

## Final adult height and endocrine complications in young adults with $\beta$ -thalassemia major (TM) who received oral iron chelation (OIC) in comparison with those who did not use OIC

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**Summary.** *Background:* Relatively little is known about endocrine function, bone mineral health, and growth during oral iron chelation therapy in  $\beta$ -thalassemia major patients (TM) on treatment with deferasirox. *Aims of the study:* To study the frequency of endocrine complications, IGF-1 levels and final adult standing height (FA-Ht) in patients with BTM in two groups of adult patients. *Patients and methods:* The first group (Group A; 15 patients, 6 females and 9 males) received oral iron chelation therapy (OIC) with deferasirox for 6 years before puberty; the second group (Group B; 40 patients) attained the FA-Ht before the use of OIC (iron chelation therapy with deferoxamine (DFO) given subcutaneously, since the age of 2 years). In both groups liver iron concentration was measured using FerriScan<sup>®</sup> R2-MRI method. Furthermore, the FA-Ht, body mass index (BMI), and insulin growth factor-1 (IGF-1) in a selected group of adult patients [9 with normal growth hormone (GH) secretion (GHN) and 8 with GH deficiency (GHD; peak GH response to provocative test with clonidine: <7 ng/ml), who were on iron chelation therapy with DFO given subcutaneously that was changed to oral deferasirox during the last 5-6 years. These 15 patients were not treated with rhGH. *Results:* Adults with BTM who received OIC for 6 years or more before attaining their FA-Ht, had lower liver iron concentration (LIC) assessed by FerriScan<sup>®</sup> R2-MRI, fasting glucose level (FBG) and liver enzymes (ALT and AST), and a better FA-Ht expressed in standard deviation score (FA-Ht-SDS), and higher IGF-1 SDS versus those who did not receive OIC before attaining FA-Ht. The prevalence of endocrinopathies, including hypothyroidism and hypogonadism were significantly lower in Group A versus Group B. Comparison between the group with normal GHN and those with GHD showed that the FA-Ht-SDS of those with GHD (159.1 $\pm$ 6.42 cm, Ht-SDS=-2.5 $\pm$ 0.9) was significantly decreased compared to the group with NGH (Ht=163.5 $\pm$ 5.2 cm, Ht-SDS=-1.74 $\pm$ 0.83). The IGF-1-SDS did not differ between the two groups. Neither ferritin level nor IGF-1 concentrations were correlated with the Ht-SDS. The FA-Ht-SDS correlated significantly with the peak GH secretion (r=0.788, p=0.0008). The FA-Ht-SDS were positively related to their mid-parental height (r=0.58, P<0.01). *Conclusions:* The use of OIC years before the end of puberty was associated with a significantly lower prevalence of endocrinopathies, improvement of LIC and FA-Ht. The final adult height of patients with BTM and GHD was significantly shorter compared to their peers with NGH. rhGH therapy can be recommended for the treatment of thalassemic children and adolescents with GHD in addition to proper blood transfusion and intensive chelation to improve their final height. (www.actabiomedica.it)

**Key words:**  $\beta$ -thalassemia major (BTM), final adult height (FA-Ht), growth hormone (GH), insulin-like growth factor-1 (IGF-1), liver iron concentration (LIC)

## Introduction

Growth retardation occurs frequently in children and adolescents with homozygous  $\beta$ -thalassemia (TM). After the age of 4 years the longitudinal growth patterns display rates behind those of normal controls. The bone age is frequently delayed after the age of 6-7 years and growth retardation becomes markedly severe with the failure of the pubertal growth spurt (1, 2).

Iron overload due to repeated blood transfusion and inadequate iron chelation therapy lead to considerable dysfunction of many organs including liver, pancreas, heart and the endocrine glands. Impaired hepatic synthesis of insulin-growth-factor-1 (IGF-1) due to defective of growth hormone (GH) secretion, hepatic iron overload and nutritional deficiencies could considerably contribute in the etiology of growth delay. Delayed puberty and/or hypogonadism which occurs in a considerable number of these patients can attenuate the pubertal growth spurt and negatively affects GH-IGF-1 axis activation during adolescence (2-4).

With the introduction of high transfusional regimes and efficient oral iron chelation therapy pre-pubertal linear growth has been improved markedly. However, abnormal growth is still observed in many TM patients during childhood and adolescence. The childhood phase of growth is GH dependent and the pubertal phase depends both on GH and sex steroids secretion. In addition, adequate nutrition and weight gain play an important role to mediate growth during all phases of growth (5-7).

Although liver biopsy is the most accurate method to diagnose liver pathology and iron content it is non-accepted by the patients and has potential complications. These obstacles can be avoided using magnetic resonance imaging (MRI) techniques. A standardized and validated MRI method is now registered in Europe and the United States (FerriScan<sup>®</sup> R2-MRI), with reproducible relationship between the observed R2 value by MRI and liver iron concentration (LIC) by biopsy. This is potentially available in any hospital with an MRI scanner and with minimal training of local staff (8, 9).

The aim of this study was to study the endocrine complications, IGF-1 levels and final adult standing height (FA-Ht) in patients with TM in two groups of

adult patients. The first group (Group A) received oral iron chelation therapy (OIC) for 6 years before puberty; the second group (Group B) attained the FA-Ht before the use of OIC.

Furthermore, we studied the FA-Ht, body mass index (BMI), and insulin growth factor-1 (IGF-1) in a selected group of adult patients [9 with normal growth hormone (GH) secretion (GHN) and 8 with GH deficiency (GHD; peak GH response to provocative test <7 ng/ml) who were on iron chelation therapy with deferoxamine (DFO) given subcutaneously that was changed to oral deferasirox during the last 5-6 years. These 15 patients were not treated with rhGH.

## Study population

We performed a cross-sectional analysis of linear growth (height and height SDS - HtSDS), weight, BMI, pubertal status and endocrine testing in two groups of patients with BTM who have completed puberty spontaneously and have attained their FA-Ht. The Group A (n=15; 7 females and 8 males) patients were treated with DFO starting from the first 2 years of age, followed by OIC (deferasirox daily dose of 20 mg/kg/ body weight) for 6 years or more before attaining FA-Ht. Group B (n=40) (47.5% patients were female and 20% had been splenectomised) received only subcutaneous chelation therapy with DFO, before attaining FA-Ht.

Furthermore, we compared the FA-Ht of two groups of BMT patients who had different response to GH provocation during adolescent age. One group included 9 patients with normal GH secretion (GHN) and another group (8 patients) with GH deficiency (GHD) (GH peak after clonidine stimulation test: <7 ng/ml). All these adolescents were treated with DFO starting from the first 2 years of age, followed by OIC (deferasirox, at the daily dose of 20 mg/kg/ body weight) for the last 6 years.

The compliance to treatment in the two groups, as determined by serum ferritin level, did not differ between the two groups and ranged between 580 and 2,220 ng/ml.

Lab. investigation, using commercial radioimmunoassay included the measurement of fasting serum

concentration of free thyroxine (FT4), thyrotropin (TSH), IGF-1, and gonadotrophins (LH and FSH). Fasting blood glucose and hepatic function (ALT, AST and ALP) were also assessed. Liver iron content was measured using the FerriScan® R2-MRI method.

All males and females with hypogonadism and/or hypothyroidism were on hormonal replacement therapy.

Student "t test" was used to compare the growth and lab. data among the different groups when the data were normally distributed and Wilcoxon rank test was used when the data were not normally distributed. Linear regression equation was used to study correlations between different parameters and FA-Ht. Chi-square ( $\chi^2$ ) test was used to compare the frequency of qualitative variables among the different groups. A p value <0.05 was considered significant.

## Results

The prevalence of different endocrinopathies, including hypothyroidism and hypogonadism was significantly lower in group A compared to Group (Table 1). Those who received OIC for 6 years or more before attaining their FA-Ht, had lower LIC (Ferriscan) and liver enzymes (ALT and AST), a better FA-Ht-SDS, and higher IGF-1 SDS (Table 2).

Comparing the group of BMT patients with normal GH secretion (GHN) (n=9) versus those with GHD (n=8) showed that the FAHt and HtSDS of those with GHD were significantly decreased ( $159.1 \pm 6.42$

**Table 1.** Growth and endocrine function in adults who received oral iron chelation (OIC) vs those who did not receive OIC before attaining final adult height

	Group A: OIC	Group B: No OIC	P value
Number of patients	15	40	-
DM	6.6%	2.5%	0.3
IFG	6.6%	17.5%*	0.09
Hypothyroidism	0.0%	10.0%*	< 0.001
IGF-1 <-2	20.0%	87.5%*	< 0.001
Fa-Ht-SDS <-2	6.6%	52.5%*	<0.001
Hypogonadism	13.3%	40.0%*	0.0056

Legend DM: Diabetes mellitus, IFG: Impaired fasting glucose, IGF-1: insulin growth factor-1; SDS: standard deviation score; (\*p<0.05)

cm, Ht-SDS=-2.5 $\pm$ 0.9) compared to the group with NGH (Ht=163.5 $\pm$ 5.2 cm, Ht-SDS=-1.74 $\pm$ 0.83). The IGF-1-SDS and serum ferritin concentrations did not differ statistically between the two groups. Neither serum ferritin level nor IGF-1 concentrations were correlated to Ht-SDS.

The Fa-Ht-SDS were correlated significantly with the peak GH secretion (r=0.788, p=0.0008) (Figure 1). The Ht-SDS were positively related to their mid-parental height (r=0.58, P<0.01).

## Discussion

Endocrinopathies are common in patients with BTM despite parenteral iron chelation therapy with DFO (5-7). Deferasirox is widely available and recent

**Table 2.** Final adult height and biochemical parameters of adolescents with BTM who were on oral chelation therapy (OCT) versus those who attained their final adult height before using OCT

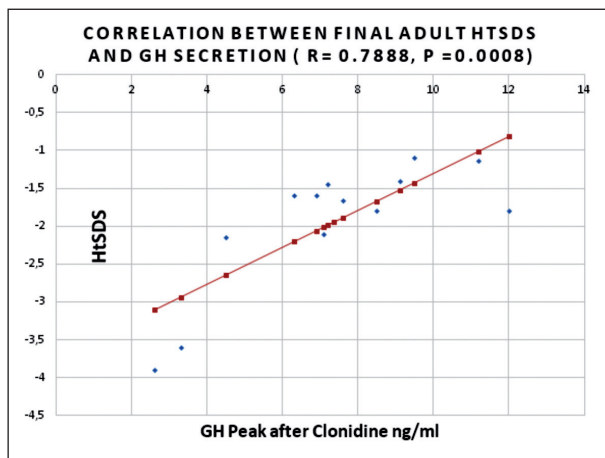
	Age years	Ht-SDS	BMI Kg/m <sup>2</sup>	FT4 pmol/L	TSH mIU/l	Serum ferritin ng/ml	IGF-1 - SDS ng/ml	LIC mg/Fe /g dw	AST U/l	ALT U/l	ALP U/l	FBG mmol/l	
Group A (OCT) n= 15	Mean $\pm$ SD	20.0 $\pm$ 1.4	-1.2* $\pm$ 0.7	21.7 $\pm$ 3.0	12.4 $\pm$ 0.8	2.6 $\pm$ 0.7	1520.0 $\pm$ 985.0	-1.3 $\pm$ 0.9	10.1 $\pm$ 6.7	39.1 $\pm$ 13.2	46.5 $\pm$ 22.2	129.4 $\pm$ 98.5	6.6* $\pm$ 4.5
Group B (no OCT) n=40	Mean $\pm$ SD	26.83* $\pm$ 8.1	-1.9 9 $\pm$ 1.1	24.2* $\pm$ 4.9	12.4 $\pm$ 1.6	2.7 $\pm$ 2.2	1726.0 $\pm$ 899.0	-2.9 $\pm$ 1.2	14.9* $\pm$ 15.4	58.2* $\pm$ 189.7	70.5* $\pm$ 308.4	113.9 $\pm$ 88.3	5.5 $\pm$ 1.3

Legend: Ht- SDS=height SDS; FT4=free thyroxine; IGF-1-SDS=insulin like growth factor-1 SDS; LIC=liver iron concentration by FerriScan; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ALP=alkaline phosphatase; (\*p<0.05).

**Table 3.** Final adult height and IGF-1 in adults with (GHD) and without (NGH) GH deficiency diagnosed before the onset of puberty

	Age years	HtSDS	BMI-SDS	Serum ferritin ng/ml	Basal GH ng/ml	Peak GH ng/ml	IGF-1 SDS
<b>GHD</b>							
Mean	21.2	-2.5	-0.3	2529	0.4	4.7	-2.7
SD	3.4	0.9	0.3	1225	0.4	1.5	0.7
<b>NGH</b>							
Mean	23.4	-1.7*	-0.6	2666	1	9.9*	-2.8
SD	4.3	0.5	0.4	1455	1.3	1.8	1.3

Legend= Ht: standing height expressed in SDS; BMI: body mass index; GHD: GH deficiency, NGH; normal GH response to clonidine provocation stimulation test.; IGF-1: insulin growth factor-1; SDS: standard deviation score; (\* $p < 0.05$ )

**Figure 1.** Correlation between peak GH secretion and final adult height expressed in SDS in patients with BTM

evidence support that it is both safe and efficacious (10-13). Deferasirox is effective in lowering serum ferritin levels and decreasing overall iron burden. An early trial that evaluated the dose-response relationship demonstrated that 20 mg/kg/day effectively chelated iron. Another trial using 20 mg/kg/day decreased liver iron concentrations in 71 adult TM patients (10, 11). A larger trial compared deferasirox (132 patients) to DFO (63 patients) for the treatment of iron overload in patients with sickle cell anemia. The median age of the deferasirox treatment group was 15 years. At the end of 1-year deferasirox (10-30 mg/kg/day) was equivalent to DFO in lowering liver iron concentrations. Similar findings were reported by Taher et al. in children in heavily iron-overloaded patients with TM (13).

Relatively little is known about endocrine function, bone mineral health, and growth during OCT with deferasirox.

Casale et al. (14) reported a multicenter retrospective cohort study of 86 BTM patients treated with once daily deferasirox for a median duration of 6.5 years, up to 10 years. A low rate of new endocrine disorders (7%), including five cases of hypogonadism and one case of hypoparathyroidism, and a stabilization of those pre-existing endocrinopathies was observed in a real clinical practice setting. Among patients with hypothyroidism or diabetes at baseline, no significant change in thyroid parameters or insulin requirements were observed. Mean lumbar spine bone mineral density increased significantly ( $P < 0.001$ ) and the number of patients with lumbar spine osteoporosis significantly decreased ( $P = 0.022$ ) irrespective of bisphosphonate therapy, hormonal replacement therapy, and calcium or vitamin D supplementation. There were no significant differences in the number of pediatric patients below the 5th centile for height between baseline and study completion. Six pregnancies occurred successfully, and four of them were spontaneous without ovarian stimulation.

In another study, Poggi et al. (15) compared the long-term effects of different iron chelation regimens (DFO, deferiprone, DFO plus deferiprone, and deferasirox) in preventing or reversing endocrinopathy (diabetes mellitus, hypothyroidism, or hypogonadism) and bone disease, assessed through DEXA, in 165 adults with TM (mean age  $39.9 \pm 8.3$  years, 43% males). After five consecutive years of therapy, patients on deferasirox



had the highest decrease in the prevalence of any endocrinopathy compared to other chelators. A serum ferritin level of  $>1,300$  ng/ml predicted the development of new endocrinopathy ( $p=0.025$ ) while a level of  $<200$  ng/ml predicted reversal of existing endocrinopathy ( $p=0.147$ ). A significant increase in mean bone mineral density (BMD) T-score ( $p<0.001$ ) and a considerable decrease in osteoporosis prevalence were observed in patients receiving deferasirox compared to other chelators. The Authors concluded that iron chelation therapy with deferasirox has a role in the prevention of endocrinopathy and reversal of existing disease.

Our study demonstrates that patients with TM on repeated blood transfusion who have received OIC (deferasirox) for 6 years or more before attaining their FA-Ht had lower hepatic iron overload, higher IGF-1 level and higher FA-Ht-SDS compared to those who did not receive OIC. In addition, they had significantly lower prevalence of endocrinopathies including hypothyroidism and hypogonadism.

Although in a recent Cochrane review deferasirox was not considered superior to DFO (16), we believe that the key factor for the significant improvement of growth and endocrine outcome of TM patients may be due due to a better compliance to treatments.

In our study, thalassaemic patients with GHD had a significantly shorter FA-Ht compared to those with NGH, although their adult level of IGF-1 were not significantly different to TM patients with GHD.

Both groups had low IGF-1 SDS. These findings are supported by our previous reports in children and adults with TM (17-19). The direct effect of GH on the growth plate (dual theory mechanism) as well as the unmeasured local secretion of IGF-1 induced by GH (autocrine/paracrine effect) can explain the difference in the final growth of these patients without difference in their systemic IGF-1 levels.

Our suggestion is that in thalassaemic patients with normal GH secretion, IGF-1 is reduced because of hepatic siderosis (GH resistance). However, the response of the growth plate to GH might be preserved (20, 21). In sustenance with our findings, recombinant human growth hormone (rhGH) replacement therapy increased the growth rate, final adult height as well as IGF-1 secretion in TM children with short stature in many studies reported in the literature (22-24).

## Conclusions

The use of OIC years before the end of puberty was associated with improvement of LIC and final adult height. In addition, those patients who received long-term OIC had significantly lower prevalence of endocrinopathies. The final adult height of patients with TM and GHD was significantly shorter compared to their peers with NGH. rhGH therapy can be recommended for the treatment of thalassaemic children and adolescents with GHD in addition to proper blood transfusion and intensive chelation to improve their final height.

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