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FREQUENCY OF HYPOTHYROIDISM IN BETA THALASSEMIA MAJOR CHILDREN

Original Research

Fara Anwar[1]*, Shazia Memon[1], Ayesha Almas[1], Kausar Keerio[1], Fiza Shah[1], Fatima Anwar[2]
[1]Department of Pediatrics, Liaquat University of Medical and Health Sciences, Jamshoro, Hyderabad, Pakistan.
[2]Department of Plastic Surgery, Liaquat University of Medical and Health Sciences, Jamshoro, Hyderabad, Pakistan.
Corresponding Author: Fara Anwar, Department of Pediatrics, Liaquat University of Medical and Health Sciences, Jamshoro, Hyderabad, Pakistan.
Faraanwar91@gmail.com
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ABSTRACT

Background: Beta-thalassemia major is a common inherited hemoglobinopathy characterized by chronic hemolysis and the need for lifelong blood transfusions. While transfusions improve survival, they lead to excessive iron deposition in various organs, including endocrine glands. Iron overload is a major contributor to endocrine dysfunctions, including hypothyroidism, which can significantly affect growth and development. Early detection of thyroid dysfunction in thalassemia patients is essential, as thyroxine therapy is cost-effective, readily available, and can prevent associated morbidity.

Objective: To determine the frequency of hypothyroidism in children with beta-thalassemia major receiving regular blood transfusions.

Methods: This cross-sectional study was conducted over six months, from January 2024 to June 2024, in the Thalassemia Ward of the Pediatrics Department at Liaquat University Hospital, Hyderabad. A total of 97 children aged 2-15 years with beta-thalassemia major, who had been receiving regular blood transfusions for more than two years, were included using a non-probability consecutive sampling technique. Newly diagnosed cases, children with thalassemia minor or intermedia, those previously on thyroxine therapy, and those with other endocrine or syndromic conditions were excluded. Thyroid function was assessed using serum TSH and T4 levels measured by the ELISA technique. Data were analyzed using SPSS version 20.0, with quantitative variables expressed as mean ± SD and qualitative variables as frequencies and percentages.

Results: The mean age of participants was 8.48 ± 2.93 years, and the mean age at diagnosis was 14.25 ± 12.20 months. The average serum TSH was 2.83 ± 1.64, T4 was 8.42 ± 2.15, and serum ferritin was 5002.44 ± 2937.2 ng/ml. Hypothyroidism was detected in 7.22% (7/97) of patients, all of whom exhibited subclinical hypothyroidism. There was no statistically significant correlation between hypothyroidism and gender (p=0.244), weight (p=0.440), or height (p=0.696).

Conclusion: Hypothyroidism is a notable endocrine complication in children with beta-thalassemia major, with subclinical hypothyroidism being the predominant form. Routine thyroid function screening is crucial to facilitate early detection and timely intervention, preventing long-term complications.

Keywords: Beta-thalassemia major, Chelation therapy, Endocrine dysfunction, Hypothyroidism, Iron overload, Subclinical hypothyroidism, Thyroid screening.

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INTRODUCTION

Thalassemia is one of the most prevalent monogenic disorders worldwide, characterized by an inherited impairment in hemoglobin production. It results in a quantitative defect in globin chain synthesis, specifically affecting either the beta or alpha globin chains. Among the various types, beta-thalassemia major is a severe form, necessitating lifelong blood transfusions for survival. The disease burden is significant, with approximately 9,000 infants born with beta-thalassemia annually, though documented data in Pakistan remains scarce. The estimated carrier rate in the country is 5-7%, translating to nearly 9.8 million individuals, and over 100,000 diagnosed cases, making up almost 5% of the global burden. Advances in medical care, particularly through regular transfusions and iron chelation therapy, have transformed beta-thalassemia from a fatal childhood illness into a manageable chronic condition. However, while these treatments prolong survival, they introduce complications such as iron overload, which can lead to multi-organ dysfunction, particularly affecting the heart, liver, and endocrine glands (1-4). Chronic transfusions expose patients to excessive iron accumulation, with each unit of packed red cells delivering approximately 250 mg of iron. The body's inability to excrete excess iron leads to its deposition in various organs, disrupting physiological functions and increasing the risk of endocrine dysfunctions such as delayed puberty, growth retardation, diabetes mellitus, hypoparathyroidism, and hypothyroidism. Among these, hypothyroidism is a significant but often underdiagnosed complication, affecting the overall development and metabolic stability of children with thalassemia major. It manifests either as overt hypothyroidism, characterized by clinically evident thyroid hormone deficiency, or as subclinical hypothyroidism, where thyroid-stimulating hormone (TSH) levels are elevated while free thyroxine (FT4) levels remain within the normal range. The prevalence of hypothyroidism in thalassemia patients varies widely across studies, reflecting differences in patient demographics, age at diagnosis, duration of transfusions, and adequacy of iron chelation therapy (5-10).

Several studies have investigated the frequency of hypothyroidism in children with thalassemia major, revealing varying results. A study conducted in Peshawar, Pakistan, reported subclinical hypothyroidism in 21.7% of patients. Another study from Rahim Yar Khan found an alarmingly high prevalence, with 93.3% of thalassemic children exhibiting subclinical hypothyroidism, while only 6.7% had overt hypothyroidism. Research from India observed a much lower prevalence of subclinical hypothyroidism, at 4.8%, whereas a study in Faisalabad, Pakistan, found hypothyroidism in 29.3% of beta-thalassemia major patients (11-14). The considerable variability in these findings highlights the need for further investigation, particularly in different healthcare settings and among diverse populations. Despite significant advancements in thalassemia management, many affected children continue to be diagnosed with hypothyroidism at later stages when irreversible complications, such as impaired cognitive and physical development, have already occurred. This underscores the importance of early screening and timely intervention. Thyroxine replacement therapy is both cost-effective and readily available, making it a viable option for managing hypothyroidism in this patient population. However, standardized screening protocols for endocrine dysfunctions, including hypothyroidism, are often lacking in resource-limited settings. Given the inconsistencies in previous research and the need for early detection to prevent long-term complications, this study aims to determine the frequency of hypothyroidism in children with beta-thalassemia major in an asymptomatic state. By establishing the prevalence of this endocrine disorder, the findings will contribute to improving screening strategies and ensuring timely therapeutic interventions, ultimately reducing morbidity and enhancing the quality of life for these children (2-3,15).

METHODS

This cross-sectional study was conducted over six months, from January 2024 to June 2024, in the Thalassemia Ward of the Pediatrics Department at Liaquat University Hospital, Hyderabad. The study aimed to assess the frequency of hypothyroidism in children with beta-thalassemia major. A non-probability consecutive sampling technique was employed to select participants, and the sample size was determined using the WHO sample size calculator. Assuming a population proportion of 6.7% (3), a confidence level of 95%, and a margin of error of 5%, the minimum required sample size was 97 children (16). Participants included children aged between 2 and 15 years who had been diagnosed with beta-thalassemia major and had received regular blood transfusions for more than two years. Children who had been newly diagnosed with thalassemia major, those diagnosed with thalassemia minor or intermedia, individuals who had previously received thyroxine therapy, and those presenting with other endocrine disorders or syndromic traits were excluded. Ethical approval was obtained from the Institutional Ethical Committee of Liaquat University of Medical and Health Sciences

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(LUHMS), Jamshoro, prior to the commencement of the study. Informed consent was obtained from the parents or guardians of all participating children, ensuring confidentiality and adherence to ethical research standards (17).

A total of 97 children meeting the eligibility criteria were enrolled. Data were collected using a structured proforma to document demographic details, including age, weight, height, age at thalassemia diagnosis, history of blood transfusions, and use of iron chelation therapy. Blood samples (5-10 ml) were collected from each participant and analyzed for thyroid function using the Enzyme-Linked Immunosorbent Assay (ELISA) technique to measure serum T4 and thyroid-stimulating hormone (TSH) levels (18). Data analysis was performed using SPSS version 20.0. Quantitative variables, including age, age at thalassemia diagnosis, weight, height, duration of blood transfusions, serum ferritin levels, T4, and TSH levels, were analyzed using mean and standard deviation. Qualitative variables, such as gender, thyroid status, current transfusion status, and iron chelator usage, were expressed as frequencies and percentages. To control for potential confounders, effect modifiers such as age, duration of blood transfusions, height, and weight were adjusted using stratification. Post-stratification analysis was conducted using the chi-square test or Fisher's exact test, with a p-value of less than 0.05 considered statistically significant (19).

RESULTS

During the six-month study period, a total of 97 children diagnosed with beta-thalassemia major who had been receiving blood transfusions for at least two years were included. The mean age of participants was 8.48 ± 2.93 years, with a median age of 8 years (IQR: 4). The mean age at diagnosis was 14.25 ± 12.20 months, with a median of 8 months (IQR: 18). The mean weight of the participants was 23.91 ± 10.01 kg, and the mean height was 125.18 ± 14.89 cm. Among the total participants, 50% were receiving chelation therapy. The mean serum thyroid-stimulating hormone (TSH) level was 2.83 ± 1.64, with a median of 2.32 (IQR: 2), while the mean serum T4 level was 8.42 ± 2.15, with a median of 8.16 (IQR: 2.8). The average serum ferritin level was found to be 5002.44 ± 2937.2, with a median of 4200 (IQR: 3383).

The overall frequency of hypothyroidism among children with beta-thalassemia major was found to be 7.22% (7 out of 97). All cases were identified as subclinical hypothyroidism, with no cases of overt hypothyroidism observed. The frequency of hypothyroidism was assessed in relation to gender and anthropometric measures, but no statistically significant difference was observed. Among male participants, 3.8% (2 out of 52) were diagnosed with hypothyroidism, while among female participants, the frequency was 11.1% (5 out of 45), with a p-value of 0.244. Similarly, stratification by weight showed that 4.3% (2 out of 46) of children weighing less than 12 kg had hypothyroidism, whereas 9.8% (5 out of 51) of children weighing more than 12 kg were affected (p = 0.440). Height-based stratification showed that among children shorter than 120 cm, 3.8% (2 out of 40) had hypothyroidism, while among those taller than 120 cm, the frequency was 8.8% (5 out of 57), with a p-value of 0.696. The analysis of serum ferritin levels in relation to hypothyroidism revealed no statistically significant correlation between iron overload and the presence of hypothyroidism among beta-thalassemia major patients. The mean serum ferritin levels were markedly elevated across the cohort, but there was no significant difference observed between children with and without hypothyroidism. Additionally, further subgroup analysis based on the use of chelation therapy showed no substantial impact on thyroid function, suggesting that while iron overload is a well-documented risk factor for endocrine dysfunctions, its direct association with thyroid dysfunction in this study population requires further investigation. The findings highlight the need for continuous thyroid function monitoring, regardless of serum ferritin levels, to ensure early diagnosis and intervention in this vulnerable group.

Table 1: Characteristics of Patients

Variables	Mean ± SD	Median (IQR)
Age (Years)	8.48 ± 2.93	8(4)
Age at diagnosed (months)	14.25 ± 12.20	8(18)
Weight (kg)	23.91 ± 10.01	24(15)
Height (cm)	125.18 ± 14.89	125(20)

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Table 2: Thyroid profile and other characteristics of Patients

Variables	Mean ± SD	Median (IQR)
T4	8.42 ± 2.15	8.16 (2.8)
TSH	2.83 ± 1.64	2.32 (2)
Serum Ferritin	5002.44 ± 2937.2	4200(3383)

Table 3: Frequency of Hypothyroidism in B-Thalassemia Major children by gender and anthropometric measures, n=97

Gender	Hypothyroidism		Total	P-Value
	Yes	No		
Male	2(3.8%)	50(96.2%)	52	0.244
Female	5(11.1%)	40(88.9%)	45	
Weight				
<12kg	2(4.3%)	44(95.7%)	46	0.440
>12kg	5(9.8%)	46(90.2%)	51	
Height				
<120cm	2(3.8%)	38(95%)	40	0.696
>120cm	5(8.8%)	52(91.12%)	57	

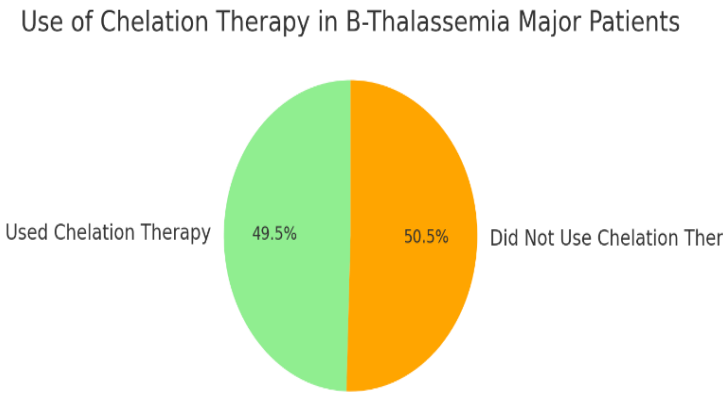


Figure 1 Use of Chelation Therapy in B-Thalassemia Major Patients

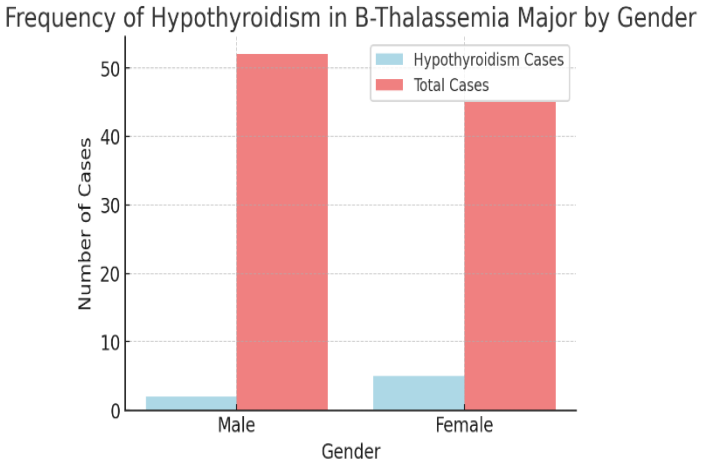


Figure 2 Frequency of Hypothyroidism in B-Thalassemia Major by Gender

DISCUSSION

This cross-sectional study investigated the prevalence of hypothyroidism among children with beta-thalassemia major, highlighting the endocrine complications associated with chronic blood transfusions and iron overload. The mean age of the study population was 8.48 ± 2.93 years, aligning with findings from previous studies that reported a similar age distribution among thalassemia major patients. The relatively young age of participants in such studies is often attributed to increased morbidity in early childhood due to iron overload,

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suboptimal chelation therapy, and poor survival rates in older age groups. In the present study, only half of the participants were receiving chelation therapy, whereas studies from other regions have reported a higher percentage of children undergoing iron chelation therapy, indicating potential variations in treatment adherence, accessibility, or physician recommendations (20). The thyroid profile results demonstrated a mean TSH level of 2.83 ± 1.64 and a mean T4 level of 8.42 ± 2.15, with an average serum ferritin level of 5002.44 ± 2937.2 ng/ml. Compared to other studies, the serum ferritin levels observed in this study were significantly elevated, reflecting substantial iron overload. However, the mean TSH and T4 values were relatively lower than those reported in some international studies, where thyroid dysfunction was more pronounced. The overall frequency of hypothyroidism was 7.22%, lower than reports from other national studies, which have documented hypothyroidism in 25-31% of thalassemia major patients. In contrast, international studies have reported a prevalence ranging from 7% to 26%, suggesting geographical and management-related differences in disease progression and endocrine dysfunction. All cases of hypothyroidism in this study were classified as subclinical, with no instances of overt hypothyroidism. This finding contrasts with reports from other regions where both subclinical and overt hypothyroidism have been observed, emphasizing the need for refined diagnostic criteria and potential modifications in TSH cut-offs tailored to thalassemia patients (21).

The observed differences in hypothyroidism prevalence across studies may be influenced by multiple factors, including variations in iron chelation therapy, differences in study populations, and disparities in healthcare settings. The lack of a statistically significant correlation between hypothyroidism and serum ferritin levels in this study suggests that additional factors, such as genetic predisposition and chelation regimens, may contribute to thyroid dysfunction in thalassemia major patients. While iron overload is a recognized contributor to endocrine dysfunction, serum ferritin alone may not be a reliable indicator of tissue iron deposition, particularly in heavily transfused individuals. Alternative iron overload assessment methods, such as liver iron concentration measurements through MRI, may provide more precise insights into the impact of iron toxicity on thyroid function (22). A major strength of this study was its focus on identifying subclinical hypothyroidism, which remains an underdiagnosed condition in thalassemia major patients. The findings underscore the importance of early thyroid screening in this population to initiate timely interventions and prevent long-term complications. However, the study had several limitations, including its single-center design and relatively small sample size, which may limit the generalizability of findings. Additionally, the lack of long-term follow-up data prevents conclusions regarding the progression of thyroid dysfunction over time. Given that serum ferritin is an imperfect marker in patients with extreme iron overload, there is a possibility of underestimating the role of iron in thyroid dysfunction, warranting further investigations with more precise iron burden assessment tools (23).

Future research should focus on large-scale, multicenter, longitudinal studies to evaluate the long-term endocrine consequences of iron overload in thalassemia major patients. Establishing standardized guidelines for thyroid screening and optimizing chelation therapy protocols could help reduce the burden of hypothyroidism in this population. The potential influence of specific iron chelators on thyroid function should also be explored, as certain chelation agents may differentially affect endocrine regulation. Furthermore, the development of tailored TSH cut-off values for thalassemia patients could improve the accuracy of diagnosing subclinical hypothyroidism, ensuring early and appropriate therapeutic interventions.

CONCLUSION

Hypothyroidism is a significant endocrine complication in children with beta-thalassemia major, with the majority of cases presenting as subclinical. The findings emphasize the necessity of routine thyroid function screening in thalassemic individuals to ensure early detection and timely intervention. Given the potential impact on growth, metabolism, and overall well-being, early identification and management through thyroxine replacement therapy can help prevent long-term complications and improve the quality of life for affected children. Integrating standardized screening protocols into thalassemia care can enhance patient outcomes and reduce the burden of endocrine dysfunctions in this vulnerable population.

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AUTHOR CONTRIBUTIONS

Author	Contribution
Fara Anwar*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Shazia Memon	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Ayesha Almas	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Kausar Keerio	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Fiza Shah	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Fatima Anwar	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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