Original Article

# Assessment of Hypothyroidism in Children with Beta-Thalassemia Major in North Eastern Iran

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## Abstract

### Background

Hypothyroidism usually appears in the second decade of life and is thought to be associated with iron overload in patients with thalassemia major. This study aimed to evaluate thyroid dysfunctions in patients with beta-thalassemia major.

### Materials and Methods

This research is a descriptive – cross sectional study, carried out in 2009 to assess thyroid function in 100 patients with beta thalassemia major at the ages between 2-18 years. The study was carried out retrospectively and 100 medical records from 400 samples of thalassemia major patients, under regular care of Sarvar Clinic, were assessed. Thyroid function and iron load status were evaluated by measuring the serum total triiodothyronine (T4), thyroid-stimulating hormone (TSH) and ferritin levels from the serum of patients, admitted to the Sarvar Clinic. TSH and T4 concentrations were estimated by enzyme-linked immunosorbent assay (ELISA). Primary hypothyroidism was defined by a TSH level >4μIU/ml. Results were analyzed by descriptive statistical methods, with the help of SPSS software.

### Results

Subclinical hypothyroidism was seen in 7% patients. All of them had normal T4 levels with elevated TSH levels, consistent with a diagnosis of subclinical hypothyroidism. Mean age of hypothyroid patients was 10.2 ± 2.5 years. Frequency of hypothyroidism was associated with increased serum ferritin levels (p=0.037).

### Conclusion

Subclinical hypothyroidism occurs in a significant proportion of thalassaemia major patients in the absence of obvious clinical signs of hypothyroidism. Regular follow-up for early detection and timely treatment of such complications could improve the quality of life of these patients.

## Keywords

Hypothyroidism, beta-thalassemia, Epidemiology

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## Introduction

Beta thalassaemia represents a group of recessively inherited haemoglobin disorders characterized by deficient synthesis of the β-globin chain. The homozygous state results in severe anaemia in infancy, which requires regular blood transfusion (1). Beta-thalassemia is one of the most common genetic diseases in Iran. Iran has about 20,000 homozygote β-thalassaemia patients and 3,750,000 carriers (2). The combination of blood transfusion and chelation therapy has dramatically prolonged the life expectancy of these patients, thus transforming thalassaemia from a rapidly fatal disease of childhood to a chronic disease compatible with a prolonged life (3). On the other hand frequent blood transfusions, iron overload, poor compliance to therapy and chronicity of the disease have in turn contributed to a whole spectrum of complications including cardiac problems, hypogonadism, diabetes mellitus, hypo-thyroidism, hypoparathyroidism and other endocrine and metabolic problems in adolescents and young adults suffering from thalassaemia major (4). In recent years, several authors reported a high incidence of endocrine abnormalities in children, adolescents and young adults suffering from thalassemia major. However the incidence of the various endocrinopathies changes among different series of the patients due to a mixture of reasons other than iron overloads (5).

The commonest form of thyroid dysfunction, seen in thalassaemics, is subclinical hypothyroidism due to abnormalities of the thyroid gland which, leads to insufficient production of thyroid hormones. However, the frequency of hypothyroidism varies depending on the region, quality of management and treatment protocols (1). The main aim of this study was to determine the frequency of hypo-thyroidism in the children suffering from thalassaemia major.

## Materials and Methods

In order to perform this study, we analyzed medical records of 100 children with beta thalassemia major that had been admitted to the Sarvar Clinic, Dr. Sheikh Pediatric Hospital, Mashhad University of Medical Sciences, Iran in 2009. This clinic provides medical services to the individuals with thalassemia and hemorrhagic disorders in north eastern Iran. All the current children are in the continuous and regular contact with Sarvar Clinic. This research is a descriptive – cross sectional study to assess thyroid function in 100 patients with beta thalassemia major between the ages of 2-18 years. The study was carried out retrospectively and 100 medical records from 400 samples of thalassemia major patients, under regular care at Sarvar Clinic, were assessed. The diagnosis of thalassaemia major was based on the usual haematological criteria i.e. peripheral blood evaluation and Hb electrophoresis. Patient history included demographic data, initiation, duration and frequency of blood transfusion as well as chelation therapy. All patients were regularly transfused every 3-4 weeks with packed red cells since early years of life and were receiving sub-optimal iron-chelating therapy.

Chelation was started many months after the onset of blood transfusions. Serum total thyroxine (T4), thyroid-stimulating hormone (TSH) and Serum ferritin levels were obtained from the patient's medical records and the most recent values were recorded for analyses. TSH and T4 concentration were analyzed by ELISA.

Hypothyroidism was defined by a TSH level >4 μIU/ml, T4 levels <4.5 μg/dl that were defined as decreased. The thyroid function status of the patients was classified as subclinical hypothyroidism (increased TSH, normal T4, and T3) and overt (increased TSH, decreased T4 and/or T3) hypothyroidism primary.

## Statistical Analysis

Data was analyzed by using Statistical Package for Social Sciences, SPSS Software for Windows (version 14.0). The results were computed as mean ± standard

deviation for quantitative variables (age, duration of transfusion, thyroid profile and serum ferritin levels) using t-test. The results for categorical variables (gender) were computed as frequencies and percentages using Chi-square (with 95% confidence interval). In all statistical analysis, only $p<0.05$ was considered significant.

## Results

Of the 100 cases of beta thalassemia, 55% patients were male and 45% were female, with an age range of 2-18 years (mean age of 10.8±4.4 years). Subclinical hypo-thyroidism was present in 7% patients (increased TSH, normal T4). We have not assessed primary hypothyroidism (Increased TSH, decreased T4 and/or T3). The mean TSH and T4 were 2±1.2 µIU/ml and 7.3±1.9 µg/dl, respectively. The mean age of hypothyroid patients was 10.2±2.5 years. Patients were divided into 2 groups on the basis of age. Group 1 had patients ranging from 2-9 years whereas group 2 patients were of ages between 10-18 years. The frequency of hypothyroidism was significantly higher in group 2 (as compared to group 1 indicating an increase in the risk of this complication with advancing age ($p\leq0.02$). The mean of T4 was significantly higher in group 1 as compared to group 2 ($p\leq0.03$). The mean of standing height (percentile) in patient with higher T4 was better than others ($p\leq0.02$). Among the 7 hypothyroid patients, there were 3 males and 4 females. Thus, there was no significant difference in the frequency of hypothyroidism between boys and girls. The mean percentile of the group with ferritin more than 2500 units was lower than those of the patients with ferritin lower than 2500 ($p\leq0.5$). Mean ferritin level was 3924±1247 ng/ml in hypothyroid and 2183±1528 ng/ml in normal patients indicating a significant difference in mean serum ferritin levels between hypothyroid patients and others ($p=0.037$). Of the 7 patients who tested positive for hypothyroidism, 7 patients showed compensated subclinical hypothyroidism and we have no patients with uncompensated hypothyroidism.

## Discussion

Hyper-transfusion has improved the life expectancy of thalassaemic patients, over the decades. However, chelation therapy is expensive, difficult to administer and not as readily available, hence the compliance is often poor despite regular transfusions resulting in iron overload (6).

It has been demonstrated that thyroid abnormalities in these patients are related to iron overload. Histological studies have supported this hypothesis (7). However, the serum ferritin is the most widely used test for assessment of iron status in these patients. In this study, a significant association was found between ferritin levels and thyroid functional status; the ferritin levels of hypothyroid patients being significantly higher than euthyroid patients. The precise mechanism by which iron overload causes tissue damage is not completely understood, though it is suggested that tissue iron deposits act at the cellular level causing damage via free radical formation and lipid peroxidation resulting in mitochondrial, lysosomal and sarcolemmal membrane damage. In the thyroid gland, this affects the production of thyroid hormones and manifests as varying degrees of primary hypothyroidism. Hence, it is postulated that higher serum ferritin levels predispose to a greater risk of developing endocrinopathies like hypothyroidism. It has been suggested that thyroid dysfunction may be reversible by intensive chelation. Also, most complica-tions can be avoided if serum ferritin levels are brought down to <1500 ng/ml (8). Apart from iron overload, other factors responsible for organ damage have been previously pointed out including anaemia and chronic hypoxia that may potentiate the toxicity of iron deposition in endocrines (9). Some studies reported a

high prevalence of primary hypo-thyroidism, reaching up to 17–18%, while others reported low prevalence of 0–9% (10, 11). It is important to note that even in the studies in which the prevalence of overt hypothyroidism as a complication of thalassemia major is relatively low, milder forms of thyroid dysfunction are much more common (9,10) though again there are wide variations in different reports. These discrepancies cannot be attributed to differences in patients' ages, but rather to difference treatment protocols, including differing transfusion rates and chelation therapies (11).

Malik et al (2010) have reported primary hypothyroidism in 18 (25.7%) out of 70 patients. Of these, 17 had normal T4 levels with elevated TSH levels consistent with a diagnosis of Subclinical hypothyroidism whereas only one patient showed a decreased T4 level with elevated TSH (overt hypothyroidism). Mean age of hypothyroid patients was 9.2 ± 2.6 years. Frequency of hypothyroidism was associated with increased serum ferritin levels. Primary hypothyroidism occurs in a significant proportion of thalassaemia major patients in the absence of obvious clinical signs of hypothyroidism. Regular follow-up for early detection and timely treatment of such complications could improve the quality of life of these patients (12). Also, viral infections as well as individual susceptibility have been implicated in causing endocrine dysfunction. The results of this study are comparable to the frequencies reported elsewhere. Thyroid dysfunction has been reported in 13-60% of patients with thalassaemia, but its severity is variable in different series (1). Thalassaemic patients having thyroid dysfunction have shown a greater incidence of other complications including multiendocrine dysfunction, worsening of already compromised cardiac function, more pronounced growth retardation, liver disease and need for splenectomy during the course of the disease (13). Several studies have reported a lack of concordance of ferritin concentrations with the thyroid function status (1,14,15). This may be, in part, due to the fact that serum ferritin levels increase linearly with the transfusion load up to 100 units of transfused blood, but thereafter, there is no simple relationship between theme (16). Also, misleading ferritin levels can occur with chronic inflammatory disease (17) as well as vitamin C deficiency (18).

## Conclusion

Subclinical hypothyroidism occurs in a significant proportion of thalassaemia major patients in the absence of obvious clinical signs of hypothyroidism. Regular follow-up for early detection and timely treatment of such complications could improve the quality of life of these patients.


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## Conflict of Interest

We have no conflict of interest.

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