:

1. Estimate the prevalence of growth retardation, growth hormone deficiency (GHD), hypogonadism, hypothyroidism, hypoparathyroidism, diabetes mellitus (DM), and impaired glucose tolerance (IGT) in β-TI.
2. Compare the spectrum of endocrine involvement between patients who remain transfusion-independent and those who receive intermittent transfusions, with reference to patterns seen in β-TM where appropriate.

3. Explore geographic and population-level differences in complication rates, considering the influence of genetic background, environmental factors, and healthcare resources.
4. Assess the methodological quality of existing studies, focusing on study design, consistency of diagnostic criteria, and adequacy of sample sizes.

Materials and Methods

Search strategy

We carried out a systematic search in PubMed/MEDLINE, Scopus, and Google Scholar, covering all publications up to March 2025. The search combined free-text terms and MeSH headings such as *beta thalassemia intermedia*, *non-transfusion-dependent thalassemia*, *growth retardation*, *endocrine complications*, *hypogonadism*, *hypothyroidism*, *hypoparathyroidism*, *diabetes mellitus*, and *iron overload*. Boolean operators ("AND", "OR") were used to maximize sensitivity. In addition, reference lists from relevant studies, reviews, and guidelines were screened manually. Grey literature—including conference abstracts and institutional reports—was included if it provided extractable prevalence data.

Eligibility criteria

Studies were included if they met the following requirements:

- ***Population:*** Patients diagnosed with β-TI confirmed by genetic analysis or well-defined clinical classification.
- ***Outcomes:*** Prevalence data or clinical/laboratory confirmation of at least one of the following: short stature, GHD, delayed puberty, hypogonadism, hypothyroidism, hypoparathyroidism, IGT or DM.
- ***Design:*** Observational studies (cross-sectional or cohort), registry-based analyses, or reviews presenting original prevalence data.
- *Language:* English.

Studies were excluded if they:

- Included fewer than 10 patients.
- Focused only on β-TM without reporting separate data for β-TI.
- Reported solely biochemical markers without clear prevalence estimates.

Data extraction

Two reviewers independently extracted information using a standardized form. Data collected included:

- Study details (first author, year, and journal).
- Study design and setting (single-center, multicenter, or registry-based).
- Sample size, age distribution, sex, and transfusion status.
- Reported prevalence of each growth and endocrine abnormality.
- Diagnostic definitions and criteria used.
- Indicators of iron overload (serum ferritin; liver iron concentration, when available).
- Methodological strengths and limitations noted by the authors.

Quality assessment

The quality of each study was evaluated using an adapted version of the Methodological Index for Non-Randomized Studies (MINORS), supplemented with elements from the Cochrane Risk of Bias tool. Assessment focused on study design appropriateness, clarity of diagnostic definitions, adequacy of sample size, use of comparison or control groups, and reporting of potential confounders. Based on these domains, studies were categorized as very high, high, moderate, or low-quality assessments. Figure 1 illustrates the process of study identification, screening, eligibility assessment, and final inclusion for qualitative synthesis. Out of 186 records initially retrieved, 142 remained after removing duplicates. Following screening and full-text evaluation, 18 studies

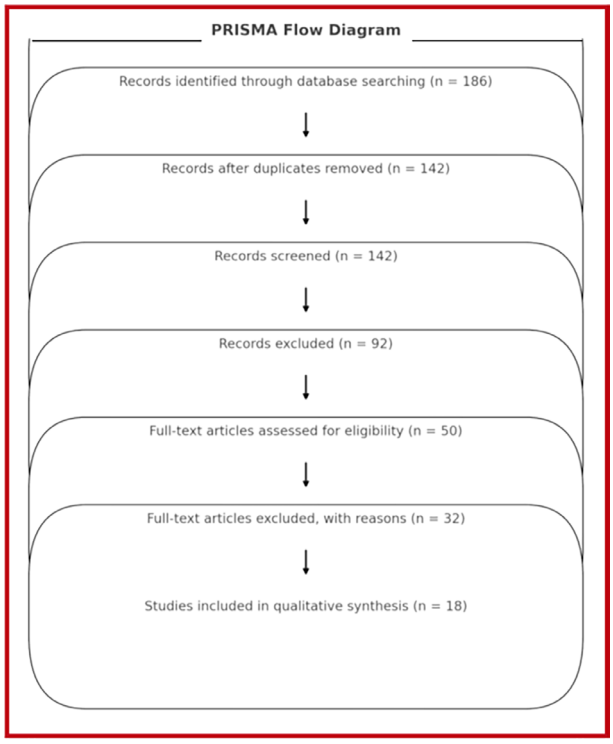

Figure 1. PRISMA flow diagram of study selection.

met the eligibility criteria and were included in the review.

Results

Eighteen studies were analyzed, reporting data from the Middle East, Asia, the Mediterranean, and North America. These studies differed significantly in design, patient numbers, and transfusion and chelation practices. However, they consistently reported a considerable burden of growth and endocrine complications in patients with β-thalassemia intermedia (Table 1).

The prevalence of growth and endocrine complications in β-TI shows considerable variation between studies but consistently reflects a significant clinical burden, largely driven by iron overload and transfusion history.

- ***Growth impairment*:** Short stature is seen in about 21–46% of patients, particularly in those not receiving regular transfusions. For comparison, β-TM shows similar or slightly higher rates (40–50%), highlighting the role of pituitary iron deposition.
- ***Growth hormone deficiency (GHD):*** Reported in 26–31% of both β-TI and β-TM, contributing to poor growth outcomes.
- ***Hypogonadism and delayed puberty:*** Affect 10–25% of patients, more commonly in those transfused irregularly.
- ***Glucose abnormalities*** Diabetes mellitus and impaired glucose tolerance occur in 2–25% of cases, strongly linked to liver iron accumulation.
- ***Thyroid dysfunction and Hypoparathyroidism:*** Hypothyroidism ranges from very low rates in non-transfused groups to over 20% in some cohorts. Hypoparathyroidism is uncommon (<5%).
- Multicenter and registry data confirm these trends, with slightly lower complication rates in β-TI compared with β-thalassemia major due to differences in transfusion dependence and disease severity. Importantly, even without transfusion, increased intestinal iron absorption drives significant endocrine dysfunction.

Across regions, endocrine abnormalities are consistently tied to iron overload, which can develop even in the absence of regular transfusions due to increased gastrointestinal absorption. In addition, population-specific genetic mutations and regional profiles appear to further influence clinical outcomes and complication risks.

In summary:

- ***Short stature/growth retardation:*** Reported in 21–46% of cases. Rates are lower in some non-transfused Middle Eastern cohorts but higher in certain Iranian studies. North American data also confirm growth impairment, though generally less pronounced than in β-TM.
- ***Hypogonadism/delayed puberty:*** Prevalence ranges widely from about 5% to 25%, with differences largely explained by transfusion practices and iron burden.

Table 1. Summary of key literature on growth and endocrine outcomes in β-thalassemia intermedia.

Citation / Source	Summary / Key Points	Growth Findings	Endocrine Findings
Cappellini MD et al., 2008 (1)	TI clinical features, complications, chelation guidance	Growth retardation possible	Delayed puberty, hypothyroidism, diabetes (iron overload–related)
Musallam KM et al., 2012 (2)	Clinical perspective; iron overload–driven morbidity	Growth delay less than TM	Hypogonadism, hypothyroidism, DM
Yassin MA et al., 2019 (3)	TI cohort (NTD vs OTD)	Short stature 25%; low IGF-1 36%	DM 25%; hypogonadism 10.7%; low IGF
Inati A et al., 2015 (4)	Review of bone and endocrine complications	Growth and bone retardation; delayed bone age	Hypogonadism, DM, HT, HPT, osteoporosis
Karamifar H et al., 2006 (5)	TI endocrine evaluation (n=93)	Short stature 46%; GH deficiency 31%	HT 21.5%, HPT 1%, DM 2%, pubertal failure
Karimi M et al., 2020 (6)	Multicenter TI endocrine study (n=1093)	Not specified	Hypogonadism 10%, HT 5.3%, osteoporosis 22%
Rafsanjani KA et al., 2011 (7)	TI complications over 14 years	Not numerically reported	Delayed puberty 15.7%, DM 1.9%
Zekavat OR et al., 2014 (8)	Hypothyroidism in TI on/off hydroxyurea	—	Hypothyroidism in both groups
Abdulla JA & Polus RK, 2019 (9)	Thyroid comparison TM vs TI	—	Overt/subclinical hypothyroidism in high ferritin
Abdel-Razek AR et al., 2013 (10)	Thyroid dysfunction in Egyptian TI	—	Higher thyroid abnormalities with age and ferritin
Abdulwahid DA & Hassan MK, 2013 (11)	α/β-TI cohort (n=152)	Short stature common	Osteoporosis, hypogonadism, HT
Luo Y et al., 2019 (12)	NTDT glucose metabolism cohort	—	DM/IGT 11.4% linked to iron load
Vogiatzi MG et al., 2009 (13)	NA registry	TI < TM for growth delay	Hypogonadism, HT, DM in TI (less than TM)
Carsote M et al., 2022 (14)	Review — TI endocrine spectrum	Growth impairment noted	Hypogonadism, DM, HT, adrenal insufficiency
De Sanctis V et al., 2018 (15)	ICET-A survey on HPT in TM/TI	—	HPT uncommon (4.4%); screening advised
Faranoush P et al., 2023 (20)	Review — endocrine complications	Growth disturbance when chelation poor	Hypogonadism, HT, HPT, DM, adrenal insufficiency
Langer AL, 2024 (21)	GeneReviews — TI & iron overload	Growth retardation risk	Hypogonadism, HT, HPT, DM
Meloni A et al., 2025 (22)	TI cross-sectional survey	Short stature described	Endocrinopathies common: hypogonadism, HT, DM

Abbreviations: NTD = Non-transfused; OTD = occasionally/infrequently transfused; TM = thal major; TI = thal intermedia; DM = diabetes mellitus; HPT = hypoparathyroidism; HT= primary hypothyroidism; IFG = impaired fasting glucose; GHD = growth hormone deficiency; PTH= parathyroid hormone.

- ***Diabetes mellitus and glucose intolerance:*** Reported from as low as 2% in earlier Iranian series to over 25% in some Asian and Middle Eastern non–transfusion-dependent patients, strongly linked to hepatic iron overload.
- ***Hypothyroidism:*** Shows marked regional variability—from negligible levels in non-transfused groups to more than 20% in some Iranian cohorts. In Egypt, pediatric thyroid dysfunction has been associated with both iron burden and advancing age.
- ***Hypoparathyroidism:*** Rare overall, affecting only about 1% of patients in regional studies.
- Quality assessment was performed using appropriate tools—Cochrane Risk of Bias 2.0 for randomized controlled trials and the MINORS criteria for observational studies (Table 3).

In brief, as expected in rare disease research, randomized controlled trials (RCTs) were scarce, and the majority of available evidence derived from observational designs. The Foster plot highlights distinct trends in the quality and scope of research on growth and endocrine outcomes in β-I (Figure 2).

Synthesis of collected data

Most studies are rated as high or very high quality, with recent large multicenter investigations providing comprehensive coverage across multiple endocrine domains. Moderate-quality studies, while narrower in focus and often based on smaller cohorts, still contribute valuable insights into specific complications. Earlier high-quality studies add important historical context, though their relevance to present-day clinical care is sometimes limited. Reviews and clinical guidelines, despite not offering original patient data, remain highly reliable and continue to shape practice. Because of heterogeneity in study design, diagnostic criteria, and reported outcomes, a narrative synthesis was applied. Where possible, prevalence ranges were calculated and compared across regions, transfusion patterns, and study quality. Descriptive statistics were used to highlight key patterns, and a Foster plot (Figure 2) provided a visual representation of the relationship between study quality, sample size, and year of publication. Collectively, the evidence base has grown stronger in recent years, driven by robust multicenter research and complemented by smaller, detailed single-center reports.

Discussion

This review demonstrates that β-thalassemia intermedia (β-TI) is far from a benign disorder. Even without the need for regular transfusions, patients frequently experience growth impairment and endocrine dysfunction. Across studies summarized in Tables 1 and 2, short stature was reported in roughly 20–50% of cases, with higher rates in older, non-transfused, or poorly monitored groups. Differences between studies reflect variations in anemia severity, iron accumulation, chelation practices, and healthcare quality. Chronic anemia and tissue hypoxia impair hypothalamic–pituitary–growth axis activity, while iron overload—present even in non-transfusion-dependent patients—can damage pituitary somatotroph cells (27–30).

Growth hormone deficiency (GHD), detected in about one-quarter to one-third of patients tested, further contributes to impaired growth. Pituitary siderosis is the main mechanism, resulting from both transfusion-related iron loading and increased intestinal absorption in non-transfused patients (31–36).

Malnutrition, chronic inflammation, and late diagnosis add to the risk, particularly in resource-limited settings (37,38). Hypogonadism and pubertal delay affect 5–25% of patients due to combined hypothalamic–pituitary–gonadal axis dysfunction. Iron deposition reduces LH and FSH secretion, while chronic illness and nutritional deficits suppress Gn-RH pulsatility. In a cross-sectional study of 168 β-TI patients, higher liver iron concentrations on MRI were significantly associated with hypogonadism and osteoporosis (39).

Almost all complications were more frequent in transfusion-dependent thalassemia (TDT) compared with non–transfusion-dependent thalassemia (NTDT) (40,41). Geographic comparisons (Table 2) reinforce this: in Qatar, lumbar spine osteoporosis

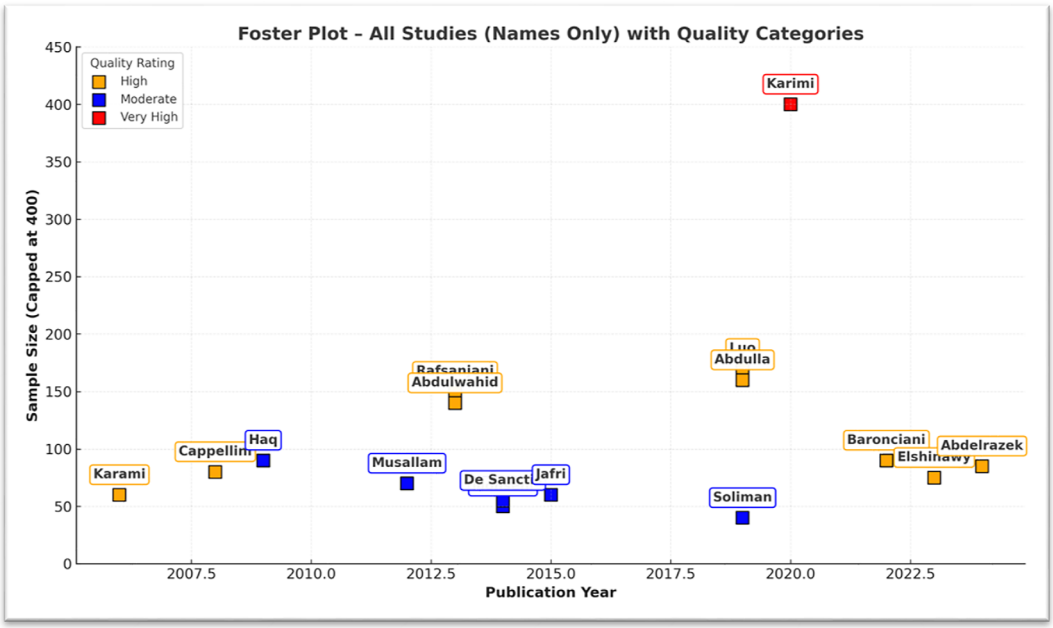

Figure 2. Quality and temporal distribution of studies on endocrine and growth outcomes in β-thalassemia intermedia.

was significantly higher in TDT than NTDT patients (69.8% vs. 40%) (3,7,11,42).

Thyroid dysfunction, both clinical and subclinical, is another recognized complication, with prevalence ranging from negligible in pediatric cohorts to over 20% in older Iranian patients. Subclinical disease is often more frequent than overt hypothyroidism, especially in individuals with long-standing disease and high ferritin levels (8–11). Iron toxicity on thyroid follicular cells, combined with pituitary–thyroid axis disruption, underpins the pathophysiology (43). In many low-resource countries, lack of routine screening delays diagnosis until symptoms are advanced (44).

Abnormal glucose metabolism is also common, with dysglycemia reported in 2–25% of cases, strongly correlating with hepatic iron load. Both pancreatic β-cell siderosis and hepatic insulin resistance contribute to impaired glucose tolerance and diabetes (3,12,20,40). These findings emphasize the importance of MRI-based hepatic iron monitoring, as serum ferritin alone may underestimate organ-specific overload.

Hypoparathyroidism remains rare (1–4.4%) but is linked to severe iron excess. Because it can be clinically subtle, targeted biochemical screening is important in patients with persistently high ferritin or suspicious features (5,7,15,45,46). Bone disease, however, is a major burden. Reduced bone mineral density (BMD) is consistently reported in adults with β-TI worldwide. Karimi et al. (47) documented markedly decreased BMD and bone mineral content in both thalassemia major and intermedia, while Baldini et al. (48) found that 76% of adults with β-TI had skeletal pathology, including osteoporosis in 37% and osteopenia in 39%. Pollack et al. also observed significantly reduced BMD in β-TI compared with healthy controls, underscoring the skeletal impact even in NTDT patients (28).

Complication rates differ substantially by region. Countries with long-established thalassemia programs (Italy, Cyprus, parts of Iran) report lower prevalence, reflecting early chelation, structured endocrine screening, and multidisciplinary care. By contrast, higher complication rates in Iraq, parts of Egypt, and other resource-limited areas reflect delayed recognition and limited therapeutic options (15–19). Chelation therapy plays a decisive role in mitigating endocrine risk. Evidence from β-thalassemia major shows that timely, sustained chelation can reverse some endocrine and cardiac complications (49,50).

Table 2. Prevalence of growth and endocrine abnormalities in β-thalassemia intermedia across countries and regions.

Country / Region	Reference(s)	Growth abnormalities (Prevalence)	Endocrine abnormalities (Prevalence)	Notes / Key points
Qatar	Yassin et al., 2019 (3)	Short stature ~21% (non-transfused), 33% (infrequent transfusion), overall 25%	DM 16% (NTD), 44% (OTD), overall 25%; Hypogonadism 5% (NTD), 22% (OTD); no HT was reported	Cohort of 28 β-TI patients analyzed with liver iron correlations
Iran	Karamifar et al., 2006 (5); Rafsanjani et al., 2011 (7)	Short stature 46% (Karamifar); Not specified (Rafsanjani)	HT 21.5%, HPT 1%, DM 2% (Karamifar); delayed puberty 15.7%, DM 1.9% (Rafsanjani)	Mostly non-transfused cohorts; endocrine complications increase with age
North America	Vogiatzi et al., 2009 (13)	Stunting/growth retardation noted but less than β-TM	Hypogonadism, DM, and HT less prevalent than in β-TM	Multi-center registry data
Iraq (Basra)	Abdulwahid and Hassan, 2013 (11)	Short stature common	Hypogonadism, HT, osteoporosis	Descriptive regional study
China (NTDT patients)	Luo et al., 2019 (12)	Not specifically reported	Glucose abnormalities (DM/IGT) in 11.4%	Focused on NTDT non-transfusion dependent patients
Egypt	Abdel-Razek et al., 2013; (10) , Abdulla and Polus, 2019 (9)	Not focused.	Thyroid dysfunction are documented with age and iron load	Pediatric populations studied
Southeast Asia	General epidemiology (23)	High prevalence areas for β-thalassemias; limited data for growth disorders.	Iron overload-related endocrinopathies are expected	Highest carrier frequencies noted here (e.g., HbE/β-thalassemia common)
Qatar and the Surrounding Middle East	Molecular data in Yassin et al., 2019 (3,24)	Not focused.	Mutation spectrum typical; endocrinopathies related to iron overload	Consanguinity contributes to prevalence
Mediterranean (Cyprus, Sardinia)	Epidemiology general (25,26)	The highest carrier frequency is reported in Cyprus (14%) and Sardinia (10.3%)	Iron overload-associated endocrinopathies are expected	High carrier rates, but detailed endocrine data are less available

Abbreviations: TI = thal intermedia; NTDT = non-transfusion-dependent thalassemia; OTD =occasionally/ infrequently transfused; DM = diabetes mellitus; IG T= impaired glucose tolerance; HPT = hypoparathyroidism; HT= primary hypothyroidism.

For β-TI, individualized regimens tailored to serum ferritin, liver iron, and MRI-based pancreas/pituitary iron assessments are most effective (49–51). Genetic factors also shape endocrine risk. Ameliorating variants such as α-thalassemia coinheritance or hereditary persistence of fetal hemoglobin (HPFH) reduce anemia and iron load, while severe β-globin mutations or iron-loading genetic modifiers accelerate injury (52,53,54). Reliance on ferritin alone underestimates organ damage (55); incorporation of MRI T2* imaging into follow-up protocols allows better risk stratification and optimization of chelation (56).

Conclusion

β-thalassemia intermedia (β-TI) is far from a mild condition. Even in the absence of regular transfusions,

Table 3. Methodological quality profile of endocrine literature in β-thalassemia intermedia.

Quality dimension	Status in the reported studies
Design	Mostly observational (cross-sectional, cohorts), few or no RCTs
Randomization	Not applicable for most
Control group	Largely absent
Sample size	Variable: some small, some large multicenter
Bias assessment	Rarely formalized in original studies
Outcome measure precision	Moderate-high (clinical, laboratory-based)
Evidence strength (GRADE)	Low to moderate (observational evidence)
Risk of confounding	Moderate to high potential

many patients develop growth restriction and a wide range of endocrine complications. The frequency and type of these problems vary across regions, influenced by iron overload, healthcare resources, and the quality and timeliness of monitoring and adherence to iron chelation therapy. Although overall prevalence is generally lower than in β-thalassemia major, the burden remains substantial—particularly for hypogonadism, thyroid dysfunction, and disturbances in glucose metabolism. Importantly, endocrine complications in β-TI do not only appear late in the disease course; they may emerge early and progress silently. This underscores the need for structured, lifelong screening and timely interventions in all patients, regardless of transfusion status, to safeguard growth, fertility, and long-term metabolic health.

Recommendations

β-TI continues to pose important clinical challenges, as many patients develop growth impairment and endocrine dysfunction even without regular transfusion support. The type and frequency of these complications vary by region and are shaped by iron overload, healthcare quality, and the adequacy of monitoring and chelation practices. While complication rates are generally lower than in β-TM, they remain considerable—especially for hypogonadism, thyroid disorders, and glucose metabolism abnormalities. Because endocrine complications may arise early and often progress silently, all patients with â-TI require structured, lifelong surveillance and timely intervention. Comprehensive monitoring programs—irrespective of transfusion status—are essential to preserving growth, reproductive health, and long-term metabolic stability.

Strengths

This review gives evidence from a variety of studies conducted across many countries and healthcare systems. By utilizing data from large, multicenter cohorts with perceptions from smaller, single-center reports, it provides a broad perspective and meaningful clinical details. Importantly, a methodological quality appraisal was included, permitting weighing the findings in light of study design and rigor. Efforts were also made to apply consistent clinical and laboratory definitions, which improves the reliability of comparisons across studies.

Limitations

There are, however, very few interventional or long-term follow-up trials among the majority of available studies, which are observational. It is challenging to establish distinct cause-and-effect relationships as a result. Direct comparisons between various regions are further complicated by differences in diagnostic criteria, outcome measures, and follow-up duration. Additionally, a number of reports lacked organ-specific iron assessment techniques (like MRI T2*), which limits the precision of the correlation between iron burden and endocrine outcomes.

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Ethical Statement: This review is based exclusively on previously published studies and did not involve new human or animal research. Ethical approval was therefore not required.

Use of AI: Not used.

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