Original Article

# A prospective cross-sectional study of thyroid dysfunction in transfusion- dependent beta-thalassemia patients

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## ABSTRACT

**Objective:** The objective of the study was to determine the hospital-based prevalence of thyroid dysfunction in transfusion-dependent beta-thalassemia in children and to study the correlation between serum ferritin levels and thyroid functions. **Methods:** This prospective cross-sectional study in transfusion-dependent thalassemia patients was conducted in the department of pediatrics of a teaching hospital in India. General and systemic examinations were done and recorded and hemoglobin (Hb)%, thyroid-stimulating hormone (TSH), T3, T4, free thyroxin 4 (FT4), serum ferritin, and anti-thyroid peroxidase (TPO) levels were estimated in the laboratory. Initially, the estimation of Hb, TSH, T3, T4, and serum ferritin was done for all the study participants. Later, the specific values of FT4 and anti-TPO were estimated in study participants with high TSH values. **Results:** Fifty beta-thalassemia children aged between 3 and 18 years were chosen in this study. The prevalence of subclinical hypothyroidism was 6% and no cases of clinical or central hypothyroidism were found. The mean serum ferritin level was 2671 ± 1592 ng/ml; however, no positive correlation between serum ferritin and TSH values was seen. **Conclusion:** In thalassemia patients, the thyroid failure usually occurs by the second decade of their life. It is important that all beta-thalassemia children should undergo annual screening of thyroid functions in addition to detection of their serum ferritin levels.

**Key words:** Beta-thalassemia, Blood transfusion, Hypothyroidism, Prevalence, Serum ferritin

Thalassemia is one of the most common inherited blood disorders resulted by a reduction/absence of the globin chains in the human body leading to mild-to-severe anemia from birth. The regular blood transfusions with adequate iron chelation remain the mainstay of the treatment in transfusion-dependent thalassemia (TDT) patients. Iron overload in TDT patients is secondary to the multiple blood transfusions and increased iron absorption [1-3]. The excessive iron accumulated in the TDT patients potentially catalyzes the free radicals generation in them. As a result, extensive iron-induced injury develops in the heart, liver, pancreas, and endocrine system of the patients [4,5].

There are 3.5 million thalassemic carriers in India with an estimate of 10,000 thalassemic births every year. The carrier rate of beta-thalassemia gene varies between 1% and 3% in South India and 5–15% in North India [6]. The primary, subclinical, and secondary hypothyroidisms are the thyroid dysfunction reported in thalassemia patients [6-11]. The frequency of hypothyroidism shows a difference depending on the region, quality of management, and treatment protocols [7,8].

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As per available data in the literature, there are few studies conducted in Karnataka regarding the prevalence of hypothyroidism in thalassemia patients. The objective of this study was to determine the prevalence and type of hypothyroidism in TDT patients in a teaching hospital in India and to study the correlation of thyroid function with the serum ferritin levels.

## METHODS

This prospective cross-sectional study was conducted in the department of pediatrics of a multispecialty teaching hospital in India from November 1, 2018, to April 30, 2020, after receiving ethics approval from the Institutional Human Ethical Committee. Sample size was calculated using the formula: $(n) = z^2 (p) (q)/d^2$. Where, n is sample size, z is confidence interval (95%), p is proportion of prevalence (3%), q is 1-p, and d is margin of error expressed as decimal (0.5). Based on the prevalence of beta-thalassemia in South India as 3%, the margin of error for the same is 5% with confidence interval 95% and sample size of 50 beta-thalassemia patients. The type of sampling used in this study is purposive sampling.

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We enrolled TDT children after obtaining written informed consent from their parents/guardians. Patients with age between 3 and 18 years and regular blood transfusions for at least 2 years and serum ferritin values of >1000 ng/ml (as iron starts to accumulate in tissues only above 1000 ng/ml) were included in the study. Patients were excluded from the study if they were known case of hypothyroidism and on treatment.

All demographic details such as age, gender, and place of residence were collected along with the details of age at thalassemia diagnosis, frequency of blood transfusions, and iron chelation therapy. General examination for pallor, jaundice, thyroid symptoms, thyroid swelling in neck, hemolytic facies, and anthropometry and the systemic examination for hepatosplenomegaly, splenectomy scar, and cardiac complications were done by the researchers. Under aseptic precautions, 3 ml of peripheral venous blood was collected in ethylenediaminetetraacetic acid (EDTA) Vacutainer and serum Vacutainer from the participants. The EDTA Vacutainer was used for pre-transfusion hemoglobin (Hb) estimation while the serum Vacutainer was used for the estimation of thyroid-stimulating hormone (TSH), T3, T4, free thyroxin 4 (FT4), serum ferritin, and anti-thyroid peroxidase (TPO). Hb was estimated using Sysmex Hematology Analyzer. The TSH, T3, T4, FT4, serum ferritin, and anti-TPO were assessed by electrochemiluminescence assay techniques using Roche Cobas E-601 Analyzer. Initially, the estimation of Hb, TSH, T3, T4, and serum ferritin was done for all the study participants. Later, the specific values of FT4 and anti-TPO were estimated in study participants with high TSH values.

The results obtained were entered into spread sheet and statistical analysis was done using SPSS 21.0 version for Windows. $P < 0.05$ was considered statistically significant. The descriptive statistics were done by mean, standard deviation, frequency, and percentage and the inferential statistics were done by Chi-square test and Pearson correlation coefficient.

## RESULTS

Out of total 50 beta-thalassemia children, 31 (62%) were male and 19 (38%) were female ($P = 0.090$). The mean age was 9.49 ± 4.82 years with minimum and maximum ages being 3 and 18 years, respectively (Table 1). The majority of cases (28%) had weight for age in the category <3rd centile ($P = 0.001$), as shown in Table 2. The majority of cases (28%) had height for age <3rd centile and Chi-square test revealed $P = 0.001$ (Table 2). The mean duration of transfusion was 8.23 ± 4.72 years with a range of 2–17.42 years (Table 3). The mean pre-transfusion Hb was 8.9 ± 1.3 g/dl (range: 5–11.3 g/dl). The mean serum ferritin value was 2671 ± 1592 ng/ml (range: 1017–7343 ng/ml). The mean TSH was 2.82 ± 1.31 µU/ml (range: 0.79–6.52 µU/ml), as shown in Table 3.

The observed correlation coefficient between serum ferritin and TSH values was 0.071 which shows that the serum ferritin and TSH values were not significantly ($P = 0.624$) correlated (Table 4). In our study, a majority of cases, that is, 45 (90%) had normal TSH levels while 5 (10%) cases had elevated TSH levels when compared to age-specific values. In patients having elevated TSH levels, FT4 and anti-TPO levels were estimated to rule out Hashimoto's disease. Among these five patients, two could not be followed up and in the remaining three patients, FT4 and anti-TPO levels were normal. The mean serum ferritin values for the normal

**Table 1: Distribution of subjects based on gender and age**

| Gender | Frequency | | Percentage | |
|---|---|---|---|---|
| Male | 31 | | 62 | |
| Female | 19 | | 38 | |
| Total | 50 | | 100 | |
| **Number** | **Minimum age** | **Maximum age** | **Mean age** | **SD** |
| 50 | 3 | 18 | 9.49 | 4.82 |

**Table 2: Distribution of subjects based on weight for age**

| Centile | Weight for age | | Height for age | |
|---|---|---|---|---|
| | Frequency | Percentage | Frequency | Percentage |
| <3rd | 14 | 28.0 | 14 | 28.0 |
| 10th | 9 | 18.0 | 8 | 16.0 |
| 10th–25th | 2 | 4.0 | 3 | 6.0 |
| 25th | 5 | 10.0 | 6 | 12.0 |
| 25th–50th | 1 | 2.0 | 1 | 2.0 |
| 3rd | 8 | 16.0 | 6 | 12.0 |
| 3rd–10th | 5 | 10.0 | 6 | 12.0 |
| 50th | 4 | 8.0 | 2 | 4.0 |
| 75th–90th | 1 | 2.0 | 2 | 4.0 |
| 90th | 1 | 2.0 | 2 | 4.0 |
| Total | 50 | 100 | 50 | 100 |

**Table 3: Mean duration of transfusion of subjects (n=50)**

| Parameters | Minimum | Maximum | Mean | Standard deviation |
|---|---|---|---|---|
| Duration of transfusion (years) | 2.00 | 17.42 | 8.23 | 4.72 |
| Pre-transfusion Hb | 5.00 | 11.30 | 8.91 | 1.38 |
| Ferritin (ng/ml) | 1017.00 | 7343.00 | 2671.98 | 1592.38 |
| TSH (µU/ml) | 0.79 | 6.52 | 2.82 | 1.31 |

**TSH: Thyroid-stimulating hormone, Hb: Hemoglobin**

**Table 4: Correlation between serum ferritin and TSH (n=50)**

| Investigation | Ferritin | TSH |
|---|---|---|
| Ferritin | | |
| Pearson correlation | 1 | 0.071 |
| Sig. (two tailed) | | 0.624 |
| TSH | | |
| Pearson correlation | 0.071 | 1 |
| Sig. (two tailed) | 0.624 | |

**TSH: Thyroid-stimulating hormone, Hb: Hemoglobin**

TSH and elevated TSH groups were 2560.40 ± 1430.24 ng/ml and 3676.20 ± 2675.83 ng/ml, respectively. However, this difference was non-significant ($P = 0.139$).

## DISCUSSION

In our study, males and females constituted 62–38%, respectively, and the mean age was 9.49 ± 4.82 years. We also observed that monotherapy was more used than combination therapy for iron chelation. We found that 28% of the thalassemic children in our study had weight for age and height for age <3rd centile as per the CDC charts. Growth failure is well-known in TDT due to chronic iron overload. Similar findings were witnessed in studies conducted by Kundu *et al*. and Singhal and Goyal [12,13].

In our study, the mean pre-transfusion Hb was 8.9 ± 1.3 g/dl. Ineffective erythropoiesis and splenic sequestration lead to a state of chronic anemia. Out of 50 patients, 5 patients were found to have elevated TSH. They were further evaluated with FT4 and anti-TPO and we ruled out autoimmune thyroiditis. Although two cases could not be followed up, remaining three cases had normal FT4 levels (subclinical hypothyroidism) with normal anti-TPO levels. Among these three children, two were on combination therapy (deferasirox and deferiprone) and one was only on deferasirox. In our study population, majority were on deferasirox only as their serum ferritin levels were being maintained without the additional need of deferiprone. None of them had experienced any adverse effects to the chelators. We do not think the choice of iron chelator affects the study. In our study, the prevalence of subclinical hypothyroidism was 6% and there were no cases with clinical or central hypothyroidism. Our study is in good agreement with studies carried out by Panchal and Patel and Mogharab and Mogharab [14,15]. However, these were in the contrary to the findings shown by Singhal and Goyal and Kundu *et al*. [12,13]. This shows that there is a wide range of the prevalence of hypothyroidism which is influenced by various factors such as sample size, patient's age, chelation regimen, and availability of chelators.

The mean age of the subclinical thyroid patients in the current study was 12.3 years. It is known that thyroid failure starts from the 2nd decade of life and worsens in the 3rd and 4th decades. Serial liver biopsies performed in much younger children have shown that iron starts accumulating in the parenchymal tissues within 1 year of transfusions. It is pertinent that early detection of subclinical hypothyroidism is done since hormone replacement therapy is readily available. The three subclinical hypothyroid patients in our study will be followed up. The thyroid function tests will be performed once in 6 months and once in 12 months for the hypothyroid and euthyroid population.

The mean serum ferritin for the euthyroid group and subclinical hypothyroid group was 2560 ± 1430 ng/ml and 3676 ± 2675 ng/ml, respectively ($P = 0.139$). Although serum ferritin is the best known marker to assess iron overload, our study showed no correlation between TSH levels and serum ferritin levels ($P = 0.624$). This was in good agreement with studies done by Panchal and Patel while it was on the contrary to results obtained by Mogharab and Mogharab [14,15].

## CONCLUSION

Hypothyroidism in thalassemic patients can progress to arrhythmias and heart dysfunction, which can lead to cardiac failure. Clinical signs of hypothyroidism are often unnoticed till the late 2nd decade. Autoimmune thyroiditis should be ruled out in children with clinical/subclinical hypothyroidism; especially, in the 2nd decade of life. It is of great importance that hypothyroidism should be detected early, and treatment must be initiated so that the quality of life of patients can be improved.

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