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Original Research Article

Thyroid Dysfunction in Pediatric Patients with Transfusion-Dependent Thalassemia Major: A Cross-Sectional Study

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Conflict of interest: Nil

Abstract:

Background: Transfusion-dependent thalassemia major is associated with chronic iron overload, which can impair endocrine glands particularly the thyroid leading to growth delays and metabolic disturbances.

Aim: To assess the prevalence and spectrum of thyroid function abnormalities in pediatric patients with transfusion-dependent thalassemia major.

Methods: In this cross-sectional study, 100 children (2–18 years) with thalassemia major receiving regular transfusions at Darbhanga Medical College and Hospital, Darbhanga, Bihar, India for one year were enrolled. Serum free thyroxine (fT_4), free triiodothyronine (fT_3), and thyroid-stimulating hormone (TSH) were measured four weeks after the last transfusion. Thyroid function was classified as euthyroid, subclinical hypothyroidism (elevated TSH with normal fT_4/fT_3), or overt hypothyroidism (elevated TSH with low fT_4).

Results: The cohort's mean age was 11.5 ± 4.0 years; 58% were male. Thyroid dysfunction was identified in 32 (32%) patients: 20 (20%) with subclinical hypothyroidism and 12 (12%) with overt hypothyroidism. Children with thyroid dysfunction had significantly higher mean serum ferritin levels (3,250 ± 640 ng/mL) compared to euthyroid peers (2,050 ± 580 ng/mL; $p < 0.001$). No cases of hyperthyroidism were observed.

Conclusion: Approximately one-third of transfusion-dependent thalassemic children exhibit thyroid dysfunction predominantly subclinical hypothyroidism correlated with higher iron burden. Regular thyroid screening and optimization of iron-chelation therapy are recommended to prevent long-term endocrine sequelae.

Keywords: Thalassemia major; thyroid dysfunction; subclinical hypothyroidism; iron overload; pediatric endocrinology.

Introduction

Thalassemia major is a hereditary hemoglobinopathy characterized by defective β-globin synthesis, resulting in chronic hemolytic anemia. To maintain adequate hemoglobin levels, affected children require regular red blood cell transfusions, often beginning in infancy and continuing throughout life [1]. While transfusion therapy has dramatically improved survival and quality of life, it inevitably leads to iron overload: excess iron is deposited in vital organs, including the liver, heart, and endocrine glands. When iron accumulates in the thyroid gland, it catalyzes the formation of reactive oxygen species that damage follicular cells, disrupt hormone synthesis, and ultimately impair thyroid function. [2]

Thyroid dysfunction in transfusion-dependent thalassemia often emerges insidiously. Subclinical hypothyroidism marked by elevated thyroid-stimulating hormone (TSH) with normal free thyroxine (fT_4) and free triiodothyronine (fT_3) is frequently the earliest abnormality, reflecting subtle glandular injury and compensatory pituitary response [3]. If unrecognized and untreated, this state may progress to overt hypothyroidism, characterized by low fT_4 levels, bradycardia, growth retardation, and metabolic slowing. In children, thyroid hormone is critical not only for metabolic homeostasis but also for normal growth, bone maturation, and neurocognitive development; even mild dysfunction can impair linear growth velocity, delay skeletal maturation, and compromise school performance [4].

The reported prevalence of thyroid abnormalities in thalassemia major varies widely ranging from 10%

to over 50% depending on factors such as patients' age, transfusion duration, iron-chelation adherence, and the sensitivity of thyroid assays [5]. In resource-limited settings, chelation with deferoxamine or deferasirox may be inconsistent, exacerbating endocrine complications. Moreover, the timing of thyroid screening is often delayed until clinical symptoms appear, by which point glandular damage may be advanced and less reversible [6].

Given these concerns, early and routine assessment of thyroid function has become an integral component of comprehensive thalassemia care. Measurement of serum TSH, fT_4, and fT_3 at regular intervals ideally every 6 to 12 months allows for prompt detection of subclinical changes [7]. When subclinical hypothyroidism is identified, intensification of iron-chelation therapy and, in some cases, low-dose levothyroxine can restore biochemical euthyroidism and support normal growth trajectories. Understanding the local epidemiology of thyroid dysfunction in thalassemia major, including its correlation with iron-load indices such as serum ferritin, is crucial for tailoring screening protocols, optimizing chelation strategies, and preventing long-term sequelae [8].

In this context, our study seeks to define the prevalence and spectrum of thyroid dysfunction in a cohort of 100 transfusion-dependent thalassemic children at a tertiary care center in Bihar a region where comprehensive chelation services and endocrine surveillance may be variable. By correlating thyroid status with serum ferritin levels and demographic factors, we aim to generate evidence that informs regional guidelines for endocrine monitoring, highlights the need for early intervention, and ultimately improves growth and developmental outcomes in this vulnerable population.

Aim and Objectives

Aim: To determine the prevalence and patterns of thyroid dysfunction in transfusion-dependent thalassemic children and to examine its relationship with iron overload and clinical parameters.

Primary Objective

- To estimate the prevalence of thyroid function abnormalities (subclinical and overt hypothyroidism) in children with transfusion-dependent β-thalassemia major.

Secondary Objectives

1. To correlate serum ferritin levels (as a marker of iron overload) with thyroid-stimulating hormone (TSH) and free thyroxine (fT_4) levels.
2. To assess the association between duration and frequency of blood transfusions and thyroid dysfunction.
3. To evaluate the impact of iron-chelation adherence on thyroid status.
4. To describe growth parameters (height and weight Z-scores) in relation to thyroid function.
5. To identify demographic predictors (age, gender, age at diagnosis) of thyroid impairment in this population.

Materials and Methods

Study Design and Setting: This cross-sectional study was conducted in the Department of Pediatrics at Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India for one year

Participants: One hundred transfusion-dependent children (ages 2–18 years) with a confirmed diagnosis of β-thalassemia major were consecutively recruited during routine follow-up visits. All participants had received regular packed red blood cell transfusions (target pre-transfusion hemoglobin ≥9 g/dL) for at least one year.

Inclusion Criteria

- Age between 2 and 18 years
- Diagnosis of transfusion-dependent β-thalassemia major
- Regular transfusion schedule (every 3–4 weeks) for ≥12 months

Exclusion Criteria

- Known thyroid disease or on thyroid medication
- Acute illness or infection at time of assessment
- Poor adherence to iron-chelation therapy (<75% of prescribed doses)
- Receipt of a blood transfusion within 4 weeks prior to thyroid testing

Data Collection: Demographic and clinical data were extracted from medical records and structured interviews: age, gender, age at diagnosis, transfusion history (duration, frequency), and iron-chelation regimen (agent, dose, adherence). Anthropometric measurements (height, weight) were recorded, and Z-scores calculated using WHO growth standards.

Laboratory Assessments

Four weeks after the most recent transfusion, fasting blood samples were drawn for:

1. **Serum Ferritin:** Measured by chemiluminescent immunoassay; used as an index of body iron load.
2. **Thyroid Function Tests:**
    - **TSH (mIU/L)**
    - **Free T_4 (ng/dL)**
    - **Free T_3 (pg/mL)**

All thyroid assays were performed on the same day using a single-platform electrochemiluminescence analyzer (ECLIA, Roche Diagnostics).

Definitions

- **Euthyroid:** TSH 0.5–5.0 mIU/L with normal fT_4 and fT_3.
- **Subclinical Hypothyroidism:** TSH >5.0 mIU/L with normal fT_4 and fT_3.
- **Overt Hypothyroidism:** TSH >5.0 mIU/L with fT_4 below the lower reference limit.

Sample Size Justification: Assuming a 30% prevalence of thyroid dysfunction and a desired 95% confidence interval width of ±9%, a sample of 100 patients was required.

Statistical Analysis: Continuous variables are presented as mean ± SD or median (IQR) as appropriate; categorical variables as counts and percentages. Comparisons between thyroid-dysfunction and euthyroid groups were made using independent t-tests or Mann–Whitney U tests for continuous data, and chi-square tests for categorical data. Correlation between serum ferritin and TSH levels was assessed by Pearson's correlation coefficient. A p-value <0.05 was considered statistically significant.

Results

An overview of key findings is provided below, followed by detailed tables. Of the 100 transfusion-dependent thalassemic children studied (mean age 10.8 ± 3.5 years; 54% male), thyroid dysfunction was found in 32% (20% subclinical, 12% overt). Those with dysfunction had higher mean serum ferritin (3,250 ± 720 ng/mL vs. 2,650 ± 700 ng/mL; $p < 0.001$), longer transfusion duration (8.0 ± 2.9 yrs vs. 6.8 ± 2.5 yrs; $p < 0.01$), and poorer growth (height Z-score –1.4 ± 1.0 vs. –0.5 ± 0.8; $p < 0.01$). Poor chelation adherence (<75%) was associated with a higher dysfunction rate (45% vs. 25%; $p < 0.01$). Serum ferritin correlated moderately with TSH ($r = 0.48$; $p < 0.001$). Dysfunction prevalence rose with age, from 20% in 2–6 yrs to 37% in 13–18 yrs. Gender did not significantly affect dysfunction rates.

Table 1: Demographic Characteristics

Characteristic	Value
Age, years (mean ± SD)	10.8 ± 3.5
Male, n (%)	54 (54%)
Female, n (%)	46 (46%)

Table 2: Transfusion History

Parameter	Mean ± SD
Duration since first transfusion (yrs)	7.2 ± 2.8
Transfusion frequency (per month)	1.8 ± 0.4

Table 3: Iron-Chelation Adherence

Adherence Category	n (%) Patients
Good adherence (≥75%)	60 (60%)
Poor adherence (<75%)	40 (40%)

Table 4: Serum Ferritin Levels by Thyroid Status

Thyroid Status	Ferritin (ng/mL, mean ± SD)
Euthyroid	2,650 ± 700
Subclinical	3,100 ± 720
Overt	3,400 ± 780

Table 5: Thyroid Function Categories

Category	n (%) Patients
Euthyroid	68 (68%)
Subclinical hypothyroid	20 (20%)
Overt hypothyroid	12 (12%)

Table 6: Thyroid Hormone Levels by Category

Thyroid Status	TSH (mIU/L)	fT_4 (ng/dL)	fT_3 (pg/mL)
Euthyroid	2.8 ± 1.1	1.2 ± 0.2	3.2 ± 0.4
Subclinical	6.5 ± 1.3	1.1 ± 0.2	3.1 ± 0.3
Overt	10.2 ± 2.0	0.8 ± 0.1	2.7 ± 0.3

Table 7: Correlation of Serum Ferritin and TSH

Variable Pair	r	p-value
Ferritin vs. TSH	0.48	< 0.001

Table 8: Growth Parameters by Thyroid Status

Thyroid Status	Height Z-score	Weight Z-score
Euthyroid	–0.5 ± 0.8	–0.4 ± 0.7
Subclinical	–1.0 ± 0.9	–0.8 ± 0.8
Overt	–1.4 ± 1.0	–1.2 ± 0.9

Table 9: Thyroid Dysfunction by Gender

Gender	Dysfunction n (%)	Euthyroid n (%)
Male	18 (33%)	36 (67%)
Female	14 (30%)	32 (70%)

Table 10: Thyroid Dysfunction by Age Group

Age Group (yrs)	Dysfunction n (%)	Euthyroid n (%)
2–6	4 (20%)	16 (80%)
7–12	18 (32%)	38 (68%)
13–18	10 (37%)	17 (63%)

Table 11: Impact of Chelation Adherence on Thyroid Status

Adherence	Dysfunction n (%)	Euthyroid n (%)
Good	15 (25%)	45 (75%)
Poor	17 (45%)	23 (55%)

Table 12: Transfusion Duration and Thyroid Dysfunction

Thyroid Status	Duration (yrs, mean ± SD)
Euthyroid	6.8 ± 2.5
Dysfunction	8.0 ± 2.9

Table 1: Describes the cohort's age and gender distribution, indicating a mean age of 10.8 ± 3.5 years with a slight male predominance (54%). Table 2: Highlights chronic transfusion exposure, with an average duration of 7.2 ± 2.8 years and a frequency of 1.8 ± 0.4 transfusions per month. Table 3: Shows that 40% of patients had poor iron-chelation adherence (< 75%), a key modifiable risk factor linked to thyroid dysfunction. Table 4: Demonstrates a stepwise increase in serum ferritin—from 2,650 ± 700 ng/mL in euthyroid children to 3,400 ± 780 ng/mL in those with overt hypothyroidism—implicating iron overload in glandular injury. Table 5: Confirms that 32% of the cohort exhibited thyroid dysfunction, with 20% subclinical and 12% overt hypothyroidism. Table 6: Details the biochemical progression, showing TSH rising from 2.8 ± 1.1 mIU/L (euthyroid) to 10.2 ± 2.0 mIU/L (overt), alongside declining fT_4 and fT_3 levels. Table 7: Reports a moderate positive correlation ($r = 0.48$; $p < 0.001$) between serum ferritin and TSH, underscoring iron load as a predictor of thyroid-stimulating hormone elevation. Table 8: Reveals progressively poorer growth metrics in hypothyroid groups, with height Z-scores falling from –0.5 ± 0.8 (euthyroid) to –1.4 ± 1.0 (overt). Table 9: Indicates similar thyroid dysfunction rates in males (33%) and females (30%), suggesting gender is not a significant risk modifier. Table 10: Shows that thyroid dysfunction prevalence increases with age—from 20% in 2–6 year-olds to 37% in 13–18 year-olds—reflecting cumulative iron exposure. Table 11: Highlights that poor chelation adherence doubles the risk of thyroid dysfunction (45% vs. 25%), emphasizing adherence as a protective factor. Table 12: Compares transfusion durations, showing children with thyroid dysfunction had a longer mean transfusion history (8.0 ± 2.9 years) than euthyroid peers (6.8 ± 2.5 years).

Discussion

Thyroid dysfunction emerged as a common complication in our cohort of transfusion-dependent thalassemic children, affecting nearly one-third of patients and manifesting primarily as subclinical hypothyroidism. This finding underscores the insidious nature of thyroid injury in the setting of chronic iron overload: even without overt symptoms, elevated TSH levels signal early glandular distress [9]. Our data align with prior studies reporting subclinical hypothyroidism prevalence of 15%–30% in similar populations, but the 12% overt hypothyroidism rate we observed is toward the higher end of published ranges, reflecting perhaps more prolonged transfusion exposure and

variable chelation adherence in our regional setting [10].

The positive correlation between serum ferritin and TSH (r = 0.48) reinforces iron's central role in thyroid injury. Iron catalyzes free-radical formation, damaging thyrocytes and disrupting iodide uptake and thyroid peroxidase activity. Children with overt hypothyroidism had the highest ferritin levels (3,400 ± 780 ng/mL), indicating that despite chelation efforts, cumulative iron burden remains critical [11]. Importantly, nearly half of those with poor chelation adherence developed thyroid impairment, compared to only one-quarter of those adherent to therapy. This striking difference highlights the need for rigorous monitoring of chelation compliance, patient education, and perhaps more intensive or combination chelation regimens to mitigate endocrine sequelae [12].

Our analysis of transfusion history demonstrated that children with thyroid dysfunction had been receiving transfusions longer (8.0 ± 2.9 years) than their euthyroid peers (6.8 ± 2.5 years), suggesting a cumulative effect of iron deposition over time. This temporal relationship argues for early initiation of chelation ideally within the first year of transfusion and consideration of thyroid screening as part of routine follow-up from as early as age 5 or after two to three years of regular transfusion [13].

The impact of thyroid dysfunction on growth was evident: overtly hypothyroid children had height and weight Z-scores approximately one standard deviation below euthyroid peers, indicating that even subclinical deficits can translate into measurable growth faltering [14]. Thyroid hormone is essential for normal growth plate maturation and IGF-1 regulation, so unrecognized hypothyroidism risks long-term stature deficits and delayed puberty. Our findings support incorporating growth monitoring with thyroid assessment to identify children who may benefit from early levothyroxine therapy to optimize both growth and metabolic health [15,16].

Gender did not significantly influence thyroid risk, with prevalence rates of 33% in males and 30% in females, suggesting that endocrine surveillance protocols need not differ by sex. However, age stratification revealed increasing dysfunction from 20% in preschoolers to 37% in adolescents mirroring iron accumulation over years. This trend emphasizes the importance of age-appropriate screening intervals: perhaps biannual thyroid function tests in children older than 7 years or after five years of transfusion [17].

Clinically, our findings advocate for a structured endocrine care pathway in thalassemia management. Baseline thyroid testing at diagnosis, repeated every 12 months (or sooner in the presence of high ferritin), coupled with aggressive chelation optimization, may detect and prevent progression from subclinical to overt hypothyroidism. For those with elevated TSH and normal fT_4, intensifying chelation and reassessing within six months could avert overt dysfunction, while children with confirmed overt hypothyroidism warrant combined chelation and thyroid hormone replacement to restore metabolic equilibrium [18,19].

Strengths of our study include its robust sample size, rigorous timing of thyroid testing relative to transfusion, and comprehensive assessment of clinical, laboratory, and growth parameters. Nonetheless, limitations exist: our cross-sectional design precludes causal inferences or assessment of longitudinal thyroid trends; reliance on single-time-point ferritin as an iron-load marker may not fully capture tissue deposition; and lacking data on other endocrine axes (e.g., growth hormone, adrenal) limits understanding of broader endocrine dysfunction in this population [20].

Future research should involve prospective cohort studies tracking thyroid function and iron-load indices over multiple years, ideally incorporating advanced metrics such as MRI R2* quantification of glandular iron. Interventional trials comparing standard versus intensified chelation, with thyroid outcomes as endpoints, could establish optimal protocols to prevent endocrinopathy. Finally, quality-of-life studies exploring neurocognitive and psychosocial impacts of thyroid dysfunction in thalassemic children would further elucidate the full burden of this complication and guide holistic patient care.

Conclusion

Thyroid dysfunction—predominantly subclinical hypothyroidism—affects nearly one-third of transfusion-dependent thalassemic children and is strongly associated with higher iron burden, longer transfusion duration, and poor chelation adherence. Early and regular thyroid screening, coupled with optimized iron-chelation strategies, is essential to detect and manage dysfunction before overt hypothyroidism and growth impairment develop. Implementing structured endocrine surveillance in thalassemia care can mitigate long-term complications and support healthier growth and development in this vulnerable population.

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