

## Endocrine Dysfunctions in Iron Overload in Patients with Major Thalassemia

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### Abstract

#### Background

The aim of the present study was to determine the endocrine dysfunction in patients with major thalassemia, who receive hyper transfusion.

#### Materials and Methods

This cross sectional study was performed during one year, which included 65 major thalassemia patients (31 females and 34 males), aged between 14 month to 27 years old (median 10,3). Growth assessment was measured by height and weight according to age and BMI. For all patients serum ferrites concentration, serum calcium and phosphorus, alkaline phosphates, fasting blood sugar, thyroid stimulating hormone, free thyroxin, FSH, LH, dehydroepiandrosterone sulfate, testosterone, estradiol were measured.

#### Results

In this study, 44.9% of patients were found to be shorter than the height of 5th percentile for their age. Diabetes mellitus and impaired fasting glucose were seen in 16% and 28.6% of patients respectively. There was significant correlation between serum ferritin level and impaired glucose tolerance test (p-value =0.043) in them. Frequency of hypocalcaemia and hyperphosphatemia were 36.9% and 10.7% respectively. Frequency of hypogonadism was 54.8%. Fourthly percent of the patients had no endocrine abnormalities.

#### Conclusion

Endocrine dysfunctions are extremely frequent in patients with thalassemia, but chelating therapy can prevent or limit these complications. Impaired glucose tolerance was one of the most frequent endocrine complications, which were related to ferritin level.

#### Key Words

Endocrine System, beta-Thalassemia, Ferritins

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## Introduction

Beta thalassemia is a type of inherited blood disorder that can cause anemia; It affects a person's ability to produce hemoglobin, the protein in red blood cells that delivers oxygen to all parts of the body (1). Patients with thalassaemia Major require multiple blood transfusions, frequent blood transfusion has increased the life expectancy of these patients, but it causes progressive iron overload (2,3). Unfortunately this type of therapy also increased the frequency of complications due to iron overload (4). Endocrine dysfunction is well recognized in patients with multi-transfused Thalassaemia Major (TM) that develop severe endocrine complications. Iron overload due to multiple transfusions is the main cause of such complications hence proper and effective iron chelation therapy is essential for the reduction of iron deposition in various endocrine glands. Iron accumulates in tissues with high levels of transferrin-receptor such as liver, heart and endocrine glands (5,6). Recently, various authors have reported a high incidence of growth disturbances and endocrine dysfunction in polytransfused and untreated patients with thalassemia (7,8). We therefore took the opportunity to investigate the effects of long term subcutaneous iron chelation treatment on growth, development, and endocrine function in our patients.

## Materials and Methods

In this cross sectional analysis study, 65 patients (34 males, 31 females) with major Beta- thalassemia that were treated with blood transfusion in Yazd center were taken under investigation with age between 14 months and 27 years old (median 10.3). The patients were classified into 2 age groups: above 10 years (31 patients) and under 10 years old (35 patients). The mean serum ferritin level of all 65 subjects was  $2966 \pm 1371 \mu\text{g/L}$ . Chelation therapy with desferrioxamine (DFX) had been started in

patients over 1-year-old (mean age of  $4.8 \pm 1.8$  years), with serum ferritin concentrations greater than  $1000 \mu\text{g/L}$ . At the time of this study, all patients were on a regular transfusion program (every 2-4 week) with the aim of maintaining pretransfusion hemoglobin levels above  $9 \text{ g/dlit}$ . Dose of DFX had been  $30 - 50 \text{ mg/kg/day}$ . The mean (SD) desferrioxamine dose was  $17 (4.7) \text{ g/kg/year}$ . These patients were using desferrioxamine 5 - 6 nights a week as an 8-12 hour subcutaneous infusion. Patients were evaluated for endocrine complications intervals at 6 months; Basic serum biochemical parameters including, thyroid functions, blood sugar, luteinizing hormone (LH) and follicular stimulating hormone (FSH), estradiol, testosterone, were obtained for all patients. Thyroid hormones including T3, T4, TSH were determined by RIA method. Diagnoses of hypothyroidism was confirmed with low T4 ( $T4 < 6$ ) and high TSH ( $TSH > 5$ ) and sub clinical hypothyroidism was diagnosed with normal T4 and high TSH. Parathyroid function's assessment was limited to serum calcium, phosphorus and alkaline phosphatase. Serum calcium less than  $8.5 \text{ mg/dL}$  of hypocalcaemia and hyperphosphatemia was correlated with ages (Child=4-7, Adult =2.5-5), hyper alkaline phosphates was normal upper limit (M=80-306, F=64-306, children 180-1200). Growth assessment was measured by height and weight for age and BMI, short stature was defined as height less than the 5th percentile for age, low weight was defined as weight less than the 5th percentile for age. Fasting glucose equal or greater than  $126 \text{ mg/dL}$  and/or post 2 hours (75 gram glucose in patients greater than 30 kg and 1.75 gram/kg in patients less than 30 kg) greater than  $200 \text{ mg/dL}$  and/or exogenous insulin administration and/or use of oral hypoglycemic medications for diabetes, fasting glucose equal or greater than 100

mg/dl and less than 126 mg/dL for impaired fasting glucose, two hours serum glucose post (75 gram glucose in patients greater than 30 kg and 1.75 gram/kg in patients less than 30 kg) equal or greater than 140 mg/dl and less than 200 mg/dL for impaired glucose tolerance test.

## Results

Clinical data of 65 patients (31 females and 34 males), aged 1.2 -27 years (mean age: 10.3 years), with thalassemia major, are shown in (Table 1). Because of the higher incidence of endocrine disorders in the second decade of life in patient with major thalassemia and with considering that transfusion increased with advancing age. Patient in 2ed decade separately investigated. In this study 34 patients was under 10 years and 31 patients above 10 years. As shown in Tab1, mean serum ferritin of 31 female patients was  $2821 \pm 8398$  and 34 male patients was  $3097 \pm 1353$ . There was no significant relation between age and sex and mean serum ferritin in major thalassemia patient. (P-value: 0.42). Among 65 patients, 14 persons (21%) had thyroid problem. One patient was obviously affected by hypothyroidism (1.5%) (Mean of the ferritin: 2113), subclinical hypothyroidism was observed in Five patients (7.6%) (Mean of the ferritin:  $2166 \pm 1222$ ) and 8 patients (12.3%) had secondary hypothyroidism (mean of the ferritin: 3460). There was no significant relation between hypothyroidism in major thalassemia patient and ferritin level (p-value: 0.38). Among 31 patients above 10 years, 25 patients (80.6%) had no disorders of thyroid (mean serum ferritin level  $3281 \pm 1328$ ) 1 patients with subclinical hypothyroidism (3.2%) (Mean ferritin: 3388) and 5 patients (16%) with secondary hypothyroidism (mean serum ferritin level:  $3349 \pm 1610$ ) There was,nt any relation between disorders of thyroid and the serum ferritin level in major thalassemia patients

above 10 years . (p-value=0.99)(Tab 2). Among the 34 men, 4 persons (11.7%) had subclinical hypothyroidism and 7 patients (20%) had secondary hypothyroidism. Mean serum calcium level was ( $8.6 \pm 0.85$ ), serum calcium level was lower than normal in 24 patients (36.9% ) . Mean serum phosphor level was ( $5.16 \pm 0.88$ ), hyperphosphatemia was reported in seven patients (10.7%). ,and none of them had high alkalinephosphatase. FBS was measured twice to evaluate diabetes in patients over 2 years old (60 patients with mean serum ferritin level  $3089 \pm 1295$ ) , five patients (16 %), (4 males and 1 females) had diabetes mellitus, mean serum ferritin level in thalassemic patients with diabetes was  $3249 \pm 975$  and all of them above 10 years, (Mean age of diabeti patients at the time of diagnosis 21) . Eleven patients (28.6%), mean age 14.7 years, (mean serum ferritin level  $3936 \pm 1396$ ) had impaired glucose tolerance test (Table 2). Mean age of normal person was 8.2. There was significantly difference between serum ferritin level in thalassemic patients with impaired glucose tolerance test (p-value =0.043). In this analysis, growth failure was commonly observed in thalassemic patients. Among all patients ,29 patients were found to be short with their height less than the 5th percentile for age (mean serum ferritin level:  $2996 \pm 1310$ ), 35 patients between 5th and 95th (mean serum ferritin level :  $2916 \pm 1450$ ), 1 patients upper than 95th with serum ferritin 3817. (38.1%) of patients under 10 years old and (56.61%) of patients above 10 years old were short ,(total 44.9). No correlation was found between iron overload (serum ferritin) and short stature ,( p-value =0.80). Among 65 patients 24 patients were found under 5th percentile weight for age (mean serum ferritin level :  $2970 \pm 1376$ ). Thirty nine patients were normal limit (between 5th and 95th) (mean serum ferritin level :  $2916 \pm 1405$ ). The mean serum FSH was

2.32±2.7 (mIU) /mL and mean serum LH was 1.82±2.4 (mIU)/mL, mean free testosterone 1.89±2.15 ,mean estradiol 106.57±91.4. In the present study 17 patients had hypogonadism (2 patients Primary hypogonadism and 15 patients Secondary hypogonadism and 15),but there was no statistically significant correlation between

serum ferritin level and hypogonadism( p-value =0.48) (Tab 2) .Table 3 compares the serum ferritin level in thalassaemic patients with and without endocrine dysfunction. There was no association between at least one endocrine dysfunction and mean serum ferritin level. (p=0.53)

Table1. Demographic characteristic relation to Serum ferritin levels in patients with thalassaemia

Variable	Ferritin	No	Mean	SD	p-value
Sex	Male	34	3097	1353	0.42
	female	31	2821	8398	
	Total	65	2965	1371	
Age	<10	34	2664	1361	0.63
	≥10	31	3296	1362	
	Total	65	2966	1371	

Table 2. Relationship between endocrine dysfunction and Serum ferritin levels

Variable	Ferritin	N	Mean	SD	p-value
Abnormal glucose	normal	44	2859	1233	0.043
	IGTT	11	3936	1396	
	Diabetes	5	3249	975	
	Total	60	3089	1295	
Gonad	Normal	14	3311	1622	0.48
	Primary hypogonadism	2	4368	642	
	Secondary hypogonadism	15	3138	1050	
	Total	31	3296	1326	
Thyroid	Euthyroid	51	2983	1397	0.99
	Primary hypothyroidism	1	2131	---	
	Subclinical	5	2166	1222	
	Secondary	8	3460	1251	
Total	65	2965	1371		

Table 3. Serum ferritin levels in relation to at least one endocrine dysfunction

Ferritin		N	Mean	SD
endocrine dysfunction				
Under 10 years (p-value =0.53)	Without any endocrine dysfunction	24	2569	1412
	With at least one endocrine dysfunction	15	2892	1272
	Total	34	2664	34
Above 10 years (p-value =0.53)	Without any endocrine dysfunction	7	3019	1767
	With at least one endocrine dysfunction	24	3376	1203
	Total	35	3296	1326

## Discussion

Iron overload due to multiple transfusions in thalassaemia major patients is the main cause of complications, such as endocrine dysfunction and effective iron chelation therapy is essential for the reduction of iron deposition on various endocrine glands (6). Transfusion and iron-chelation therapy are critical for prolonging life and improving quality of life in thalassaemic patients, however, Blood transfusion therapy for thalassaemia should maintain hemoglobin in the normal range, in order to prevent deleterious effects of anemia (9,10). Endocrine organs plagued by iron deposition secondary to multiple transfusions include the pancreas, thyroid, and parathyroid glands leading to Diabetes Mellitus (DM), acquired hypothyroidism and hypoparathyroidism respectively (11).

Growth failure in thalassaemia is multi factorial in etiology. Chronic anemia, hypersplenism, chronic liver disease, nutritional deficiency and hormonal dysfunctional have been implicated as major causes of growth retardation. Adequate transfusion and aggressive chelation therapy are initiated early in life to ensure a favourable prognosis for growth (12,13).

In this study, 44.9% patients were found to be short with their height less than the 5th percentile for age which is comparable to the study of Rashid et al that 57.14% of patients were short, although no correlation between iron overload (serum ferritin) and short stature (7) and compare with prevalence of

short stature in study of Heshmat Moayeri et al which reported (62%). They found hypogonadism (69%) in 158 patients, and a low serum level of gonadotropins in patients over 14-year-old with impaired puberty (14). Short stature has been reported as a common complication in transfusion-dependent thalassaemia (15). Mostafavi et al studied 44 thalassaemia major patients with 8.5 to 25 years old. They have stated that height of 90.9% of patients was under the 5th percentile (standard deviation score of height less than -2) (16). This percentage is higher than what we obtained from our study. They reported hypocalcemia in 22.7% of thalassaemic patients and hyperphosphatemia was found in 70%, this is similar to our finding which was reported hypocalcaemia in 36.9% of patients and hyperphosphatemia was reported 10.7%.

Soliman et al studied thalassaemic patients, between the ages of 13 and 21 years, and reported that 49 % of the cases had height standard deviation scores less than -2 and 83% of thalassaemic patients had height standard deviation score less than -1(17).

In a study by George et al reported the difference in the growth parameter between thalassaemic and non-thalassaemic siblings was evident in both boys and girls over 9 years old (18).

In Ghosh,s study, in West Bengal (2008 ) was reported ,68 patients Hypogonadism ( 52.3% males and 35.9% females ),reduced growth hormone reserve 7.4%, Subclinical hypothyroidism 23.5% ,Growth retardation

20.58%(19),these are all comparable to the reported incidence in the present study.

Borgna– Pignatti et al evaluated 720 thalassemia major and reported that 54.7% of the cases were hypogonadism (20) . Chern et al studied 29 patients with thalassemia major, aged 15 years or older, with prevalence of 72% hypogonadotropic hypogonadism (21). In our study, prevalence of hypogonadism was 54.8% .However, the serum ferritin level in thalassemic patients with impaired glucose tolerance test was found significantly different (p-value =0.043) compare with report of Nagafipor which serum ferritin level in thalassemic patient with diabetes and without diabetes was not significantly different (4).

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### **Conflict of Interest**

None declared

### **References**

- 1-JAMES N. PARKER, M.D. AND PHILIP M. PARKER, PH.D., EDITORS, Beta Thalassemia A Bibliography and Dictionary for Physicians, Patients, and Genome Researchers,Health Care: Philip Parker, edition 2007.
- 2- Fosburg MT, Nathan DG. Treatment of Cooley's anemia. *Blood*. 1990;76(3):435-44.
- 3-Hoffbrand AV, Wonke B. Iron chelation therapy. *J Intern Med Suppl*. 1997; 740: 37 – 41.
- 4-Najafipour F, Evaluation of Endocrine Disorders in Patients with Thalassemia Major, *Int J Endocrinol Metab*. 2008; 2: 104-113.
- 5-Grundy RG, Woods KA, Savage MO, Evans JP, Relationship of endocrinopathy to iron chelation status in young patients with thalassaemia major. *Archives of Disease in Childhood* 1994; 71: 128-132
- 6- Berkovitch M, Bistrizter T, Milone SD, Perlman K, Kucharczyk W, Olivieri NF.Iron deposition in the anterior pituitary in homozygous beta-thalassemia: MRI evaluation and correlation with gonadal function. *J Pediatr Endocrinol Metab*.2000 ;13(2):179-84.
- 7-Rashid H. Merchant , Amruta Shirodkar ,Javed Ahmed . Evaluation of Growth, Puberty and Endocrine Dysfunctions in Relation to Iron Overload

in Multi Transfused Indian Thalassemia Patients, *Indian J Pediatr* 2011;78(6):679–683 .

8- Anita Saxena,Growth Retardation in Thalassemia Major Patients. *Int J Hum Genet*, 2003 ;3(4): 237-246.

9- Nathan DG. Pioneers and modern ideas. Prospective on thalassemia. *Pediatrics*.1998;102(1 Pt 3):281-3; discussion 288-9.

10- Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, Del Vecchio GC, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica* 2004; 89: 1187-93.

11- De Sanctis V, Eleftheriou A, Malaventura C; Thalassaemia International Federation Study Group on Growth and Endocrine Complications in Thalassaemia. Prevalence of endocrine complications and short stature in patients with thalassaemia major: a multicenter study by the Thalassaemia International Federation (TIF). *Pediatr Endocrinol Rev*. 2004 Dec;2 Suppl 2:249-55.

12- De Virgiliis S, Cossu P, Toccafondi C, Sanna G, Frau F, Lobrano R, et al. Effect of subcutaneous desferrioxamine on iron balance in young thalassemia major patients. *Am J Pediatr Hematol Oncol*.1983 Spring;5(1):73-7.

13- Fargion S, Taddei MT, Gabutti V, Piga A, Di Palma A, Capra L, et al. Early iron overload in beta-thalassaemia major: when to start chelation therapy? *Arch Dis Child*. 1982 Dec;57(12):929-33.

14- Moayeri H, Oloomi Z. Prevalence of growth and puberty failure with respect to growth hormone and gonadotropins secretion in beta-thalassemia major. *Arch Iran Med*. 2006 ;9(4):329-34.

15- Borgna-Pignatti C, De Stefano P, Zonta L, Vullo C, De Sanctis V, Melevendi C, et al. Growth and sexual maturation in thalassemia major. *J Pediatr*. 1985 Jan;106(1):150-5.

16- Mostafavi H, Afkhamizadeh M, Rezvanfar MR. Endocrine disorders in patients with thalassemia major. *Iranian Journal of Endocrinology and Metabolism* 2005; 7(2): 143-7.

17- Soliman AT, elZalabany M, Amer M, Ansari BM. Growth and pubertal development in transfusion-dependent children and adolescents with thalassaemia major and sickle cell disease: a comparative study. *J Trop Pediatr*. 1999 ;45(1):23-30.

18-George A, Bhaduri A, Sen S, Choudhry VP. Physical growth parameters in thalassemic children. *Indian J Pediatr*. 1997;64:861–71.

19- Ghosh S, Bandyopadhyay SK, Bandyopadhyay R, Roy D, Maisnam I, Ghosh MK. A study on endocrine dysfunction in thalassaemia. *J Indian Med Assoc*. 2008;106(10):655-6, 658-9.

20- Borgna-Pignatti C, De Stefano P, Zonta L, Vullo C, De Sanctis V, Melevendi C, et al. Growth and sexual maturation in thalassemia major. *J Pediatr.* 1985;106(1):150-5.

21- Chern JP, Lin KH, Lu MY, Lin DT, Lin KS, Chen JD, et al. Abnormal glucose tolerance in transfusion-dependent beta-thalassemic patients. *Diabetes Care.* 2001;24(5):850-4.