Prevalence of Hypothyroidism in Transfusion-Dependent Thalassemia

Tarinee Thareepern, MD[1], Surakarn Jansutjawan, MD[2]

[1] Department of Pediatrics, Phra Nakhon Si Ayutthaya Hospital, Phra Nakhon Si Ayutthaya, Thailand; [2] Department of Pediatrics, Bhumibol Adulyadej Hospital, Royal Thai Air Force, Bangkok, Thailand

Abstract

Background: Thalassemia is an inherited blood disorder. It affects the synthesis of globin chains within red blood cells, leading to anemia. The manifestations range from non-transfusion-dependent to transfusion-dependent thalassemia (TDT), the latter requiring regular blood transfusions for survival. Iron overload due to frequent transfusions can result in various complications, including hypothyroidism.

Objective: To determine the prevalence of hypothyroidism in TDT patients and explore its relationship with serum ferritin levels.

Materials and Methods: A cross-sectional descriptive study was conducted at Bhumibol Adulyadej Hospital between October 2022 and December 2023. Thalassemic patients receiving regular blood transfusions every 2-8 weeks for at least 2 years were enrolled, and demographic, clinical, and laboratory data were collected.

Results: Of the 52 eligible patients, the median age was 13 years (range 2 to 59 years). The most prevalent genotype was beta-thalassemia/HbE (69.2%). The mean pre-transfusion hemoglobin was 7.5 g/dL, and the median serum ferritin level was 1,657 ng/mL. Subclinical hypothyroidism was identified in 11.5%. While a longer duration of transfusion was significantly associated with subclinical hypothyroidism, no significant association was found between serum ferritin levels and hypothyroidism.

Conclusion: The present study emphasizes the importance of regular thyroid function evaluations in TDT patients with a long duration of transfusion.

Keywords: Hypothyroidism; Thalassemia; Transfusion dependent thalassemia

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Thalassemia is an inherited blood disorder. It is caused by a problem in the synthesis of globin chains of hemoglobin (Hb) within red blood cells (RBC), affecting both the quantity and quality of RBC. This leads to increased susceptibility to RBC destruction, resulting in subsequent anemia[1].

The clinical manifestations of thalassemia can be categorized into two types based on severity. Transfusion-dependent thalassemia (TDT) requires regular blood transfusions for patient survival. Non-transfusion-dependent thalassemia (NTDT) requires only occasional transfusions, such as during periods of severe illness leading to anemia[2].

Correspondence to:

Thareepern T.

Department of Pediatrics, Phra Nakhon Si Ayutthaya Hospital, 46/1 U Thong Road, Pratu Chai Sub-district, Phra Nakhon Si Ayutthaya District, Phra Nakhon Si Ayutthaya 13000, Thailand.

Phone: +66-86-1375680

Email: Tarinee.bream@gmail.com

ORCID: 0009-0003-2400-871X

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What is already known about this topic?

Previous studies in Thailand reported hypothyroidism prevalence ranging from 4.4% to 17.6% when iron-chelating therapy was not widely used. However, investigations into other potential causes affecting thyroid function in hypothyroid patients were not conducted.

What does this study add?

This study found a prevalence of subclinical hypothyroidism at 11.5% among all patients on iron-chelating agents. All patients with abnormal thyroid function underwent further evaluation to exclude autoimmune hypothyroidism or hypocalcemia as causative factors, all of which were found to be within normal limits.

In Thailand, there were approximately 600,000 patients diagnosed with thalassemia in 2017. Around 23,000 of them required regular blood transfusions for management[2].

Regular blood transfusions remain the primary treatment for TDT. However, it can lead to iron overload. Furthermore, thalassemia contributes to increased iron absorption from the intestines due to ineffective erythropoiesis. Thus, patients with thalassemia usually experience a worsening of the condition of iron overload[3].

Under normal circumstances, iron binds to serum transport proteins known as transferrin, which facilitate

iron transportation to various cells. Typically, about 30% of transferrin is saturated with iron. However, in cases of iron overload, excess iron that surpasses transferrin's capacity appears in the serum in the form of non-transferrin-bound iron (NTBI). NTBI can rapidly enter cells of the liver, heart, and endocrine glands[4], resulting in iron accumulation and affecting the functions of these organs. In the thyroid gland, the accumulation of iron may result in thyroid hormone deficiency (or hypothyroidism)[5].

Hypothyroidism significantly affects growth, development, and neurological function, leading to issues such as poor growth and delayed development in children. Timely diagnosis and prompt treatment are crucial for affected individuals[6].

Studies conducted in Malaysia, Iran, and India revealed the prevalence of subclinical hypothyroidism ranging from 10.4% to 13.6% and clinical hypothyroidism from 0% to 6.8% among the population aged 2 to 25 years[7-9].

Jaruratanasirikul et al.'s work in Southern Thailand in 2007 found the prevalence of subclinical hypothyroidism among children with TDT patients at 17.6%[10]. In 2018, Teawtrakul et al.'s work in Northeastern Thailand revealed a subclinical hypothyroidism prevalence of 4.4% in adolescent and adult TDT patients[11].

The objective of the present study was to determine the prevalence of hypothyroidism among TDT patients. The relationship between hypothyroidism and serum ferritin levels was also investigated.

Materials and Methods

A cross-sectional descriptive study was conducted among TDT patients visiting the outpatient department (OPD) of Bhumibol Adulyadej Hospital (BAH) between October 2022 and December 2023. The study protocol was approved by the ethics committee of BAH. (protocol number 68/65) After providing information, written informed consents were obtained from the patients or guardians of the children.

The inclusion criteria were thalassemia patients who had been receiving regular blood transfusions every 2 to 8 weeks for a minimum period of 2 years. The exclusion criteria included individuals who had congenital heart disease, chronic lung disease, chronic kidney disease, hyperthyroidism, hypothyroidism, or who experienced an acute illness at the time of data collection.

Method of data collection

Subjects who had visited the OPD at BAH within one year before the study initiation (since September 2021) were searched using ICD-10 codes: D560-569. After reviewing electronic OPD cards, patients meeting all criteria were enrolled.

Demographic data and clinical characteristics were obtained from electronic OPD cards. Normally, TDT patients underwent blood collection to assess Hb level before receiving blood transfusions. In this study, an additional 6 mL of venous blood samples were collected during the same session for laboratory analysis. Patients with abnormal thyroid function tests were referred to an endocrinologist for further investigation.

Demographic data included gender and age. Clinical characteristics included classification of thalassemia, duration of transfusion, frequency of transfusion, whether patients were on iron-chelating agents, type of chelating agent used, and whether patients had undergone splenectomy.

Laboratory investigations included pre-transfusion Hb and hematocrit (Hct), which were measured using the flow cytometry method of Sysmex XN-9000™ Automated Hematology Analyzer. Thyroid-stimulating hormone (TSH), free thyroxine (FT4), serum ferritin, 25OH-vitamin D level, and calcium level were measured using the electrochemiluminescence (ECL) immunoassay on the Cobas e801 machine. All laboratory data were collected concurrently at a single time point.

Sample size estimation

According to Jaruratanasirikul et al.[10], the prevalence of hypothyroidism in TDT patients in Thailand was 17.6%. Acceptable error was 0.1, and the significance level was 0.05. The sample size was calculated using an infinite population proportion. The minimal sample size needed was 56 samples.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). Normality was assessed using the Kolmogorov-Smirnov test. In descriptive analysis, continuous variables were presented as means and standard deviations (SD) or as medians and interquartile range (IQR). Categorical variables were shown as frequencies and percentages. Univariate analysis was performed using logistic regression modeling. A level of p-value less than 0.05 was considered statistically significant.

Results

Thalassemia patients who visited the OPD at BAH

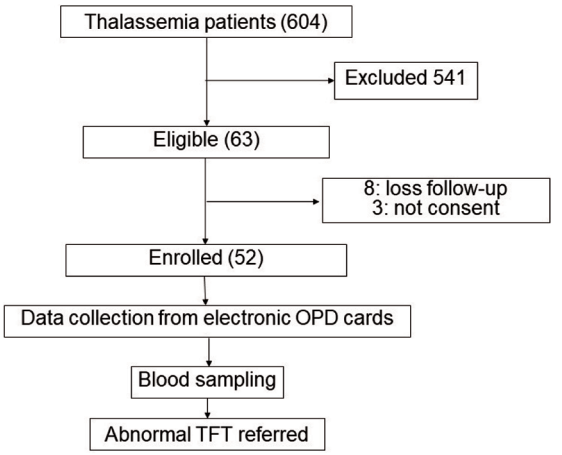

Figure 1. Study flow of hypothyroidism in transfusion-dependent thalassemia.

OPD: outpatient department, TFT: thyroid function test, referred: referred to endocrinologist

up to September 2021 were reviewed using ICD-10 codes: D560-569. Six hundred and four were found (Figure 1). Then, 541 patients were excluded due to not meeting all criteria. Sixty-three patients were chosen for the intervention. Subsequently, eight patients were lost during the follow-up before the beginning of the study. Three patients refused to participate in the study. A total of 52 patients were enrolled.

Demographic data and clinical characteristics were presented in Table 1. Female patients comprised half of the participants. Age ranges from two to 59 years of age, with the median of 13 years (IQR 10 to 25.7). Thirty-two patients (61.5%) were children (less than 18 years old). Median duration of transfusion was 6 years (IQR 4 to 16) and transfusion frequency was every 4 weeks (IQR 4 to 6). All patients were on iron-chelating agents. And a quarter of them used more than one type of iron-chelating agent. The chelating agents used are listed in Table 2.

Regarding the classification of thalassemia by genotype(1), the most common genotype found in the present study was beta-thalassemia/HbE (36 patients, 69.2%), followed by EF Bart's disease (4 patients, 7.7%), HbH with Constant Spring (CS) disease (4 patients, 7.7%), and HbH disease (3 patients, 5.8%).

Laboratory data were also shown in Table 1. Mean pre-transfusion Hb was 7.5 g/dL (SD ±1.4), with 17.3% (9 patients) having a pre-transfusion Hb of at least 9 g/dL. Additionally, the median ferritin level was 1,657 ng/mL (IQR 1,254-3,324). The mean ferritin level was 2,497.1 ng/mL (SD ±1,944.7).

Sufficiency, insufficiency, and deficiency of vitamin D status were classified based on 25-OH

Table 1. Demographic data, clinical characteristics, and laboratory data in transfusion-dependent thalassemia (n=52)

	Value
Female; n (%)	27 (51.9)
Age (years); median (IQR)	13 (10-25.7)
<18 years; n (%)	32 (61.5)
DT (years); median (IQR)	6 (4-16)
Frequency (weeks); median (IQR)	4 (4-6)
On iron-chelating agent(s); n (%)	52 (100)
≥1 chelation	13 (25.0)
Splenectomy; n (%)	6 (11.5)
Hb (g/dL); mean±SD	7.5±1.4
Hct (%); mean±SD	23.4±4.1
Ferritin (ng/mL); median (IQR)	1,657 (1,254-3,324)
Vitamin D status; n (%)	
Deficiency	34 (65.4)
Insufficiency	13 (25.0)
Normal	5 (9.6)

IQR=interquartile range; SD=standard deviation; DT=duration of transfusion; Hb=hemoglobin, Hct=hematocrit
Frequency: frequency of transfusion

Table 2. Type of iron-chelating agents used in patients (n=52)

Type	n (%)
Deferoxamine only	0 (0.0)
Deferiprone only	19 (36.5)
Deferasirox only	20 (38.5)
Deferoxamine with Deferasirox	2 (3.9)
Deferiprone with Deferasirox	10 (19.2)
Deferoxamine with Deferiprone with Deferasirox	1 (1.9)

vitamin D levels of 30 to 100, 20 to 29, and lower than 20 ng/mL, respectively[12]. More than half of the patients (65.4%) had vitamin D deficiency.

Thyroid status was categorized into two groups: subclinical hypothyroidism, which was characterized by normal FT4 but elevated TSH, and clinical hypothyroidism, which was characterized by low FT4 and elevated TSH. In the present study, 6 patients (11.5%) had subclinical hypothyroidism, while there was no patient with clinical hypothyroidism. All patients with abnormal thyroid status were subsequently tested for serum calcium levels and autoimmune hypothyroidism antibodies. All further investigations revealed normal results.

Comparison of clinical characteristics and laboratory data of patients with subclinical hypothyroidism and normal thyroid status is shown in Table 3. Duration of transfusion was the only statistically significant factor between the two

Table 3. Comparison of clinical characteristics and laboratory data of patients with subclinical hypothyroidism (n=6) and normal thyroid status (n=46)

	Subclinical	Normal	p-value
Age (years); median (IQR)	27.5 (19.8 to 40.5)	13 (10 to 22)	0.057
DT (years); median (IQR)	23.5 (12.5 to 33.8)	6 (4 to 12)	<0.001
Splenectomy; n (%)	2 (33.3)	4 (8.7)	0.136
Hb (g/dL); mean±SD	6.63±0.96	7.65±1.4	0.078
Ferritin (ng/mL); median (IQR)	1,301 (942 to 3,679)	1,757.5 (1,255 to 3,530)	0.636
Vitamin D status; n (%)			0.298
Deficiency	5 (83.3)	29 (63.0)	
Insufficiency	1 (16.7)	12 (26.1)	
Normal	0 (0.0)	5 (10.9)	

IQR=interquartile range; SD=standard deviation; DT=duration of transfusion; Hb=hemoglobin
Normal: normal thyroid status, Subclinical: subclinical hypothyroidism

Table 4. Comparison of the present to previous literature

	Tan[7]	Baghersalimi[8]	Khandelwal[9]	Jaruratanasirikul[10]	Teawtrakul[11]	Present
Year	2019	2019	2020	2007	2018	2023
Site	Malaysia	Iran	India	S, Thailand	NE, Thailand	C, Thailand
Cases (n)	82	67	60	51	91	52
Female (%)	45.1	62.7	41.7	56.9	61.5	51.9
Age (years)	13.7 (2.5 to 25.3)	15.4±3.7	7.7±2.9	13.5±3.9	19.5±10	13 (10 to 25.7)
DT (years)	8.3 (0.9 to 22.8)	14.3				6 (4 to 16)
Most genotype (%)	BTM (60)			BE (78.4)	BE (100)	BE (69.2)
On ICA (%)	100	100	5	31.4	92.3	100
Splenectomy (%)				13.7	51.6	11.5
Mean Hb	9.1 (6.0 to 10.9)	9.1±1.0	7.2±1.9	7.5±0.9	7.8±2.5	7.5±1.4
Mean ferritin	2,165.5	2,251.8	1,296.6	5,215	2,091	2,497.1
Hypothyroidism (%)						
Subclinical	13.4	10.4	13.6	17.6	4.4	11.5
Clinical	4.9	0	6.8	0	0	0

BE=beta-thalassemia/HbE; BTM=beta-thalassemia major; C=central; DT=duration of blood transfusion; Hb=hemoglobin; ICA=iron-chelating agent; NE=northeastern; S=southern

groups. Median duration of transfusion in patients with subclinical hypothyroidism was 23.5 years (IQR 12.5 to 33.8), while in normal thyroid status was 6 years (IQR 4 to 12). However, age, percentage of patients undergone splenectomy, pretransfusion Hb, ferritin level, and vitamin D status had no statistically significant differences.

Discussion

In Table 4, compared to previous studies conducted in Asian countries, the present study revealed a prevalence of hypothyroidism that was similar to that of Baghersalimi et al.[8] in Iran but lower than that reported by Tan et al.[7] in Malaysia and Khandelwal et al.[9] in India.

The prevalence of hypothyroidism in the present study was 11.5%, which is higher than the prevalence in the normal population in Thailand (around 4.16%)[13].

When compared with other studies conducted in Thailand, the present study showed a slightly higher prevalence of hypothyroidism than that of Teawtrakul et al. in 2018[11]. However, it was lower compared to Jaruratanasirikul et al. in 2007[10]. The difference may be associated with the mean serum ferritin levels, reflecting iron overload[14]. In Jaruratanasirikul et al., the percentage of patients on iron-chelating agents was lower than in the present study (31.4% vs. 100%). This resulted in a higher mean serum ferritin, potentially explaining the differences in prevalence[10].

Mean pretransfusion Hb was 7.5 g/dL, consistent with previous studies in Thailand. However, only 9 patients (17.3%) had pretransfusion Hb levels exceeding 9 g/dL, which is the target level according to the guidelines for thalassemia patient care in

Thailand[2].

In the present study, patients who had vitamin D deficiency and insufficiency were 65.4% and 25%, respectively. This percentage was higher compared to the healthy Thai population, which reported 5.7% and 45.2%, respectively[15].

The present study revealed an association between the duration of transfusion and thyroid status, indicating a longer duration in individuals with hypothyroidism ($p<0.001$). This association was not reported in previous studies in Thailand. However, no significant difference was shown in Tan et al[7].

When comparing the mean ferritin levels between the hypothyroidism and euthyroidism groups, no association was found, which is consistent with findings from previous studies in Thailand. Consequently, a single serum ferritin measurement may not accurately reflect the long-term cumulative iron deposition within the thyroid gland. Furthermore, most patients in this study were receiving iron chelation therapy, which can affect current serum ferritin levels.

The strengths of the present study included the various ages of patients, from children to adults. Additionally, further investigations were done in patients with abnormal thyroid status to rule out autoimmune hypothyroidism or hypocalcemia, which may be associated with hypothyroidism[16,17].

Future studies utilizing the average of multiple serum ferritin measurements may provide a more accurate representation of iron overload and its relationship with the development of hypothyroidism.

Conclusion

Hypothyroidism remains one of the complications in TDT patients with iron overload. The present study identified an 11.5% prevalence of subclinical hypothyroidism, which was significantly associated with a longer duration of blood transfusion. However, no significant correlation was observed between serum ferritin levels and thyroid dysfunction. Consequently, regular thyroid function screening is strongly recommended for TDT patients, particularly those with a transfusion history exceeding 12 years. This recommendation aligns with the Thailand clinical practice guideline for the management of thalassemia, which advises annual screening of TSH and FT4 in TDT patients starting from 10 years of age.

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Authors' contributions

TT was responsible for the study's design, data collection, statistical analysis, and the revision of the manuscript. SJ provided expert consultation on the research framework and supervised the study. Both authors have read and approved the final version of the article.

Clinical trial registration

Not applicable, this study is a cross-sectional study.

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Bhumibol Adulyadej Hospital (Protocol Number: 68/65). Written informed consent was obtained from all individual participants or their legal guardians included in the study.

Use of artificial intelligence

The authors declare that Gemini 3 Flash was used in the preparation of this manuscript only for language editing and grammar correction. The authors have reviewed and edited the content as needed and take full responsibility for the final content of the manuscript.

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