

# Linear Growth Deficiency in $\beta$ -Thalassemia Patients: Is It Growth Hormone Dependent?

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## Abstract

**Background:**  $\beta$ -Thalassemia major is a serious medical problem. Growth retardation is commonly seen in poly-transfused  $\beta$ -thalassemia patients. The exact mechanism of short stature in children with thalassemia major is not well understood, however, it is believed to be multi-factorial.

**Objective:** To study the growth state and its relationship to growth hormone (GH) deficiency in  $\beta$ -thalassemia patients.

**Methods:** The extent of growth and growth hormone deficiency were evaluated in 150 patients aged 10-22 years (84 males, 66 females) residing in Shiraz. The age, sex, height, weight and serum ferritin levels were recorded using a questionnaire. Growth hormone secretion was determined with L-Dopa provocative test in 138  $\beta$ -thalassemia patients.

**Results:** Short stature was present in 64% of patients (63.6% of girls, 69% of boys). Growth hormone deficiency was present in 57.5% of 138 patients, (53.5% of boys, 46.5% of girls). Short stature was found in 83.5% of GH deficient and 74.6% of GH sufficient ( $p=0.22$ ) subjects. There was no difference between the height of GH deficient and GH sufficient patients ( $p=0.297$ ). Age at the start of chelating therapy, height deficiency and serum ferritin levels did not differ in GH deficient compared to GH sufficient patients.

**Conclusion:** This study suggests that growth retardation and GH deficiency are common in thalassemic patients and that height deficiency may not be related to GH reserve with the current testing methods for measurement of GH reserve.

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**Keywords** • Thalassemia major • growth hormone • L-Dopa test

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## Introduction

**E**ndocrine dysfunctions are well-recognized in patients with  $\beta$ -thalassemia major.<sup>1-3</sup> Investigations have documented the presence of hypothalamic-pituitary axis dysfunction,<sup>4,5</sup> hypothyroidism,<sup>6</sup> hypoparathyroidism,<sup>7</sup> adrenal insufficiency,<sup>8</sup> and pancreatic dysfunction.<sup>9</sup> Transfusion-related iron overload is among the primary complications seen in  $\beta$ -thalassemia major individuals.<sup>1,6</sup> The use of iron chelating agents delays the development of iron-

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induced damage to cardiac and liver tissues, thus improving the overall survival.<sup>1,10</sup> However, the ability of desferrioxamine in preventing the endocrine damage is not well established.<sup>1</sup>

Endocrine problems could result from a variety of factors, nevertheless, most studies suggest that chronic iron overload secondary to hypertransfusion therapy is the major cause of the observed abnormalities.<sup>2,11</sup> To the best of our knowledge, there are no studies addressing the prevalence of endocrine dysfunctions in patients with  $\beta$ -thalassemia major in Iran.

The aim of this study was to evaluate the prevalence and relationship of short stature and growth hormone (GH) deficiency in patients with  $\beta$ -thalassemia major.

### Subjects and Methods

One hundred and fifty patients with  $\beta$ -thalassemia major (84 males, 66 females) aged 10-22 years were studied at the Pediatric Department of Shiraz University of Medical Sciences.

Patients had received their first blood transfusion between the ages of one month and 11 years (mean  $\pm$ SD: 23 $\pm$ 26.9 months) to maintain their minimum pretransfusion hemoglobin concentration above 9.5 g/dL. Subcutaneous desferrioxamine injection was started in patients over 3 years of age with a serum ferritin concentration of >1000  $\mu$ g/L. Medical history was obtained and a complete physical examination was done for each patient. Age, sex, weight and height were recorded, using a questionnaire. Height was measured by a single observer using a stadiometer. Serum ferritin level was determined by ELISA. Growth hormone was evaluated in 138 patients. Twelve patients were excluded because of diabetes mellitus and adrenal failure. At the time of the study, 90% of patients were receiving desferrioxamine by pump (40-50 mg/kg/day, 5 nights/week). The patients had no evidence of congestive heart failure. Patients with hypothyroidism received adequate hormone replacement therapy. The GH secretion was determined after 2 provocative L-Dopa tests, with Levodopa (500 mg/1.73 m<sup>2</sup>) primed by propranolol (0.75 mg/kg, maximum 40 mg) orally. Blood samples were taken at 0 (baseline), 30, 60, 90 and 120 minutes after an overnight fasting and GH was measured by immunoradiometric assay with standard commercial kit (Orion Diagnostica, Finland). Girls and boys over 11 and 13 years of age, received estrogen (0.02 mg) and methyltestosterone (10 mg), respectively three times a day and for 2 days<sup>12</sup> before L-Dopa test, (GH deficiency was diagnosed if GH level in all samples was below 10 ng/ml). Serum insulin-like growth factor 1 (IGF1) was measured in 46 out of 138 patients (23 GH deficient and 23 GH

sufficient).

Liver function tests, hepatitis B surface antigen (HBsAg), anti hepatitis C virus (HCV) antibody, serum calcium, phosphorus and blood sugar were measured. Blood samples were taken at least 2 weeks after the last blood transfusion. For data analyses student's *t*-test, Chi-square test, Fisher exact test and Pearson's correlation coefficient test were performed.

### Results

The age of the patients ranged from 10-22 years (mean $\pm$ SD: 14.4 $\pm$ 2.8 years). The mean $\pm$ SD age at the start of blood transfusion was 23 $\pm$ 26.9 months (range 1-132 months). The mean $\pm$ SD age at the start of desferrioxamine was 7.14 $\pm$ 4 years. The mean $\pm$ SD serum ferritin level was 3365 $\pm$ 2172  $\mu$ g/L. Hepatitis B surface antigen was positive in 4% of patients. Antibody against hepatitis C virus was positive in 21.5% of the patients. The mean $\pm$ SD weight was 33.4 $\pm$ 7.53 kg. The mean $\pm$ SD height was 138.8 $\pm$ 10.7 cm in boys and 136.6 $\pm$ 10.4 cm in girls. Sixty-four percent of patients (63.6% of girls and 69% of boys) had short stature defined by height below the 3<sup>rd</sup> percentile for age. GH deficiency was found in 57.5% of 138 patients (53.5% in males and 46.5% in females) ( $p=0.4$ ). Short stature was found in 83.5% of GH deficient and 74.6% of GH sufficient subjects with no statistically significant difference ( $p=0.22$ ).

There was no correlation between height and serum ferritin level, in GH deficient ( $r= -0.005$ ,  $p=0.572$ ) and GH sufficient patients ( $r= -0.097$ ,  $p=0.733$ ). The mean $\pm$ SD height in GH deficient patients was 136.8 $\pm$ 10.8 cm and in GH sufficient individuals was 138.7 $\pm$ 10.4 cm, with no statistically significant difference ( $p=0.297$ ). There was no correlation between the GH concentrations and serum ferritin levels above and below 2000  $\mu$ g/L ( $p=0.477$ ). The mean $\pm$ SD serum ferritin level in GH deficient and GH sufficient patients, was 3543.6 $\pm$ 2398  $\mu$ g/L and 3185 $\pm$ 2065  $\mu$ g/L, respectively ( $p= 0.7$ ).

The mean $\pm$ SD age of patients with GH deficiency was 14.3 $\pm$ 2.9 and that of patients with sufficient GH was 13.7 $\pm$ 2.50 ( $p= 0.19$ ). Patients received desferrioxamine from the mean $\pm$ SD age of 6.8 $\pm$ 4.2 years. IGF1 deficiency was found in 73.9% of GH deficient and 65.5% of GH sufficient patients, the difference was not statistically significant ( $p= 0.2$ ).

The mean $\pm$ SD height in girls below 12 years was 129.05 $\pm$ 6.94 cm and in those above 12 years was 140.79 $\pm$ 9.72 cm, the difference was statistically significant ( $p<0.001$ ). The mean $\pm$ SD height in boys below 14 years was 132.77 $\pm$ 7 cm and in those above 14 years, it was 146 $\pm$ 9.8 cm ( $p< 0.001$ ). Thirty-nine

percent of girls below 12 years of age and 60.5% of those over 12 years were short (height below the 3<sup>rd</sup> percentile for age). Eighty-three percent of boys over 14 years and 70% of those under 14 years of age were short.

### Discussion

Sixty-four percent of the patients were below 2SD of the mean for normal height. Growth hormone deficiency was found in 57.5% of patients with  $\beta$ -thalassemia and there were no differences between GH deficient and GH sufficient patients regard to age, height, age at the start of chelation therapy and mean serum ferritin levels. Pekrun et al. reported the prevalence of GH deficiency as 33% in thalassemia patients and suggested that reduced GH secretion in patients is related to neurosecretory dysfunction.<sup>13</sup> In a study by Cavallo et al., 45% of thalassemic patients were GH deficient; height deficiency, serum ferritin levels and age at the start of chelating therapy did not differ in low as compared to normal responders to GH provocative tests.<sup>5</sup> We conclude that GH deficiency is a common complication of the thalassemia patients treated with current protocols. On account of a lack of difference in linear growth between GH deficient and sufficient patients, GH reserve perhaps, does not have an important role in growth deficiency. The exact mechanism of growth retardation in children with thalassemia major, who are regularly transfused and are on chelation therapy with desferrioxamine is unclear and seems to be multifactorial.<sup>13</sup> Stimulated GH secretion after provocative tests has been reported as normal<sup>14</sup> or reduced<sup>15</sup>. This discrepancy could be due to different degrees of iron deposition in the anterior pituitary.<sup>13</sup> The high percentage of GH deficiency can not be attributed to an inappropriate transfusion regimen and/or chelation therapy.<sup>5</sup> Growth failure has been attributed to GH deficiency, hypothyroidism, delayed sexual maturation, diabetes mellitus, zinc deficiency, low hemoglobin levels, bone disorders, desferrioxamine toxicity,<sup>16</sup> and IGF1 deficiency. Most of our patients suffered from poor control, irregular follow-up, under-nutrition and were of low economic status.

In conclusion, our study shows that a high percentage of  $\beta$ -thalassemia patients have growth retardation and GH deficiency and that GH deficiency perhaps, is not one of the main causes of short stature. It is suggested that more appropriate protocols of treatment and optimization of transfusion and chelation therapy be used for these patients.

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**Linear Growth Deficiency in  $\beta$ -Thalassemia Patients?**

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