# Thyroid Function in β-Thalassemic Children Receiving Hypertransfusions with Suboptimal Iron-Chelating Therapy

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*A cross-sectional study of thyroid function, free thyroxine ($FT_4$) and thyrotropin (TSH) concentrations, was carried out in 51 transfusion-dependent β-thalassemic patients receiving suboptimal iron-chelating therapy. Nine patients had normal $FT_4$ levels with elevated TSH levels (5.9-15.6 mIU/L), consistent with the diagnosis of compensated primary hypothyroidism and giving a prevalence of abnormal thyroid function of 17.6%. All patients with abnormal thyroid function had negative thyroid antibodies. No particular risk factor for abnormal thyroid function could be identified. Of the nine patients with compensated primary hypothyroidism, one patient showed a further increase in TSH level after 1 year of follow-up. The results of the present study emphasize the importance of thyroid function monitoring in hypertransfused β-thalassemic patients.*

**Keywords:** *Hypothyroidism, Subclinical hypothyroidism, Thalassemia, Thyroid dysfunction*

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In Thailand, thalassemia is a major health problem with a prevalence of disease of 0.5% and prevalence of carriers of 1.5-2.0%[1,2]. The treatment of β-thalassemia in the institute consists of hypertransfusions to keep hemoglobin level > 8 g/dL. Due to limitations in the treatment budget, an iron-chelating agent was available in only 30-40% of the patients, and even then only at a suboptimal dosage. The majority of thalassemic patients receiving hypertransfusions develop hemochromatosis at the end of the first decade of life.

Thyroid gland dysfunction is a well-documented endocrine complication after long-term hemochromatosis in transfusion-dependent β-thalassemic patients[3-6]. Previous studies in hypertransfused β-thalassemic patients have found the prevalence of hypothyroidism to range from 0-35% depending on the age of studied population, the duration of receiving blood transfusions, the amount of iron overload, the dosage of iron-chelating agent, and the procedure used for evaluation[7-20].

The authors conducted a cross-sectional study in the present β-thalassemic patients who were receiving hypertransfusions without or with only suboptimal iron-chelating therapy to determine the prevalence of abnormal thyroid function and the clinical characteristics associated with this defect.

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## Material and Method

Pediatric patients with β-thalassemia who were under a regular follow-up schedule at the Pediatric Hematology Clinic in Songklanagarind Hospital were invited to participate in the present study. The inclusion criteria were patients who 1) were older than 8 years, 2) had received blood transfusion 10 mL/kg every 2-4 weeks for more than 3 years, and 3) agreed to participate in the present study. In the authors' clinic, the patients received a blood transfusion 10 mL/kg every 2-4 weeks to keep their hemoglobin level above

8 g/dL and hematocrit above 25%. Due to the limitations of treatment budget, an iron-chelating agent (desferoxamine) can be given in only some patients, and then with an average dosage of 20 mg/kg/day for 2 days/week, a suboptimal level (the standard dose of desferoxamine is 30-50 mg/kg/d for 5 days/week). The data collection included the age at diagnosis, the age at the first blood transfusion, the amount of total blood transfusion, use of the chelating agent, family history of thyroid diseases, body weight, and height of the patients, height of the parents, liver function test, hemoglobin, hematocrit, and ferritin levels.

From January 2005 to March 2006, the authors recruited 51 patients who met the criteria. The clinical characteristics of the studied patients are summarized in Table 1. Of the total 51 patients, only 16 (31.4%) had received iron-chelating agent. To account for sex- and age-dependency, height and weight of the patients were calculated to standard deviation score (SDS) by using the actual measurement minus the mean, then divided by the standard deviation, using the reference data of Thai children[21].

Blood samples were drawn in the morning after an overnight fasting and at least 2 weeks after the last blood transfusion.

The protocol for the present study was approved by the Ethics Committee of Songklanagarind Hospital and written informed consent was obtained from each subject.

### *Assay for thyroid function test*

Free thyroxine ($FT_4$) was measured by radioimmunoassay (RIA), and thyroid-stimulating hormone (TSH) was measured by immunoradiometric assay (IRMA). The minimal detectable levels of $FT_4$ and TSH were 0.02 ng/dL, and 0.005 mIU/L, respectively. The interassay and intra-assay coefficients of variations of $FT_4$ were 6.6%, and 2.9%, respectively, and those of TSH were 5.4%, and 2.1%, respectively.

The normal range for $FT_4$ was 0.70-1.75 ng/dL and TSH 0.25-5.00 mIU/L. The cut-points for thyroid dysfunction were as follows: $FT_4 < 0.70$ ng/dL with TSH > 5.00 mIU/L was considered overt primary hypothyroidism; $FT_4$ in the normal range with TSH > 5.00 mIU/L was consistent with compensated hypothyroidism; $FT_4 < 0.70$ ng/dL with low or normal TSH was considered secondary hypothyroidism.

### *Statistical analysis*

Characteristics of the studied patients were summarized by mean $\pm$ standard deviation, number, and percent. Differences between patients with and without abnormal thyroid function were tested with unpaired t-test, $X^2$ test, and Fisher's exact test to identify the potential risk factors. A p-value of $< 0.05$ was considered statistically significant.

## Results

Serum $FT_4$ concentration was in the normal range in all patients with the mean level of $1.16 \pm 0.20$ ng/dL (range 0.72-1.52). TSH concentration was in the normal range in 42 patients with the mean level of $3.10 \pm 1.02$ mIU/L (range 0.54-4.89). Nine patients (17.6%) had a TSH level above 5.00 mIU/L (5.9-15.6) and were classified as compensated hypothyroidism. Of the nine patients who had elevated TSH, two of them had $FT_4$ in the low normal range of 0.70 and 0.79 ng/dL. $FT_4$ and TSH were followed up over the following 12 months. All nine patients showed persistent elevation of TSH with one patients having elevation of TSH up to 18.3 mIU/L. All nine patients had negative results for anti-thyroglobulin and anti-microsomal antibodies. There were no clinical signs or symptoms of hypothyroidism in any patients. The clinical characteristics of patients in both groups are compared in Table 2. There was no statistical difference in any clinical characteristics between these two groups.

## Discussion

Thyroid dysfunction in β-thalassemic patients has been reported in various prevalence, ranging from a low prevalence of 0-12%[7-9,11,13,14,18-20], to a high prevalence of 16-35%[10,12,15-17]. The discrepancies of prevalence in those previous studies can be related to the different methods used for thyroid function studies (serum thyroxine and thyrotropin concentrations, or thyrotropin-releasing hormone test), the different ages of the studied patients (pediatric or adult), difference amount of blood transfusion, and the differing dosages of iron-chelating therapy[7-20]. To evaluate thyroid function abnormality, the thyrotropin-releasing hormone (TRH) stimulation test is more sensitive than the conventional method of measurement of thyroxine and TSH levels in detecting hypothyroidism. A study by Masala et al found that the prevalence of hypothyroidism diagnosed by the concentrations of $T_4$ and TSH was only 5%, whereas hypothyroidism diagnosed by TRH stimulation tests increased the dysfunction rate up to 35%[11]. The more sensitive detection by TRH stimulation test over conventional $FT_4$ and TSH measurements was explained by two reasons; firstly, TRH test can detect subclinical primary hypothyroidism by demonstrating

**Table 1.** Clinical characteristics of the studied patients (n = 51)

| | |
|---|---|
| Male : Female | 22/29 |
| Age at time of test (yr) | 13.5 ± 3.9 (range 8.4-25.4) |
| Type of thalassemia | |
| β thal/HbE | 40 (78.4%) |
| β thal$^{+}$/β thal$^{+}$ | 8 (15.7%) |
| β thal□/β-thal$^{+}$ | 3 (5.9%) |
| Age at diagnosis (yr) | 3.2 ± 3.0 (range 0.2-13.8) |
| Age at first blood transfusion (yr) | 3.7 ± 3.2 (range 0.5-14.9) |
| Amount of blood transfusion (L) | 40.5 ± 18.7 (range 10.6-80.0) |
| No. of patients who had a splenectomy | 7 (13.7%) |
| Age at splenectomy (yr) (n = 7) | 7.8 ± 2.5 (range 4.1-11.1) |
| No. of patients receiving desferoxamine | 16 (31.4%) |
| Hemoglobin (g/dL) | 7.8 ± 0.9 (range 5.9-10.3) |
| Hematocrit (%) | 23.1 ± 2.8 (range 18-31) |
| Ferritin level (μg/L) | 5,215 ± 3,233 (range 1,314-16,100) |
| Weight SDS | -1.01 ± 1.03 (range -3.83- +1.17) |
| Height SDS | -1.47 ± 1.52 (range -5.49- +1.90) |
| Midparental height SDS | -0.19 ± 1.05 (range -2.85- +2.15) |

SDS = standard deviation score

**Table 2.** Comparison of characteristics and laboratory results of patients with normal thyroid function (n = 42) and abnormal thyroid function (n = 9)

| | Normal thyroid function (n = 42) | Abnormal thyroid function (n = 9) | p-value |
|---|---|---|---|
| Age at time of test (yr) | 13.6 ± 3.9 | 13.9 ± 2.2 | 0.63 |
| Age at diagnosis (yr) | 3.2 ± 3.0 | 3.2 ± 2.3 | 0.98 |
| Age at initial blood transfusion (yr) | 3.8 ± 3.4 | 3.3 ± 2.2 | 0.67 |
| Amount of blood transfusion (L) | 37.8 ± 10.7 | 40.7 ± 16.8 | 0.69 |
| Ferritin level (μg/L) | 5,240 ± 2,417 | 4,825 ± 2,064 | 0.33 |
| Weight SDS | -0.96 ± 1.01 | -1.23 ± 1.18 | 0.47 |
| Height SDS | -1.42 ± 1.37 | -1.70 ± 1.23 | 0.36 |
| Midparental SDS | -0.23± 1.08 | -0.06 ± 0.94 | 0.63 |
| Patients receiving desferoxamine | 14/42 | 2/9 | 0.70 |
| Patients who had a splenectomy | 7/42 | 2/9 | 0.65 |

SDS = standard deviation score

the exaggerated response of TSH in the presence of prolonged low normal $FT_4$ levels, and secondly, the method of $FT_4$ measurements by RIA was the conventional method. However, since the scarcity of TRH, the concentrations of $T_4$ and TSH are commonly used and accepted for evaluation of thyroid function.

The present study demonstrated the prevalence of abnormal thyroid function to be 17.6%, which was in the high prevalence range. This high prevalence was probably due to the protocol treatment of hypertransfusions with suboptimal iron-chelating therapy, as evidenced by the very high ferritin levels. The importance of iron-chelating therapy in thalassemic patients receiving hypertransfusions has been shown by the low prevalence of thyroid dysfunction in patients who has been treated with adequate dosages of a chelating agent and the ferritin levels < 2,500 μg/L[13]. However, there was no correlation between thyroid dysfunction and ferritin levels in most of the previous studies.

The abnormal thyroid function found in the presented patients was the isolated elevation of TSH, which was consistent with the diagnosis of compensated hypothyroidism, the most common thyroid

dysfunction in all previous reports[7-20]. Overt primary hypothyroidism and secondary hypothyroidism were not found in the presented patients. However, the thalassemic patients with mild or subclinical hypothyroidism might be undetected by using the conventional methods of measurement for $FT_4$ (RIA) and TSH (IRMA). The persistent elevation of TSH after 1-year follow-up of the thyroid function in the presented patients with one patient showing a progressive increase in TSH levels, which suggested that there was persistent damage to the thyroid tissue by chronic iron deposition. However, the other common cause of acquired compensated hypothyroidism, autoimmune thyroiditis, has to be excluded. The presented patients were all negative for thyroid auto-antibodies.

The treatment for compensated primary hypothyroidism in hypertransfused β-thalassemic patients is still the subject of controversy. The longitudinal study by Landau showed that there was no significant change in $T_4$ and TSH levels after the duration of 15 years follow-up[22]. Of the nine thalassemic patients with elevated TSH in the present study, only one patient who had further elevation of TSH levels. All these patients have been followed-up yearly.

In conclusion, the present study demonstrated compensated hypothyroidism in hypertransfused β-thalassemic patients, who received suboptimal iron-chelating therapy. No definite risk factor for abnormal thyroid function was identified. These finding emphasizes the importance of monitoring of thyroid function in all hypertransfused thalassemic patients, particularly who received suboptimal chelating agents. Patients who have elevated TSH levels should be followed-up yearly.

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## *การทำงานของไทรอยด์ฮอร์โมนในผู้ป่วยเด็กโรคธาลัสซีเมียชนิดเบต้าที่ได้รับเลือดปริมาณมากแต่ได้รับยาขับเหล็กในปริมาณที่ต่ำกว่ามาตรฐาน*

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*การศึกษาแบบตัดขวางโดยการเจาะเลือดเพื่อประเมินการทำงานของไทรอยด์ฮอร์โมน (free thyroxine, $FT_4$ และ thyrotropin, TSH) ในผู้ป่วยเด็กโรคธาลัสซีเมียชนิดเบต้าที่ได้รับเลือดปริมาณมากแต่ได้รับยาขับเหล็กในขนาดที่ต่ำกว่ามาตรฐาน จำนวน 51 คน ผลการศึกษาพบว่ามีผู้ป่วย 9 คนที่มีภาวะต่อมไทรอยด์ทำงานผิดปกติโดยมีระดับ $FT_4$ ปกติแต่มีระดับ TSH สูงกว่า 5.00 มิลลิยูนิต/ล. (5.9-15.6 มิลลิยูนิต/ล.) เข้าได้กับการวินิจฉัย compensated primary hypothyroidism ความชุกของความผิดปกติของไทรอยด์ฮอร์โมนเท่ากับร้อยละ 17.6 ผู้ป่วยทุกรายที่มีความผิดปกติของไทรอยด์ฮอร์โมนตรวจไม่พบ thyroid antibody และไม่พบภาวะอื่นที่เกี่ยวข้องกับความผิดปกติของไทรอยด์ฮอร์โมน การติดตามผู้ป่วย 9 คนในปีถัดมา พบว่า 1 ราย มีระดับ thyrotropin สูงเพิ่มขึ้น จากผลการศึกษานี้แสดงให้เห็นถึงความสำคัญของการติดตามประเมินการทำงานของไทรอยด์ฮอร์โมนในผู้ป่วยธาลัสซีเมียชนิดเบต้าที่ได้รับเลือดปริมาณมาก*