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ASSESSMENT OF STATUS OF THYROID FUNCTIONS IN CHILDREN WITH B-THALASSEMIA MAJOR

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Abstract

Background: *β-thalassemia major is a hereditary blood disorder characterized by defective hemoglobin synthesis leading to severe anemia and lifelong dependence on blood transfusions.*

Objective: *To assess the status of thyroid function in children with β-thalassemia major and determine its association with age, duration of blood transfusions, serum ferritin levels, and compliance with iron chelation therapy.*

Methdology: *This cross-sectional study was conducted at the Department of Pediatrics, Fauji Foundation Hospital, Rawalpindi from December 2024 to May 2025. A total of 305 children were included. Children fulfilling the selection criteria were enrolled after obtaining informed consent from their parents or guardians. Demographic details, including age, gender, residence, socioeconomic status, and treatment history, were recorded. A 3 mL venous blood sample was drawn to assess thyroid function tests (TSH, T3, and T4).*

Results: *The mean age of the participants was 8.6 ± 3.4 years, with 178 (58.4%) males and 127 (41.6%) females. Abnormal thyroid function was detected in 28 children (9.2%), including 21 (6.9%) with subclinical hypothyroidism and 7 (2.3%) with overt hypothyroidism. A significant association was found between thyroid dysfunction and higher serum ferritin levels ($p = 0.002$), longer duration of transfusions ($p = 0.001$), increasing age ($p = 0.04$), and irregular chelation therapy ($p = 0.01$).*

Conclusion: *It is concluded that thyroid dysfunction is a frequent and important endocrine complication in children with β-thalassemia major, commonly presenting as subclinical hypothyroidism. The risk increases with advancing age, prolonged transfusion therapy, higher ferritin levels, and poor adherence to chelation therapy.*

INTRODUCTION

β-thalassemia major is an inherited hemoglobinopathy that requires lifelong red blood cell transfusions and iron chelation therapy to prevent complications due to iron overload. Traditionally, β-thalassemia has been more common in certain regions of the world such as the Mediterranean, Middle East, and Southeast Asia. However, the prevalence of β-thalassemia is increasing in other regions, including

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Northern Europe and North America, primarily due to migration [1]. Thalassemia has a burden on the healthcare systems of many countries. About 56000 conceptions result in thalassemia, globally [2]. Endocrinopathies are now amongst the common complications of thalassemia but determining the exact prevalence is difficult because of differences in age of first exposure to chelation therapy and the continuing improvement in survival in well-chelated patients. Hypothyroidism is the second most common endocrine disorder after hypogonadism, having been reported in 5.6% to 17% of patients [3]. In Beta Thalassemia Major patients the frequency of hypothyroidism ranges from 6 to 30% among various countries depending on chelation strategies [4]. Upadya et al., conducted a study in India found that percentage of abnormal TSH level was reported in 4.8% children with beta thalassemia major [5]. But Pirinççioğlu et al., found that 100% children of beta thalassemia had normal thyroid function test [6]. Ansaf e al.,, conducted in Iraq, it was found that 46.96% had hypothyroidism; out of which 10.6% had primary hypothyroidism, 24.2% had subclinical hypothyroidism and 12.1% had central hypothyroidism [7].

Several studies worldwide have reported a high prevalence of endocrine abnormalities in thalassemic patients, particularly hypothyroidism. Research from the Mediterranean, Middle Eastern, and South Asian populations have indicated that up to 30–40% of transfusion-dependent thalassemia patients develop thyroid dysfunction, depending on age, transfusion duration, and adequacy of chelation therapy [8]. Iron chelators such as deferoxamine, deferasirox, and deferiprone are crucial in minimizing iron-induced toxicity. However, poor compliance, delayed initiation, or inadequate dosing of chelation therapy continues to be a major problem in developing countries. Consequently, endocrine dysfunctions, including hypothyroidism, diabetes mellitus, hypogonadism, and hypoparathyroidism, remain prevalent among thalassemia patients in these regions [9].

In Pakistan, β-thalassemia is a significant hereditary health burden, with an estimated 5–7% carrier rate in the population. Each year, thousands of children are born with β-thalassemia major, many of whom depend on regular transfusions throughout their lives. Despite improvements in diagnosis and transfusion practices, there remain considerable challenges in long-term care [10]. The pathophysiology of thyroid dysfunction in β-thalassemia involves both direct and indirect mechanisms. Direct iron deposition in the thyroid gland causes parenchymal fibrosis and follicular cell destruction. Indirectly, chronic anemia and hypoxia affect the hypothalamic-pituitary-thyroid (HPT) axis, impairing thyroid-stimulating hormone (TSH) release and thyroidal responsiveness [11]. Liver dysfunction, a common complication of iron overload, also alters the metabolism and conversion of thyroid hormones, further compounding the hormonal imbalance. In addition, certain chelation therapies may have secondary effects on thyroid hormone levels, although evidence remains mixed [12].

Objective

To determine the frequency of abnormal thyroid function test levels in children with β thalassemia major

Methodology

This cross-sectional study was conducted at the Department of Pediatrics, Fauji Foundation Hospital, Rawalpindi from December 2024 to May 2025. A total of 305 children were included in the study. The sample size was calculated using the WHO sample size calculator, assuming a 95% confidence level, 2.4% margin of error, and an expected prevalence of abnormal TSH levels of 4.8% among children with β-thalassemia major. Non-probability consecutive sampling was used to recruit participants who met the inclusion criteria.

Inclusion Criteria:

- Children aged 1–16 years of either gender.
- Diagnosed cases of β-thalassemia major (as per operational definition).

Exclusion Criteria:

- Children diagnosed with β-thalassemia minor or intermedia.
- Children presenting with acute illness, those on any hormonal therapy, or with a family history of hypothyroidism.

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- Children already receiving treatment for any thyroid disorder as documented in their medical records.

Data Collection Procedure:

A total of 305 children fulfilling the selection criteria were enrolled in the study through the OPD after obtaining informed written consent from their parents or guardians. Demographic and clinical details, including name, age at presentation, age at diagnosis, gender, current weight, residence, socioeconomic status, and current treatment regimen, were recorded on a predesigned proforma. For thyroid function assessment, 3 mL of venous blood was drawn aseptically using a 3cc disposable syringe. Serum thyroid function tests (TSH, T3, and T4) were analyzed in the hospital's biochemistry laboratory using standard immunoassay techniques. Thyroid function was categorized based on serum TSH levels. If serum TSH was ≥5 IU/mL, the patient was labeled as having abnormal thyroid function as per the operational definition. Children identified with thyroid dysfunction were managed according to institutional protocols and referred for further endocrinological evaluation.

Data Analysis:

All data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 26.0. The Shapiro–Wilk test was applied to check the normality of continuous data. Descriptive statistics were used for data presentation. For continuous variables such as age at presentation, age at diagnosis, weight, and thyroid hormone levels, mean ± standard deviation (SD) were calculated. For categorical variables such as gender, residence, socioeconomic status, treatment status, and abnormal thyroid function, frequency and percentage were computed. Data were stratified according to key demographic and clinical variables, including age at presentation, age at diagnosis, gender, current weight, residence, socioeconomic status, and treatment status to control for confounders. Post-stratification, the chi-square test was applied to assess associations between categorical variables, particularly between abnormal thyroid function and stratified groups. A p-value ≤0.05 was considered statistically significant.

Results

A total of 305 children with β-thalassemia major were included in the study. The mean age at presentation was 8.6 ± 3.4 years, while the mean age at diagnosis was 1.8 ± 1.2 years, showing that most children were diagnosed early in life and had been on transfusion therapy for several years. Out of the total participants, 178 (58.4%) were males and 127 (41.6%) were females, showing a slight male predominance. The mean current weight was 24.5 ± 6.8 kg, indicating growth limitation commonly seen in transfusion-dependent thalassemia. Most patients, 184 (60.3%), resided in urban areas, while 121 (39.7%) were from rural settings. More than half, 163 (53.4%), belonged to the low socioeconomic class, 109 (35.7%) to the middle class, and 33 (10.8%) to the high class. Almost all children, 289 (94.8%), were receiving regular blood transfusions, while only 16 (5.2%) had irregular transfusions.

Table 1: Baseline Characteristics of the Study Population (n = 305)

Variable	Mean ± SD / n (%)
Age at presentation (years)	8.6 ± 3.4
Age at diagnosis (years)	1.8 ± 1.2
Gender	Male: 178 (58.4%) Female: 127 (41.6%)
Current weight (kg)	24.5 ± 6.8
Residence	Urban: 184 (60.3%) Rural: 121 (39.7%)
Socioeconomic status	Low: 163 (53.4%) Middle: 109 (35.7%) High: 33 (10.8%)

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Regular transfusions	Yes: 289 (94.8%) No: 16 (5.2%)
Chelation therapy compliance	Regular: 218 (71.5%) Irregular: 87 (28.5%)

Out of 305 children, 277 (90.8%) had normal thyroid function, while 28 (9.2%) had abnormal thyroid function. Among the affected children, 21 (6.9%) had subclinical hypothyroidism and 7 (2.3%) had overt hypothyroidism. No child was found to have hyperthyroidism.

Table 2: Thyroid Function Status Among Participants (n = 305)

Thyroid Status	**Frequency (n)**	**Percentage (%)**
Normal thyroid function	277	90.8
Subclinical hypothyroidism	21	6.9
Overt hypothyroidism	7	2.3
Total abnormal function	**28**	**9.2**

Thyroid dysfunction was more frequent in children older than 10 years, with 15 (14.1%) affected, compared to 13 (6.3%) in those aged 10 years or younger, and this difference was statistically significant (p = 0.04). Gender, residence, and socioeconomic status showed no significant association with thyroid function, as the p-values were 0.38, 0.47, and 0.33 respectively. However, a significant association was observed with chelation therapy compliance, as children who were irregular with chelation had a higher prevalence of thyroid dysfunction (17.2%) compared to those with regular chelation (6.0%) (p = 0.01).

Table 3: Association of Abnormal Thyroid Function with Demographic and Clinical Variables (n = 305)

Variable	**Subgroup**	**Abnormal Thyroid Function n (%)**	**p-value**
Age group (years)	≤10 years	13 (6.3%)	0.04*
	>10 years	15 (14.1%)	
Gender	Male	14 (8.0%)	0.38
	Female	14 (11.0%)	
Residence	Urban	15 (8.2%)	0.47
	Rural	13 (10.7%)	
Socioeconomic status	Low	17 (10.4%)	0.33
	Middle	9 (8.3%)	
	High	2 (6.1%)	
Chelation therapy compliance	Regular	13 (6.0%)	0.01*
	Irregular	15 (17.2%)	

Children with ferritin levels below 1000 ng/mL had a low rate of abnormal thyroid function (2.4%), which increased to 5.8% in those with ferritin between 1000–2500 ng/mL, and was highest at 15.1% in children with ferritin levels above 2500 ng/mL. This difference was statistically significant (p = 0.002).

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Table 4: Relationship Between Serum Ferritin Levels and Thyroid Dysfunction (n = 305)

Serum Ferritin Level (ng/mL)	Total (n)	Abnormal Thyroid Function n (%)	p-value
<1000	42	1 (2.4%)	0.002*
1000–2500	137	8 (5.8%)	
>2500	126	19 (15.1%)	
Duration of Transfusions (years)			
<5 years	72	2 (2.8%)	
5–10 years	129	9 (7.0%)	
>10 years	104	17 (16.3%)	0.001*

Discussion

This study evaluated thyroid function among children with β-thalassemia major and found that 9.2% of the participants had abnormal thyroid function. Subclinical hypothyroidism was more common (6.9%) than overt hypothyroidism (2.3%). This shows that thyroid gland involvement is an important endocrine complication in children with transfusion-dependent thalassemia. The findings indicate that the risk of thyroid dysfunction increases with age. Older children had a higher frequency of abnormal thyroid function compared to younger ones. This is likely due to the cumulative effect of repeated blood transfusions and gradual iron overload over time. Iron deposition in the thyroid tissue can cause oxidative damage, fibrosis, and altered hormone synthesis. The progressive nature of this damage explains why thyroid disorders appear more frequently in patients who have been receiving transfusions for longer periods. The relationship between serum ferritin levels and thyroid function was also significant in this study. Children with ferritin levels greater than 2500 ng/mL had a higher rate of thyroid dysfunction. This clearly reflects that poor control of iron overload contributes directly to thyroid impairment. When ferritin levels remain persistently high, it indicates ineffective chelation therapy or poor treatment adherence, both of which allow iron to accumulate in endocrine organs [14-16].

Chelation therapy compliance was another factor that showed a strong association with thyroid dysfunction. Children who were irregular with their chelation regimen had a much higher prevalence of abnormal thyroid function compared to those who were consistent with treatment. This reinforces the importance of regular and effective iron chelation to prevent endocrine complications [17]. Good compliance with chelation helps minimize iron accumulation and protect the thyroid from progressive injury. Duration of transfusion was also a major contributor. Children who had received blood transfusions for more than ten years were found to have the highest frequency of thyroid dysfunction. This suggests that the longer a patient remains transfusion dependent, the greater the cumulative iron load and subsequent risk to endocrine organs. This emphasizes the need for early initiation of chelation therapy and continuous monitoring from early childhood to minimize iron toxicity [18].

There was no significant difference in thyroid dysfunction with respect to gender, residence, or socioeconomic status. This indicates that thyroid abnormalities are more closely linked to biological and treatment-related factors than to demographic characteristics. However, children from lower socioeconomic backgrounds may face barriers to consistent medical care and chelation, indirectly increasing their risk of complications. The predominance of subclinical hypothyroidism in this

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study highlights the importance of early and routine screening for thyroid function in all thalassemia patients. Subclinical cases may remain unnoticed without laboratory evaluation, yet they can progress to overt hypothyroidism if not detected and managed in time. Regular monitoring allows for early detection and timely treatment, which can improve growth, energy levels, and overall quality of life in affected children [19].

The pathophysiological explanation behind these findings centers on the chronic accumulation of iron in endocrine glands. Iron catalyzes the production of free radicals, leading to oxidative damage of thyroid cells and impaired hormone synthesis. In addition, secondary effects such as pituitary involvement and liver dysfunction can alter hormone regulation and metabolism. Together, these mechanisms contribute to the development of thyroid insufficiency in thalassemia major [20]. This study emphasizes that regular thyroid function testing should be a standard part of follow-up care for children with β-thalassemia major, especially those with high ferritin levels or long transfusion histories. Early detection of subclinical hypothyroidism allows for prompt intervention, potentially preventing progression to overt disease. Maintaining optimal chelation and monitoring ferritin levels are essential steps in protecting the endocrine system and improving long-term outcomes. The main limitation of this study was its cross-sectional design, which does not allow assessment of the progression of thyroid dysfunction over time. Serum ferritin was used as the indicator of iron load, which may not precisely reflect total body iron content. Despite these limitations, the study provides valuable evidence of the need for proactive endocrine screening in children with thalassemia major.

Conclusion

It is concluded that thyroid dysfunction is a significant endocrine complication in children with β-thalassemia major, with an overall prevalence of 9.2%. Subclinical hypothyroidism was more frequently observed than overt hypothyroidism, suggesting that thyroid involvement often begins as a mild and asymptomatic disturbance before progressing to more severe forms. The occurrence of thyroid dysfunction showed a strong association with increasing age, longer duration of transfusion therapy, higher serum ferritin levels, and poor compliance with iron chelation.

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