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Medicine

Prevalence of Hypothyroidism in Children with Transfusion Dependent Thalassemia Patient Attending in A Tertiary Care Hospital of Bangladesh

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Abstract **Original Research Article**

Background: Blood transfusions and iron chelation are standard treatments for β-thalassemia major and Hb E-Beta-Thalassemia. However, repeated transfusions raise body iron levels, leading to secondary hemosiderosis and complications in the heart, endocrine system, and liver. Thyroid dysfunction results from gland infiltration, chronic hypoxia, free radical damage, and iron overload. This study aimed to find out the prevalence of hypothyroidism in transfusion-dependent thalassemic children attending Bangladesh Shishu Hospital & Institute. ***Methods:*** A descriptive cross-sectional study was conducted at the Thalassemia Centre, Department of Hematology and Oncology, Bangladesh Shishu Hospital & Institute, from December 2019 to November 2020. The study included 140 children with thalassemia, aged 5 to 16 years, who were receiving blood transfusions. Data were collected using a structured questionnaire with participant consent. Statistical analysis was performed using SPSS version 23.0. ***Results*:** In this study, hypothyroidism was observed in 26.2% of patients, with 23.5% having subclinical and 2.9% overt hypothyroidism. In most of the patients (n=85), aged 11-16 years, 58.3% had normal thyroid function, 36.5% had subclinical, and 4.7% had overt hypothyroidism, which was statistically significant ($p<0.05$). Of the 91 patients with hemoglobin levels below 11.5 g/dL, 85.7% had normal thyroid function, 13.2% had subclinical hypothyroidism, and 1.1% had overt hypothyroidism, also significant ($p<0.05$). In the group with ferritin levels of 1200-2000 ng/mL, 78.1% had normal thyroid function, 18.8% had subclinical hypothyroidism, and 3.1% had overt hypothyroidism, which was not statistically significant ($p>0.05$). ***Conclusion:*** Subclinical hypothyroidism is commonly seen in thalassemia patients aged 5 to 16 years who undergo regular blood transfusions. Regular physical exams and thyroid function assessments are crucial to detect overt hypothyroidism early. Timely hormone replacement can prevent complications like growth failure and delayed puberty, ultimately improving life expectancy and quality of life in these patients.

Keywords: Children, Hypothyroidism, Prevalence, Subclinical hypothyroidism, Transfusion dependent thalassemia.

INTRODUCTION

Thalassemia is the most common monogenic disorder worldwide [1, 2]. β-thalassemia is a genetic disorder affecting the beta-globin gene, resulting in either reduced (β+) or absent (β0) production of β-globin chains. While more than 200 mutations can lead to β-thalassemia, 20 specific alleles are responsible for 80% of global cases [3, 4]. Hemoglobin E-β-thalassemia accounts for approximately 50% of severe beta-thalassemia cases [5]. The deficiency in beta globin chain production leads to ineffective erythropoiesis, further complicated by the decreased affinity of circulating hemoglobin F for 2,3-diphosphoglycerate [6]. Standard treatments for thalassemia include blood transfusions and iron chelation therapy. However, repeated transfusions increase total body iron levels, resulting in secondary hemosiderosis, which can cause cardiac, endocrine, and hepatic complications [7, 8]. Iron chelation therapy is initiated with deferoxamine when serum ferritin levels reach 1000 ng/ml, or when a child reaches the age of three or has undergone 10–20 blood transfusions. The iron chelators currently used in clinical practice include subcutaneous or intravenous deferoxamine, oral deferiprone, and oral deferasirox. Deferoxamine is typically administered via subcutaneous infusion over 8–10 hours, 5–7 days per week, while oral deferiprone and deferasirox are primarily reserved for patients who cannot tolerate or

respond inadequately to deferoxamine [7, 8]. Endocrinopathies are now common complications in thalassemia patients, with a multifactorial origin. The prevalence of hypothyroidism varies between 6% and 30%, depending on factors such as age, transfusion history, ferritin levels, and the type and dose of iron-chelating agent used [9]. In cases of severe iron overload in patients with thalassemia major, the prevalence of primary hypothyroidism has been reported at 26.8% [9]. Various studies indicate that thyroid dysfunctions occur in 13% to 60% of thalassemic patients after the age of 10, most commonly presenting as subclinical hypothyroidism [1]. The reported prevalence of hypothyroidism in patients with thalassemia major (TM) ranges from 4% to 29%, with the wide variation attributed to factors such as patient genotype, age, ethnic differences, transfusion and chelation treatment protocols, and adherence to therapy. Hypothyroidism in these patients can result from primary gland failure or insufficient stimulation of the thyroid gland by the hypothalamus or pituitary gland [10]. Thyroid dysfunction is primarily caused by iron overload from repeated transfusions, leading to gland infiltration, chronic tissue hypoxia, free radical injury, and organ siderosis. The thyroid gland is often affected before the thyroid-pituitary axis, which is less susceptible to iron-induced damage than the gonadal axis [6]. Thalassemic patients with overt hypothyroidism have been reported to experience stunted growth, delayed puberty, cardiac failure, pericardial effusion, and psychological changes by their second decade of life. These individuals tend to be shorter and have a more delayed bone age compared to euthyroid thalassemic patients [9]. The objective of this study is to determine the prevalence of hypothyroidism in children with thalassemia who are undergoing regular blood transfusions and iron chelation therapy. While a similar study was previously conducted at Dhaka Medical College Hospital among Hemoglobin E-Beta thalassemia patients, no such research has been carried out at Bangladesh Shishu Hospital & Institute until now. The objective of this study was to find out the prevalence of hypothyroidism in transfusion-dependent thalassemic children attending Dhaka Shishu (Children) Hospital.

METHODOLOGY

This was a descriptive cross-sectional study that was carried out at the Thalassemia Centre, Department of Hematology and Oncology, Bangladesh Shishu Hospital & Institute from December 2019 and November 2020. The study involved 140 children with thalassemia, aged 5 to 16 years, who were undergoing regular blood transfusions. The study received approval from the ethical committee of Dhaka Shishu Hospital. Informed consent was obtained from all participants before data collection. The entire study was conducted under the principles of human research outlined in the Helsinki Declaration [11] and adhered to relevant regulations and the General Data Protection Regulation (GDPR) [12]. The inclusion criteria consisted of thalassemia patients aged between 5 and 16 years who were attending the thalassemia center for blood transfusion. The exclusion criteria included patients with chronic viral hepatitis, cardiac complications such as arrhythmia or heart block, renal failure, and those who had undergone splenectomy. The main variables in the study are serum FT4 and TSH levels. Other variables include age, sex, height, presence of splenomegaly, hemoglobin levels, and serum ferritin. Data were collected using a structured questionnaire, administered with the participants' consent and convenience, encompassing all relevant variables. The questionnaire was finalized after a pretesting phase. Collected data were reviewed daily and edited as necessary. Data analysis was performed using SPSS version 23.0. Statistical significance was determined with a P value of less than 0.05.

RESULT

In this study, among the 140 patients, 60.7% were in the age group of 11-16 years, with a mean age of 10.6 ± 4.3 years. The male-to-female ratio was 1:1.3. More than half (55.0%) of the patients came from middle-class families. Anemia was present in 65.0% of the patients, jaundice in 5.0%, and facial dysmorphism in 10.7%. Nearly two-thirds (65.7%) of the patients were found to be stunted. The palpable liver was observed in 68.8%, while splenomegaly was present in 100.0% of the patients. Regular blood transfusions were administered to 76.4% of the patients, with 77.9% receiving transfusions monthly. The mean age at first blood transfusion was 1.2 ± 0.8 years, and the mean total number of blood transfusions over the years was 9.7 ± 3.5. Chelation therapy was given to 92.1% of the patients, and 67.9% had a family history of thalassemia. In the study, 65.0% of patients had hemoglobin levels below 11.5 g/dL. Among the participants, 45.7% had serum ferritin levels between 1200 and 2000 ng/mL, 71.4% had TSH levels ranging from 0.5 to 5.5 µIU/L, and 93.6% had FT4 levels between 10.4 and 37.5 pmol/L. Hypothyroidism was observed in 26.2% of the patients, with 23.5% having subclinical hypothyroidism and 2.9% having overt hypothyroidism. The majority of the 85 patients in the 11-16-year age group had normal thyroid function (58.3%), while 36.5% had subclinical hypothyroidism and 4.7% had overt hypothyroidism, with this distribution being statistically significant ($p < 0.05$). Among the 91 patients with hemoglobin levels below 11.5 g/dL, 85.7% had normal thyroid function, 13.2% had subclinical hypothyroidism, and 1.1% had overt hypothyroidism, which was also statistically significant ($p < 0.05$). For the 64 patients with ferritin levels between 1200 and 2000 ng/mL, 78.1% had normal thyroid function, 18.8% had subclinical hypothyroidism, and 3.1% had overt hypothyroidism, but this finding was not statistically significant ($p > 0.05$).

Table 1: Demographic characteristics of the respondents (N=140)

Variables	n	%
Age group (years)		
5-10 yrs.	55	39.3
11-16 yrs.	85	60.7
Mean ±SD	10.6±4.3	
Sex		
Male	61	43.6
Female	79	56.4
Socio-economic condition		
Low/poor class	46	32.9
Middle class	77	55
Upper class	17	12.1
Marital consanguinity of parents		
Yes	9	6.4
No	131	93.6

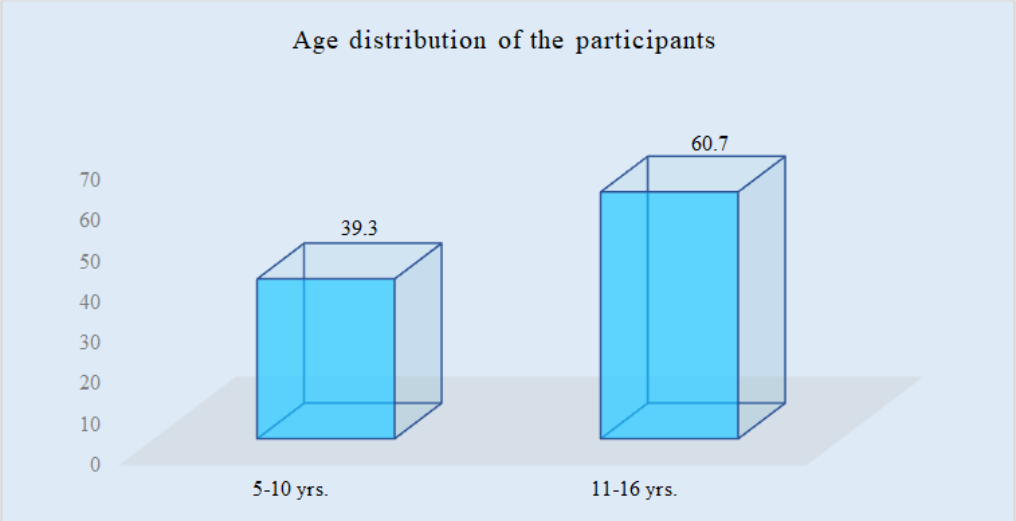

Figure I: Column chart showed age wise respondents (N=140)

Table 2: Physical findings of respondents

Physical findings	n	%
Anemia	91	65
Jaundice	7	5
Facial dysmorphism	15	10.7
Growth		
Stunted	92	65.7
Not stunted	48	34.3
Liver		
Palpable	96	68.6
Not palpable	44	31.4
Spleen		
Palpable	140	100
Blood transfusion		
Regular	107	76.4
Irregular	33	23.6
Interval of blood transfusions		
Weekly	1	0.7
Bi-monthly	4	2.9
Monthly	109	77.9
After every two months	26	18.6

Age at first BT (years)	1.2±0.8	
Total number of BT (years)	9.7±3.5	
Taking Chelation therapy	129	92.1
Family history of thalassemia	95	67.9

Table 3: Investigations of respondents

Investigations findings	n	%
Hemoglobin (gm/dl)		
<11.5	91	65
≥11.5	49	35
Serum ferritin level (ng/mL)		
<1200	21	15
1200-2000	64	45.7
>2000	55	39.3
TSH (µIU/L)		
<0.5	3	2.1
0.5–5.5	100	71.4
>5.5	37	26.4
FT4 (pmol/L)		
<10.4	4	2.9
10.4-37.5	131	93.6
>37.5	5	3.6
Hypothyroidism	37	26.2
Sub-clinical hypothyroidism	33	23.5
Overt hypothyroidism	4	2.9

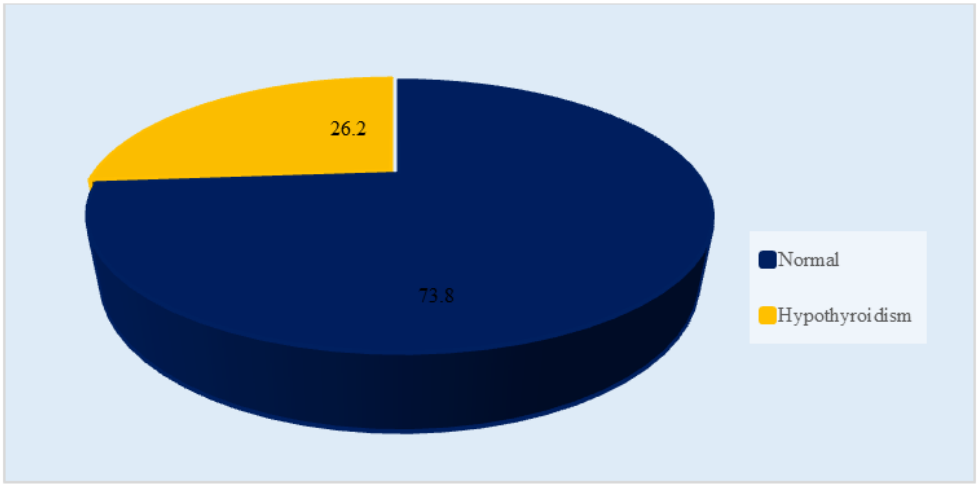

Figure II: Pie chart showed thyroid status of study patients (N=140)

Table 4: Case distribution according to thyroid profile with different age groups

Age (Year)	Total	Normal thyroid profile		Subclinical hypothyroidism		Overt hypothyroidism		p-value
		(n=103)		(n=33)		(n=4)		
		n	%	n	%	n	%	
5-10 yrs.	55	53	96.4	2	3.6	0	0	0.001[s]
11-16 yrs.	85	50	58.8	31	36.5	4	4.7	

Table 5: Case distribution according to thyroid profile with sex distribution

Sex	Total	Normal thyroid profile		Subclinical hypothyroidism		Overt hypothyroidism		p-value
		(n=103)		(n=33)		(n=4)		
		n	%	n	%	n	%	
Male	61	46	75.4	14	23	1	1.6	0.730[ns]
Female	79	57	72.2	19	24.1	3	3.8	

Table 6: Case distribution according to thyroid profile with hemoglobin level

Hemoglobin level (gm/dL)	Total	Normal thyroid profile		Subclinical hypothyroidism		Overt hypothyroidism		p-value
		(n=103)		(n=33)		(n=4)		
		n	%	n	%	n	%	
<11.5	91	78	85.7	12	13.2	1	1.1	0.001[s]
≥11.5	49	25	51	21	42.9	3	6.1	

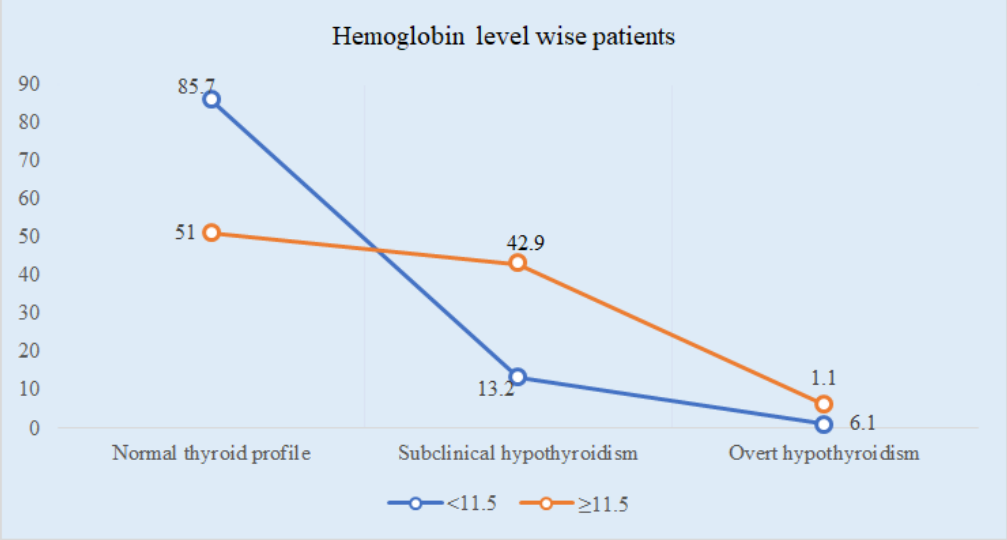

Figure III: Line chart showed hemoglobin level among patients (N=140)

Table 7: Case distribution according to thyroid profile in relation to ferritin level

Ferritin level (ng/mL)	Total	Normal thyroid profile		Subclinical hypothyroidism		Overt hypothyroidism		P-value
		(n=103)		(n=33)		(n=4)		
		n	%	n	%	n	%	
<1200	21	14	66.7	5	23.8	2	9.5	0.160[ns]
1200-2000	64	50	78.1	12	18.8	2	3.1	
>2000	55	39	70.9	16	29.1	0	0	

DISCUSSION

In this study, the majority of patients (60.7%) were aged between 11 and 16 years, with a mean age of 10.6±4.3 years. This differs from Imran *et al*., [13], who reported that most patients were under 5 years of age. The study found a male-to-female ratio of 1:1.3, with males constituting 43.6% and females 56.4%. This is consistent with Mogharab and Mogharab [14], who reported 42% male and 58% female thalassemia patients. Regular blood transfusions were reported in 76.4% of patients, with 77.9% receiving transfusions monthly. Upadya *et al*., [6] also observed that 78.3% of patients received monthly transfusions, while bi-monthly, tri-monthly, and once every 40 days were less common. In this study, 65.0% of patients had hemoglobin levels below 11.5 g/dL, 45.7% had serum ferritin levels between 1200-2000 ng/mL, 71.4% had TSH levels ranging from 0.5–5.5 µIU/L, and 93.6% had FT4 levels between 10.4-37.5 pmol/L. Hypothyroidism was identified in 26.2% of patients, with 23.5% having subclinical hypothyroidism and 2.9% having overt hypothyroidism. In contrast, Pirinccioglu *et al*., [15] reported mean hemoglobin levels of 8.7±0.6 before blood transfusions and 12.8±1.2 after. Serum ferritin levels were found to be 0-1000 ng/mL in 6 patients, 1000-2000 ng/mL in 22, 2000-4000 ng/mL in 35, and >4000 ng/mL in 12. Elevated TSH levels were observed in only three patients, with no instances of low TSH levels. Total T3, T4, serum FT3, and FT4 levels were normal in these three patients. Imran *et al*., [13] found that among 70 thalassemia patients, 43 (61.43%) were euthyroid, 22 (31.43%) had subclinical hypothyroidism, and 5 (7.14%) had overt hypothyroidism. Subclinical hypothyroidism, characterized by isolated elevated TSH levels, was present in 31.43% of these children, consistent with findings by Pirinccioglu *et al*., [15] and Drema *et al*., [16]. In the current study, among 85 patients aged 11-16 years, 58.3% had normal thyroid function, 36.5% had subclinical hypothyroidism, and 4.7% had overt hypothyroidism, with these findings being statistically significant ($p<0.05$). In contrast, Imran *et al*., [13] reported that among 39 children under 5 years, 35 had normal thyroid profiles, 4 had subclinical

hypothyroidism, and none had overt hypothyroidism. In our study, the mean age of euthyroid children was 2.1 years, while the mean age of hypothyroid children was 10.9 years, with this difference being statistically significant. Malik *et al*., [17] reported that primary hypothyroidism was found in 18 (25.7%) patients, with a mean age of 9.2 ± 2.6 years. Patients were categorized into two age groups: Group 1 (ages 5-9 years) and Group 2 (ages 10-14 years). The frequency of hypothyroidism was significantly higher in Group 2 (47%) compared to Group 1 (20%), indicating that the risk of developing hypothyroidism increases with age. In the study by Mogharab and Mogharab [14], no cases of hypothyroidism were observed in patients younger than 5 years old or those aged 5 to 10 years. Hypothyroidism was found in 2 patients (1.8%) in the 5–10-year age group and in 4 patients (3.5%) older than 15 years. This study identified a statistically significant relationship between hypothyroidism prevalence and age, with a notable increase in prevalence among older patients, peaking in those over 15 years. Similarly, Soliman *et al*., [18] reported that the prevalence of overt hypothyroidism increased from 0% at age 7 to 35% by age 18, with 94% of cases occurring after the age of 10 years. In this study, of the 79 female patients, 72.2% had normal thyroid function, 24.1% had subclinical hypothyroidism, and 3.8% had overt hypothyroidism, with no significant difference observed ($p>0.05$). Mogharab and Mogharab [14] found that 6 patients (5.4%) had hypothyroidism, including 2 males (1.8%) and 4 females (3.5%). They reported 45 males (46%) and 61 females (54%) with normal thyroid function, with no statistically significant gender differences. Similarly, Soliman *et al*., [18] reported no significant difference in prevalence between males (7/22 or 32%) and females (10/26 or 38%). In our study, 91 patients had a hemoglobin level <11.5 gm/dl; among these, 85.7% had normal thyroid function, 13.2% had subclinical hypothyroidism, and 1.1% had overt hypothyroidism, with this finding being statistically significant ($p<0.05$). Sharmin *et al*., [19] observed that pre-transfusion hemoglobin levels were significantly different between hypothyroid and euthyroid thalassemic patients, with levels of 5.57±0.98 g/dl in the hypothyroid group and 6.37±0.09 g/dl in the euthyroid group ($p=0.02$). They found a high prevalence of subclinical hypothyroidism among children with transfusion-dependent Hb-E β-thalassemia and noted a significant correlation between hypothyroid status and low hemoglobin levels. In our study, among the 64 patients with a ferritin level of 1200-2000 ng/mL, 78.1% had normal thyroid function, 18.8% had subclinical hypothyroidism, and 3.1% had overt hypothyroidism. However, these differences were not statistically significant ($p>0.05$). Imran *et al*., [13] reported that among 43 euthyroid children, 18 (41.86%) had serum ferritin levels <2000 µg/dl, 10 (23.26%) had levels between 2001-3000 µg/dl, 12 (27.90%) had levels between 3001-4000 µg/dl, and 3 (6.98%) had levels >4000 µg/dl. In the subclinical hypothyroid group of 22 children, 6 (27.27%) had ferritin levels <2000 µg/dl, 2 (9.09%) had levels between 2001-3000 µg/dl, and the remaining had levels between 3001-4000 µg/dl. Among 5 children with overt hypothyroidism, 1 (20%) had ferritin levels <2000 µg/dl, and 4 (80%) had levels between 2001-3000 µg/dl. While serum ferritin is a key indicator of iron status in thalassemic patients, Pirinccioglu *et al*., [15] found a statistically significant difference in mean serum ferritin levels between euthyroid and hypothyroid groups. Conversely, Drema *et al*., [16], Shamshirsaz *et al*., [20], and Jaipuria [21] did not observe a statistically significant difference in mean serum ferritin levels between hypothyroid and euthyroid groups.

LIMITATION OF THE STUDY

The study was conducted at a single hospital in Dhaka city, which may limit the generalizability of the results to the broader national context. Additionally, the small sample size is a significant limitation, highlighting the need for future research with a larger sample to obtain more comprehensive and generalizable findings.

CONCLUSION & RECOMMENDATION

Subclinical hypothyroidism is commonly observed in thalassemia patients aged 5 to 16 years who undergo regular blood transfusions. Regular physical exams and thyroid function assessments are essential for early detection of overt hypothyroidism. Timely hormone replacement can prevent complications such as growth failure and delayed puberty, ultimately improving life expectancy and quality of life in these patients. To enhance understanding and management, further studies involving larger patient populations are recommended. These studies could provide deeper insights into the prevalence, progression, and optimal management strategies for hypothyroidism in thalassemia patients.

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