

# HYPOTHYROIDISM IN BETA THALASSEMIA MAJOR PATIENTS AT RAHIM YAR KHAN

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## ABSTRACT

**Background:** Hypothyroidism is one of the common complications among beta thalassemia. **Objective:** To determine the frequency of hypothyroidism in patients of beta thalassemia major in Thalassemia center, Rahim Yar Khan. **Methodology:** Study design: Single center cross-sectional study. Place and duration of study: This study was carried out in “Thalassemia Center”, Sheikh Zayed Hospital, Rahim Yar Khan over a period of one year from 1<sup>st</sup> January to 31<sup>st</sup> December 2015. This study was carried out on 144 patients of thalassemia major aged 5-16 years. The data was collected regarding demographic variables, serum ferritin, T4 and TSH and duration of transfusion. The data was entered and analyzed by using SPSS version 19. **Results:** Hypothyroidism was found in 45 (31.2%) patients. Of these, 42 (93.3%) had sub clinical hypothyroidism (normal T4 level with elevated TSH) whereas only 3 (6.7%) patients has overt hypothyroidism (decreased T4 level with elevated TSH). Frequency of hypothyroidism has significant association with patient's age and duration of transfusion. **Conclusion:** Sub clinical hypothyroidism occurs in a significant proportion of thalassemia major patients. Frequency of hypothyroidism has significant association with age and duration of transfusion. Regular follow-up of thalassemic patients to detect and timely treat such complication could improve the quality of life of these patients.

**Key Words:** Thalassemia major, Iron overload, Hypothyroidism.

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## INTRODUCTION

Beta-thalassemia is one of the most common hereditary hemolytic anemia in our country which is characterized by the defect in the synthesis of the beta chains of hemoglobin which may manifest clinically as asymptomatic to severe anemia. Thalassemia is present in a high frequency in Mediterranean basin, Middle East, Indian subcontinent and Southeast Asia.<sup>1</sup> Worldwide 15 million patients have clinically apparent thalassemic disorder. Every year about 100,000 babies are born with severe form of thalassemia worldwide.<sup>2</sup> About 200 million people of the world have  $\beta$ -thalassemia gene (carriers).<sup>3,4</sup>

In Pakistan, the carrier frequency of  $\beta$ -thalassemia is 5% - 8% and may increase up to 62.2% in immediate family members of thalassemia patients.<sup>5</sup> There are approximately 9 million carriers of  $\beta$ -thalassemia in Pakistan, resulting in birth of more than 5000 thalassemia major patients every year.<sup>6,7,8</sup> Presently there are estimated 100,000 cases of thalassemia in Pakistan, which makes up for almost 5% of world cases.<sup>6</sup> The only curative treatment for thalassemia major is stem cell/ bone marrow transplantation but it is very

costly, not free from hazards and is not easily available.<sup>9</sup> In Pakistan, the main treatment option in practice is repeated blood transfusion along with iron chelation therapy. The combination of regular blood transfusion and iron chelation therapy has remarkably extended the life expectancy of thalassemic patients who can now survive up to fourth and fifth decades of life in many centres of the world.<sup>7</sup> Iron overload if not treated properly, can lead to most common endocrine complications like growth retardation, delayed puberty, hypothyroidism, hypoparathyroidism, diabetes mellitus and others include cardiomyopathy and liver cirrhosis.<sup>10</sup> These complications lead to compromised quality of life and poor survival with average life expectancy around 10 years in majority of the centers of Pakistan.<sup>2</sup>

The commonest form of thyroid dysfunction seen in thalassemia patients is primary hypothyroidism which results due to iron deposition in the thyroid gland that ultimately leads to parenchymal fibrosis. The frequency of hypothyroidism may vary from 6 to 30% depending upon the geographical location and quality of iron chelation being practiced.<sup>11</sup> Primary hypothyroidism is defined by a TSH level more than 4mIU/ml. The primary hypothyroidism is divided

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into Sub clinical hypothyroidism which is characterized by elevated TSH with normal free T4 and Overt/Clinical hypothyroidism characterized by elevated TSH with Low freeT4. Secondary or Central hypothyroidism is uncommon in thalassemics before adult age having decreased T4 and low TSH.<sup>11,12</sup> The classical clinical signs of hypothyroidism in thalassemia major patients are not easily appreciated because most of the symptoms, especially in mild cases, are nonspecific and are frequently attributed to anemia or associated diseases.

Thalassemic patients with overt/clinical hypothyroidism exhibit stunted growth, delayed puberty, cardiac failure and pericardial effusion.<sup>12</sup> Good compliance with iron chelation therapy may prevent or improve sub-clinical hypothyroidism. Patients with overt hypothyroidism should be given L-thyroxine. According to the Thalassemia International Federation (TIF) guidelines, free T4 and TSH need to be performed annually at  $\geq 9$  years in all  $\beta$  thalassemia major patients.<sup>13</sup> The objective of our study was to determine the frequency of hypothyroidism in thalassemia major patients at Rahim Yar Khan.

## METHODOLOGY

This cross-sectional study was carried out on 144 patients of beta thalassemia major with age (5-16 years) who were registered at Thalassemia Center, Sheikh Zayed Hospital, Rahim Yar Khan. This study was approved by the Institutional Review Board and informed verbal consent was obtained from parents of all patients. Study was carried out over a period of one year from 1<sup>st</sup> January to 31<sup>st</sup> December 2015. The Inclusion criteria was:

1. Thalassemia major patients (registered at Thalassemia Center for at least 6 months)
2. Received at least 10-20 transfusion
3. Serum ferritin  $>1000\text{ng/ml}$
4. The patients without iron chelation therapy

The data was collected regarding demographic variables, duration of transfusion. Serum ferritin, freeT4 and TSH were performed in pathology laboratory of Sheikh Zayed Hospital, Rahim Yar Khan. T4, and TSH assays were done using enzyme-linked immunosorbent assay (ELISA). Hypothyroidism was defined by a TSH level  $>4\mu\text{IU/ml}$  and T4 levels  $<4.5\mu\text{g/dl}$ . It was further divided as sub clinical hypothyroidism (increased

TSH, normal T4) and overt hypothyroidism (increased TSH, decreased T4). Data was analyzed by using SPSS software version 19.0. The results were calculated as mean  $\pm$  standard deviation for quantitative variables (age, transfusion duration, and serum ferritin levels) while frequency and percentage was calculated for categorical variables. P value  $<0.05$  was taken as significant.

## RESULTS

Total patients were 144 with 67% male and 33% female with 79% of the patients in age group 5-10 years while 21% in age group 11-16 years. Mean age of the study subjects was  $7.97 \pm 2.73$  years. Out of 144 study subjects, 45 (31.2%) were having primary hypothyroidism with mean age of  $8.53 \pm 3.16$ . Of these hypothyroid cases, 42 (93.3%) having sub-clinical hypothyroidism and 3(6.7%) having clinical or overt hypothyroidism.(Figure II) Among the 45 hypothyroid patients, there were 34 (76%) males and 11 (24%) females. Mean ferritin level of study subjects was  $3348 \text{ ng/ml} \pm 1794 \text{ ng/ml}$  while of hypothyroid cases was  $3805 \text{ ng/ml} \pm 1912 \text{ ng/ml}$ .

Figure I: Frequency of hypothyroidism

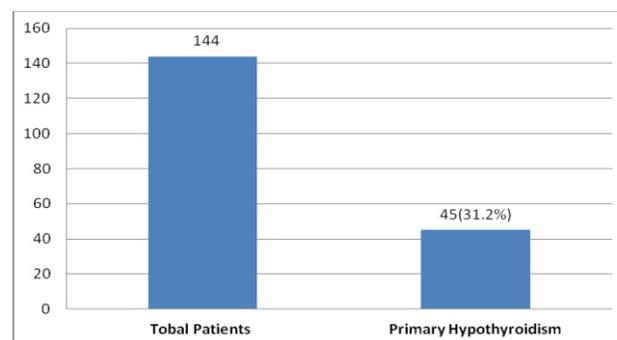
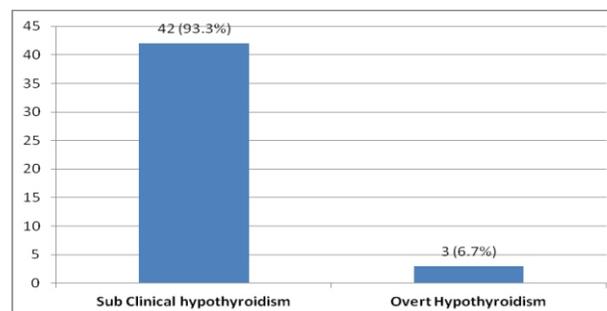


Figure II: Frequency of types of hypothyroidism



In stratification, the frequency of hypothyroidism was more significant in age group 5-10 years (76.2%) as compared to age group 11-16 years (23.8%) with p value of 0.005. The serum ferritin level and

hypothyroidism has proportional increase with p value of 0.222. The duration of transfusion was associated with overt hypothyroidism with p value of 0.019.

**Table I: Age, ferritin level and duration of transfusion versus hypothyroidism.**

Age (Years)	Sub Clinical Hypothyroidism	Overt Hypothyroidism	Total	P-value
5-10	32 (100%)	0 (0.0%)	32(100%)	0.05
11-16	10 (76.9%)	3 (23.1%)	13 (100%)	
Total	42 (93.3%)	3 (6.7%)s	45 (100%)	
<b>Ferritin (ng/ml)</b>				
<2000	10(100%)	0 (0.0%)	10 (100%)	0.22
2001-3000	6 (100%)	0 (0.0%)	6 (100%)	
3001-4000	10 (100%)	0 (0.0%)	10 (100%)	
>4000	16 (84.2%)	3 (15.8%)	19 (100%)	
Total	42 (93.3%)	3 (6.7%)	45 (100%)	
<b>Duration of Transfusion (years)</b>				
<5	7(100%)	0 (0.0%)	7 (100%)	0.019
5-10	25(100%)	0 (0.0%)	25 (100%)	
>10	10 (77%)	3 (23%)	13 (100%)	
Total	42 (93.3%)	3 (6.7%)	45 (100%)	

## DISCUSSION

Although, the combination of blood transfusion and iron chelation therapy has dramatically prolonged the life expectancy of thalassemic patients. However, chelation therapy is expensive, not freely available in every center and the compliance is often poor, resulting in iron overload and its complications.

Primary hypothyroidism is one of the complications of iron overload. In our study, frequency of primary hypothyroidism was 31.2% with sub clinical hypothyroidism 29.1% and overt hypothyroidism 2.1% of the total cases. The frequency of hypothyroidism is high in our study as compared to 25.6% in study conducted in Lahore,<sup>14</sup> 21.6% in Italy<sup>15</sup>, 16% in Tabriz,<sup>16</sup> 7.7% in Tehran<sup>17</sup> and 7% in Shiraz.<sup>18</sup> The probable reason of high frequency of hypothyroidism in our setup is the lack of proper iron chelation. Prevalence of overt hypothyroidism as a complication of thalassemia major in general is relatively low while milder forms of thyroid dysfunction are more common,<sup>12,19</sup> which is similar to the present study.

The mean age of hypothyroid patients in present study was (8.53±3.16 years) comparable to the study of Sara malik<sup>14</sup> but lower as compared to study in Shiraz (14.6 ±1.9 years).<sup>18</sup> The reason for lower age is more iron overload in younger

patients, poor iron chelation and less survival of older children. It is a general belief that thyroid dysfunctions appear with a frequency of 13-60% in thalassemic patients after 10 years of age<sup>14,17</sup> largely as in the form of subclinical hypothyroidism. In this study, 93.3% of cases were in the form of subclinical hypothyroidism which is comparable but majority (76%) were in the age group less than 10 years which is different from other studies and may be due to less survival of older patients and more iron overload complications.

A significant association was found between age and hypothyroidism with p value of 0.05 particularly for overt hypothyroidism where 100% cases were in older age group (11-16 years). Our results are comparable to many national and international studies.<sup>11,12</sup>

The association of serum ferritin levels with hypothyroidism was not significant, which is not similar with few studies.<sup>14,15</sup> The p value was also significant for association of duration of transfusion and hypothyroidism which is comparable to certain other studies.<sup>20</sup> Majority of sub clinical hypothyroidism cases received transfusion for 5-10 years but all overt hypothyroidism cases received transfusion for > 10 years.

## CONCLUSION

Primary hypothyroidism occurs in a high frequency in thalassemia major patients. Majority of hypothyroid cases belong to sub clinical category. Frequency of hypothyroidism has significant association with age, and duration of transfusion. Regular follow-up and screening for hypothyroidism should be done even before 9 years of age to prevent thyroid dysfunction.

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