

# Prevalence of Hypothyroidism in Patients with Thalassemia Major in Jahrom City: A Descriptive & Cross-Sectional Study

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## Abstract

**Introduction:** Thalassemia major is the most common genetic heritable disorder in the world passed from carriers to offspring. Combined therapy for thalassemia major (blood transfusion and iron chelation) significantly increases lifetime of the patients. However, frequent blood transfusions lead to iron overload and multiple endocrine disorders such as hypogonadism, diabetes, hypothyroidism and hypoparathyroidism in transfusion-dependent homozygous beta-thalassemia patients. Hypothyroidism is a major problem in thalassemia patients that seriously affects human development. Therefore, preventive measures should be considered to treat hypothyroidism. The present study aimed to estimate the prevalence of hypothyroidism in patients with thalassemia major in Jahrom City.

**Materials & Method:** This was a descriptive, cross-sectional study in which 112 patients with thalassemia major were evaluated in Cooly's Center in Motahari Hospital in Jahrom City. Thyroid function was measured using T3 uptake and TSH, T4 and T3 concentrations. Serum ferritin level was evaluated by radioimmunoassay. Data analysis was performed using SPSS 11, t-test and Pearson correlation coefficient.

**Results:** Thyroid hormone level was normal in 106 of 112 total examined patients (94.6%). Six patients (5.4%) suffered from hypothyroidism. The highest prevalence of hypothyroidism belonged to the patients older than 15 (4 patients) based on age group. Hypothyroidism was also more prevalent in females (n = 4 and 66.7%). Mean ferritin levels in patients with hypothyroidism and euthyroid were respectively as 2413-2830 and 3200-5000 mg/l. Therefore, there was a direct relationship between prevalence of hypothyroidism and serum ferritin level.

**Conclusion:** According to the above-mentioned materials, prevalence of hypothyroidism in thalassemia major patients is relatively low in Jahrom city due to regular monitoring and evaluation of thyroid function, young age and duration of blood transfusions in these patients.

**Keywords:** thalassemia major, serum ferritin, hypothyroidism.

## INTRODUCTION

Iran is one of the countries located on thalassemia belt in the world. The most common types of thalassemia are the most frequent genetic disorders in the global scale. Carriers of the disease are commonly found in various

countries. Therefore, it is necessary to differ thalassemia from iron deficiency anemia through differential diagnosis. Geographic dispersion of the disease can be depicted as a belt expanding from the Mediterranean and the Middle East to some parts of Africa, India and Europe. The disease is divided into two main types: a) alpha thalassemia: synthesis of globin alpha chain is either reduced or stopped; b) beta-thalassemia: synthesis of beta-globin chain is impaired. Carriers of beta thalassemia genes suffer from varying degrees of beta thalassemia major. Bone marrow transplantation was successfully used for treatment of beta thalassemia. However, this treatment was associated with high mortality rates due to donor-related post-bone marrow transplantation

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complications. Such medication as hydroxy urea were successfully used in multiple clinical trials for treating anemia in beta-thalassemia patients. These medications increase fetal hemoglobin level (HbF) [1]. High distribution and frequency of beta thalassemia genes in malaria prone areas increase the rate of mutation in these genes, which leads to malfunctioned synthesis of beta globin chain that ultimately reduces the risk of malaria [2]. Couples are more aware of the risk of having children with thalassemia given the development [advent] of in vitro diagnostics and popularity of genetic counselors [3]. A problematic case is raised when one spouse is carrier of thalassemia gene and HbA2 and MCV levels are relatively normal in the other one (e.g. HbA2 = 3.3%, MCV = 80 Fl). Currently, all the couples with the same afore-mentioned problems should undergo gene mutation analysis in order to eliminate any rare overlooked error or inaccuracy in earlier genetic tests. This analysis can identify all known causes of beta thalassemia in couples with different ethnic groups and reduce the risk of harboring a child with major thalassemia to zero [3]. Molecular disorder either reduces or stops synthesis of beta chain in beta thalassemia. The main characteristic of the disease is reduced synthesis of beta chain from biochemical perspective. The rate of synthesis of beta chain is half the normal rate and ratio of beta chain to alpha chain is 5-7% in heterozygotes. Beta chain is almost not synthesized in homozygotes (about a third of thalassemia patients). The rate of synthesis of beta chain varies from 5 to 30% in homozygotes ( $\beta^+\beta^+$ ) and double homozygotes ( $\beta^+/\beta^0$ ) [4]. In addition, 70-85% of normoblast cells are destructed in homozygotes. Therefore, red blood cells contain a relatively large amounts of fetal hemoglobin in thalassemia major patients. Moreover, delta chain synthesis is normal and A2 hemoglobin is relatively increased in these patients [4]. Severity of clinical symptoms of beta thalassemia homozygosity can be predicted through the ratio of synthesis of gamma chain to alpha chain in bone marrow cells. Those individuals with higher rates of gamma chain to alpha chain have less free alpha chain and represent clinical symptoms of thalassemia intermediate rather than thalassemia major [5]. Other causes of Hypothyroidism: iatrogenic hypothyroidism is a common cause of hypothyroidism that can be diagnosed through screening test prior to representation of symptoms. Transient hypothyroidism is followed up by 3-4 months radioactive treatment due to irreversible damages caused by radiation regardless of cell destruction. Since TSH is inhibited due to hypothyroidism, free T4 levels are measured instead of TSH to determine thyroid function in months after radioactive iodine treatment. Mild post- thyroidectomy hypothyroidism may be healed after a few months. Since the remaining thyroid gland is stimulated with

increased TSH levels, subclinical hypothyroidism occurs in the patients with biochemical evidence of thyroid hormone deficiency with no apparent or mild clinical symptoms of hypothyroidism. No universally accepted guideline is found for treatment of subclinical hypothyroidism. Unnecessary treatments should also be avoided since only a slight increase is detected in TSH levels. In additional, some patients do not benefit from treatment in clinical terms. On the other hand, the risk of apparent hypothyroidism increases, especially when TPO antibodies with low dose of levothyroxine (25-50  $\mu\text{g}/\text{d}$ ) are used to normalize TSH level [6]. The present study aimed to evaluate the prevalence of hypothyroidism in patients with thalassemia major in Jahrom City.

## MATERIALS AND METHOD

This was a descriptive, cross – sectional study in which 112 patients with thalassemia major were examined in Cooly's Center in Motahari Hospital in Jahrom City. Thyroid function test was requested for a number of patients since no similar test was performed earlier. The results of these tests were evaluated in order to identify hypothyroid patients. All the patients had thalassemia major. Regular blood transfusion and desferal were used to treat these patients. Other parameters such as age, gender, type of thalassemia and serum ferritin levels were also taken into account in this study. There were no restriction in terms of age. Thyroid function was evaluated by measuring T3 uptake, TSH, T4, T3 concentrations and serum ferritin levels through radioimmunoassay. Data analysis was performed using SPSS 11, t-test and Pearson correlation coefficient.

## RESULTS

In this study, 112 thalassemia patients were examined. Four males and females (3.6%) were younger than 5, 22 males and females (19.6%) were from 5 to 10 years old, 23 females and males (56.3%) were older than 15. Total number of males thalassemia patients was 47 (42%) and

**Table 1: Age group distribution of thalassemia major patients in Jahrom City in 2005**

Gender Age group	Males		Females		Total	
	Number	Percent	Number	Percent	Number	Percent
Younger than 5 years old	0	0	4	6	4	3.6
10-15	14	30	9	14	23	20.5
Older than 15 years old	26	55	37	57	63	56.3
Total	47	100	65	100	112	100

**Table 2: Distribution of hypothyroidism in patients with thalassemia major in Jahrom City in 2005**

Age Status	Younger than 5		5-10		10-15		Older than 15		Total
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	
Hypothyroidism	0	0	0	0	2	8.7	4	6.3	6
Normal	4	100	22	100	21	91.3	59	93.7	106
Total	4	100	22	100	23	100	63	100	112

**Table 3: Distribution of hypothyroidism in patients with thalassemia major in Jahrom City in 2005 by gender**

Gender Status	Males		Females		Males and females	
	Number	Percent	Number	Percent	Number	Percent
Hypothyroidism	2	4.3	4	6.2	6	5.4
Normal	45	95.7	61	93.8	106	94.6
Total	47	100	65	100	112	100

**Table 4: Distribution of mean serum ferritin levels in patients with thalassemia major based on hypothyroidism or absence of the disease**

Hypothyroid	3200-5000 mg/l
Normal	2413-2830 mg/l

total number of female thalassemia patients was 65 (58%). No statistically significant relationship was found between age and gender in different groups in this study.

In this study, no trace of hypothyroidism was found in the patients younger than 5 and from 5 to 10 years old; 2 patients (1.8%) in 5-10 age group suffered from hypothyroidism and 4 patients (3.5%) patients older than 15 experienced hypothyroidism.

There was a statistically significant relationship between prevalence of hypothyroidism and age in this study. Accordingly, the prevalence of hypothyroidism increased with increased age. The highest prevalence of hypothyroidism belonged to patients older than 15.

According to Table 3, 47 males (42%) and 65 females (58%) participated in this study. Six patients (5.4%) were diagnosed with hypothyroidism (2 males (1.8%) and 4 females (3.5%)). Moreover, 45 males (46%) and 61 females (54%) had normal thyroid function. No statistically significant relationship was found between hypothyroidism and gender in this study.

Mean serum ferritin levels in patients with hypothyroidism and euthyroid were respectively as 3200-5000 mg/l and 2413-2830 mg/l. Therefore, there was a direct relationship between prevalence of hypothyroidism and serum ferritin level.

## DISCUSSION

Beta-thalassemia refers to a group of inherited hemoglobin disorders that was explained by Cooley and Lee for the first time. The disease is characterized by reduced synthesis of  $\beta$ -globin chain. The disease would be associated with severe anemia and demand blood transfusion in case that the offspring inherits the thalassemia gene from both parents [7]. A combined therapy of blood transfusions and iron chelating significantly increases survival rate and lifetime of the patients (the patients live until 40s or 50s). However, frequent blood transfusions lead to iron overload and multiple endocrine disorders such as hypogonadism, diabetes, hypothyroidism and hypoparathyroidism [8]. There are more than 20000 patients with thalassemia major in Iran. The thyroid status in patients with thalassemia was studied in adolescence in this study. This factor has a considerable effect on quality of life of patients in the future. In this study, 112 patients with thalassemia regularly visited Cooley's Center in Motahari Hospital in Jahrom City. Among these patients, 47 were males (42%) and 65 were females (58%). Thyroid function test was carried out for all patients in six-month intervals. Iron chelation therapy was performed for all patients using desferal. Blood samples were taken from fasting patients. Thyroid function was evaluated by measuring TSH, H4, T3 concentrations and radioimmunoassay in order to diagnose hypothyroidism. The prevalence of hypothyroidism was 5.4% in this study. Prevalence of thyroid disorder was reported from 13 to 60% in numerous studies. However, severity of the disease varies in different population of patients. High prevalence of hypothyroidism was reported as 17-18% [9-10] and low prevalence of hypothyroidism was reported as 0-9% [11-12] in different studies. However, milder thyroid disorders are more common in studies with low prevalence of primary

hypothyroidism [9, 12 and 13]. Certainly, the prevalence of hypothyroidism varies in different studies. Age group, treatment methods and iron chelation therapy are involved in prevalence of hypothyroidism in different centers [11]. The highest prevalence of hypothyroidism belonged to age group older than 15 (4 patients). Hypothyroidism was also more prevalent in females than males ( $n = 4$ , 66.7%). Most scholars related hypothyroidism to iron overload. Histological studies have also confirmed this hypothesis [14]. Serum ferritin level was considerably higher in hypothyroid patients compared to normal individuals in this study. These findings support the effect of iron overload on endocrine disorders. However, other reports found no relationship between thyroid disorder and serum ferritin level. Although thalassemia patients with serum ferritin level  $< 2500 \mu\text{g/dl}$  have excellent prognosis, serum ferritin level was lower than  $2000 \mu\text{g/dl}$  in a number of patients with thyroid disorder. Therefore, it seems that other factors except iron overload affect this issue. These risk factors are as follows:

1. Chronic liver disease secondary to iron overload (viral infection)
2. Increased collagen deposition secondary to an increase in iron-dependent prolyl collagen proline hydroxylase activity that causes thyroid microcirculation.
3. Chronic anemia
4. Individual differences in susceptibility to damage caused by iron overload

In general, thyroid disorders were not associated with age, gender, hemoglobin and nationality in this study but iron overload and frequent blood transfusions were higher in patients with hypothyroidism than normal individuals. Treatment of the disease depends on its severity. Patients who were severely affected were treated with levothyroxine.

## CONCLUSION

Thyroid dysfunction in Cooley's patients in Motahari Hospital in Jahrom City was not a major problem but regular assessment of thyroid is necessary in the patients older than 15.

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