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Title: Beta Thalassemia Patients and Their Growth, a Mini Review and Our Clinical Experience

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Abstract:

Context: Prevalence of short stature reported high in thalassemia major (TM) patients. It causes mental and social problems for them. As different cut-off point for growth retardation suggested in these patients, so it is very desirable if we find a careful cut-off age using statistical analysis to help patients before it is too late.

Evidence Acquisition: Data from 803 TM patients extracted from questionnaires filled face to face by operator. It contained demographic data, family, medical and drug history. All of height and weight measurements did only by one device. Mean age was 20 ± 7 y/o and 420 were females. Children (less than 20 y/o) formed 47% of participants. Patients that reported a major risk factor for osteoporosis omitted from this study. SPSS software used for statistical analysis

Results: Short stature found in 32% of patients. Being 10 and 11 y/o and older increased the risk of short stature, 28.5 and 21.4 times, respectively compared to younger patients (both P values <0.001). On the other hand after 7 y/o and to 18 y/o -like 10 y/o and 11 y/o- increases the risk of short stature. Also being 27 y/o and 30 y/o and older increases the risk short stature, 1.4 and 1.7 times, respectively compared to younger patients (P values, 0.042 and <0.018, respectively).

Conclusion: By our findings, we suggest that awareness about short stature and monitoring for it in thalassemics, should be done in their childhood. As we found being 7 y/o and older increases of risk of short stature, we suggest start of monitoring as early as 5 y/o.

Key words: Cut-off point, Growth, Thalassemia, Bone mineral density, Short stature

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Context:

The first complete and global study on human growth diversity is performed by Eveleth and Tanner. According to boundaries of that time, their study was a descriptive one. They were not agreeing with a previous study that growth of all populations can feet on one universal reference**.** They suggested "no guarantee that all children have the same growth potential". Based on their study, growth pattern of children with same age is different because of genetic variation **(1).**

Their work explained growth patterns in normal children but growth and growth deceleration problems in chronic disease is another entity. Thalassemia major is a chronic disease and is not an exception. Prevalence of short stature reported 31-55% in these patients **(2-7)**.

Beta-thalassemia major is the one of the most severe forms of these disorders. Inability of body to produce beta chain of hemoglobin leads to beta thalassemia diseases. Patients need frequent blood transfusion during their life time **(8)** and blood transfusion in long-term period cause iron overload.

Iron overload and secondary hemochromatosis that happen following frequent blood transfusion lead to production of free radicals and oxidative destruction. So many complications including heart failure, liver cirrhosis, and endocrine disorder such as hypogonadism, hypothyroidism, diabetes, calcium homeostasis disturbances and bone disease, fatigue, joint pain and darkening of skin occur.

The incidence of hypothyroidism, diabetes and impaired fasting glucose and hypogonadism between beta-thalassemia patients reported from 6.6-16%, 5-8% and 26-27% and 16-44% respectively **(2, 5, 9-11)**. In addition the rate of low bone mass density and fracture were 10-51% and 30-50% among patients **(2, 5, 12-14).**

Endocrine glands are more susceptible to iron overload, and even small increases of iron in early stage of life can cause many disturbances **(9).** Some believe that structure of pituitary gland in first four years of life becomes abnormal and the rate of growth hormone secretion also reduces due to high amount of iron **(15).** The production of IGF-I, whole GH-IGF, IGFBP-3, secondary due to liver hemosiderosis or chronic viral hepatitis may also decreases **(16).**

Increasing accumulation of iron in the body decreases sex and growth hormone secretion that are the main reasons of short stature in beta-thalassemic patients. Other main reasons of short stature in beta-thalassemic children are hypothyroidism, decreased bone density (mainly in spine) and bone deformity **(1, 15-17).**

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Malnutrition is another problem. Apart from low economic status or gastrointestinal disorder, there are also other factors contributing to malnutrition. Hyper-metabolic status in beta-thalassemia patients and difficulty in managing a sufficient balanced diet are important. Reducing the consumption of food containing iron will reduce the intake of adequate calories. The recommendation to tea consumption to reduce iron absorption leads to reduction in milk consumption, thereby the intake of essential nutrients for normal growth such as protein, calcium, and zinc decreases **(18).**

Other contributing factors in growth retardation are pre-transfusion of hemoglobin level **(19),** lack of folic acid **(16),** frequent use of chelating drugs **(20),** emotional factors **(8)**, low socioeconomic level **(21)**, autoimmune factors **(22),** and even genotype of thalassemia **(7).**

About chelating agents, Desferrioxamine (DFX) is a chelator agent that its intensive use and/or premature use (for example, before 3 y/o and more than 50mg/kg/day), may have bone complications **(23).** Taking these agents in patients with hyper transfusion is necessary, because Desferrioxamine (DFX) binds to iron and removes excess iron from body, but it may cause metaphyseal long-bone dysplasia, spinal changes, and growth retardation. DFX also prevents from synthesis of DNA and cell proliferation, collagen formation and degradation of cooper, zinc, or calcium in bone matrix. Lack of essential micro nutrients reduces alkaline phosphatase activity, decreases spinal height, so leads to truncal shortening, even in the presence of normal stature **(24).** Body disproportion between the upper lower body segment (former is shorter than normal and latter is normal) is a common feature of short stature in thalassemia patients. Male sex is suggested as an independent risk factor **(19)**. However there are several studies that argue otherwise **(25-27).**

The exact age of growth retardation in beta-thalassemia patients does not have the same depth of research for its correlated results. According to Saxena, growth retardation occurs at the age of 8 years old **(21).** So, it can be considered that most of children with thalassemia have normal growth during childhood period. But, Soliman and his colleagues claimed the process of growth development is declining at the age 4 **(16)**. Nokeaingtong et al, reported in children with thalassemia, mean height Z-score is reduces by 0.19 SD yearly from 5 to 14 years old **(19)**. Other study that performed in 1973, showed short stature in boys begins at age of 8 years old, and at 11 years old becomes clearly visible. This process in girls begins at 10 years old and becomes visible at 12 **(21).**

Generally, growth development occurs in two stages. The first occurs during the childhood period that depends on growth hormone and the second stage is during the in puberty period

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which depends both on growth and sex hormone secretion **(1, 16, 21)**. In children with beta-thalassemia, growth retardation occurs in both to stages of childhood and puberty. But there is study which claimed, growth retardation in children with beta-thalassemia establishes within three phases. The first phase starts in children with the age of less than 5 years old because of ineffective erythropoiesis and anemia. The second phase happens between the ages of 5 to 9 years old due to iron overload which effects on the pituitary gland, and last phase occurs in pre-pubertal period **(18).**

As different cut-off points for growth retardation in thalassemia patients reported and short stature is more treatable in early periods, it is desirable if we find a careful cut-off age for its incidence and help patients before that it is too late. In this study we tried to find such cut-off point via statistical analysis.

Methods:

Study protocol:

In this cross-sectional study, data from 803 beta-thalassemia major patients analyzed. Information extracted from questionnaires of a bone mineral densitometry (BMD) department of a referral center from around the country. Location was Special Medical Center of Charity Foundation for Special Diseases**.** Questionnaires filled during a face to face interview by BMD operator during 2003-2010. Exclusion criteria was being current user or chronic user of systemic steroids. Also patients that reported a major risk factor for osteoporosis omitted from this study. Inclusion criteria was referring to above BMD department to measure height and weight carefully and with one device.

Height and weight measured by one device as all of BMD scans did by one DXA machine (Norland XR-46 densitometer). A medical history obtained about any drug or disease that affects BMD, positively or negatively.

Short stature in children was defined by height percentile less than 3%. Hypothyroidism defined as current use of levothyroxine. History of diabetic based on suggestion of patients.

Low bone mass considered as Z scores ≤ -2 BMD relative to age and sex specific norms.

Deformities reported by BMD operator. The operator reported it in spine or femur if deformity remained after a good positioning of patients and did not disappear after careful repositioning.

As diabetes and hypothyroidism (here, levothyroxine use regarded as a surrogate of hypothyroidism), are minor risk factor, patients with medical history of diabetes and levothyroxine use did not omitted. On the other hand, these two diseases are generally known

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disorders by people with known medications that increase accuracy of data received from patients.

The procedures were approved by the ethics committee of the Endocrinology and Metabolism Research Institute of Tehran University of Medical Sciences (EMRI of TUM) and performed accordant to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments **(28).** The data used for this project obtained from routine and scientific investigations of thalassemia patients. Also, at that time, it was beneficial for them. Moreover, considering the confidentiality of this information, it does not seem to be harmful to the patients. Also, considering that the implementation of this projects, helps to check the health and help the health of other thalassemia patients, it seems that conducting this study without the consent-letter of the patients does not create an ethical problem.

Statistical analysis:

Continuous variables summarized as means, SDs, and ranges. Categorical variables summarized as simple percentages. The Independent-Samples T Test procedure was used for comparison of means for the two groups of cases. For assessment of association between dichotomous variables we used crosstab. Statistical significance was set at 0.05.

We used odd ratio calculation for finding cut-off age for incidence of short stature. An odds ratio is a relative measure of effect, which allows the comparison of the intervention group of a study relative to the comparison or placebo group. So if the outcome is the same in both groups the ratio will be 1, which implies there is no difference between the two arms of the study. Odd ratio calculation usually contains a confidence interval that if it cross the "1", it is non-significant. On the other hand, if confidence interval don't cross 1, it is significant. This means one arm of study (for example, here, being at an age and higher), significantly (with a confidence interval of 5%) changes the risk of an outcome (here, for example "diabetes in thalassemic patients"), significantly. No doubt, the primary independent parameter (for example, "age", here) must have a significant correlation with dependent parameter (for example, "being diabetic" here). We used such analysis for finding cut-off age for incidence of endocrine complication in thalassemic patients. We tried to find being "which age (and older)", significantly raises the risk of any complication that found significantly related to age (at first we tested these correlation).

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Results:

Participant characteristics and prevalence of disorders:

Mean age of patients was 20 ± 7 y/o and female to male ratio was 420/383. Children (less than 20 y/o) formed 47% of participants. Mean ages of males and females was 20.1 and 19.9 years, respectively (no significant difference, P value= 0.693). Short stature found in 32% of patients and youngest short stature patient was 6 y/o. Diabetes and hypothyroidism found in 3.3% and 2% of cases respectively. Prevalence of low BMD of neck and spine was almost equal and found in 30%.

Associations:

Significant correlations found between age, sex, diabetes and short stature (P values, <0.001, 0.042 and <0.001, respectively). Male sex was a risk factor for short stature.

As we found age in a significant correlation with short stature and it is a continuous parameter, odd ratio calculation used to find which age significantly increases the chance of being short and considered it as cut-off age for short stature. Being 10 and 11 y/o and older increased the risk short stature, 28.5 and 21.4 times, respectively compared to younger patients (both P values <0.001). On the other hand after 7 y/o and to 18 y/o –like 10 y/o and 11y/o- increased of risk of short stature. Also being 27 y/o and 30 y/o and older increases the risk short stature 1.4 and 1.7 times, respectively compared to younger patients (P values, 0.042 and <0.018, respectively). In table 1 you can find significant increases of risk of short stature according to the age levels. In this table we also showed the results for men and women separately.

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Patients / Age-cutoff	All patients	Female patients	Male patients
6 y/o and older	0.00† (0.00- -)	0.00 (0.00- -)	0.00 (0.00- -)
7 y/o and older	***19.8 (2.7-145.2)**	7.0 (0.9-53.5)	0.00 (0.00- -)
8 y/o and older	***13.3 (3.2-55.1)**	***4.6 (1.0-20.1)**	0.00 (0.00- -)
9 y/o and older	***16.3 (3.9-67.2)**	***6.3 (1.4-27.1)**	0.00 (0.00- -)
10 y/o and older	***21.4 (5.1-86.4)**	***7.9 (1.8-33.4)**	0.00 (0.00- -)
11 y/o and older	***28.5 (6.9-116.8)**	***10.9 (26-45.8)**	0.00 (0.00- -)
12 y/o and older	***11.4 (4.9-26.4)**	***6.8 (2.4-19.3)**	***21.8 (5.2-90.9)**
13 y/o and older	***6.8 (3.7-12.5)**	***4.1 (1.9-8.9)**	***12.7 (4.5-35.9)**
14 y/o and older	***4.2 (2.6-6.7)**	***2.9 (1.5-5.5)**	***6.2 (3.0-13.0)**
15 y/o and older	***2.8 (1.8-4.2)**	***2.1 (1.2-3.7)**	***3.6 (2.0-6.6)**
16 y/o and older	***2.5 (1.4-2.8)**	***2.2 (1.3-3.8)**	***2.7 (1.6-4.6)**
17 y/o and older	***2.0 (1.4-2.8)**	***1.6 (1.0-2.7)**	***2.3 (1.4-3.9)**
18 y/o and older	***1.5 (1.1-2.1)**	1.4 (0.9-2.3)	***1.7 (1.0-2.6)**
19 y/o and older	1.2 (0.9-1.6)	1.1 (0.7-1.7)	1.3 (0.8-2.0)
20 y/o and older	1.1 (0.8-1.5)	1.1 (0.7-1.7)	1.1 (0.7-1.7)
21 y/o and older	1.0 (0.8-1.4)	1.0 (0.7-1.6)	1.1 (0.7-1.6)
22 y/o and older	1.2 (0.9-1.6)	1.3 (0.8-2.0)	1.1 (0.7-1.7)
23 y/o and older	1.2 (0.9-1.7)	1.3 (0.8-2.0)	1.1 (0.7-1.8)
24 y/o and older	1.3 (0.9-1.7)	1.3 (0.8-2.0)	1.2 (0.8-1.9)
25 y/o and older	1.2 (0.9-1.7)	1.2 (0.7-2.0)	1.2 (0.7-1.9)
26 y/o and older	1.3 (0.9-1.9)	1.3 (0.8-2.2)	1.3 (0.8-2.1)
27 y/o and older	***1.4 (1.0-2.1)**	1.5 (0.8-2.5)	1.4 (0.8-2.3)
28 y/o and older	1.4 (0.9-2.1)	1.3 (0.7-2.2)	1.6 (0.9-2.8)
29 y/o and older	1.4 (0.9-2.2)	1.5 (0.8-2.8)	1.4 (0.7-2.5)
30 y/o and older	***1.7 (1.1-2.7)**	***1.9 (1.0-3.6)**	1.5 (0.8-2.9)
31 y/o and older	1.3 (0.7-2.3)	1.5 (0.7-3.1)	1.4 (0.7-2.9)
32 y/o and older	1.3 (0.7-2.4)	1.1 (0.5-2.5)	1.5 (0.7-3.1)
33 y/o and older	1.0 (0.5-2.0)	1.0 (0.3-2.7)	1.5 (0.7-3.4)
34 y/o and older	0.9 (0.4-2.0)	0.6 (0.2-2.0)	1.3 (0.5-3.2)

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35 y/o and older	0.9 (0.4-2.0)	0.7 (0.1-2.6)	1.0 (0.4-2.6)
36 y/o and older	0.8 (0.3-1.8)	0.2 (0.0-2.3)	1.0 (0.3-2.6)
37 y/o and older	0.5 (0.2-1.5)	0.00 (0.00- -)	0.7 (0.2-2.3)
38 y/o and older	0.6 (0.2-1.7)	0.00 (0.00- -)	0.8 (0.2-2.6)
39 y/o and older	0.4 (0.1-1.6)	0.00 (0.00- -)	0.6 (0.1-2.4)
40 y/o and older	0.1 (0.2-1.2)	0.00 (0.00- -)	0.2 (0.0-1.7)
41 y/o and older	0.2 (0.0-1.7)	---	0.2 (0.0-2.0)
42 y/o and older	0.00 (0.00- -)	---	0.3 (0.0-2.9)
43 y/o and older	0.5 (0.5-4.5)	---	0.4 (0.0-3.9)
44 y/o and older	0.00 (0.00- -)	---	0.00 (0.00- -)
45 y/o and older	0.00 (0.00- -)	---	0.00 (0.00- -)

*** P-value < 0.05**

† Results of odds ratio (odds ratio range)

Table 1: Age levels and the increased risks of short stature

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Discussion:

In our study we found prevalence of short stature as high as 32%. Prevalence of short stature reported previously 31-55% **(2).** It seems the prevalence of short stature in our patients is among lowest rates. This can be considered the result of the implementation of an active 'health network service' for thalassemic patients in Iran. The thalassemia prevention program established in 1995. It is extended all over the country (it is based in 64 medical universities and faculties). Almost all thalassemia patients are supported by these centres. It is reported that mean of hemoglobin of patients on the day of transfusion is almost 8.0g/dL; that can be translated to a relatively good distribution of blood supply for them. Besides, for appropriate management of iron overload, iron chelation agent that are internally manufactured, are free for all thalassemics.

In previous discussed studies, 2 phases and 3 phases of growth retardation reported in thalassemic patients. Our findings are more close to authors that suggest 3 phases or there cut-offs for growth retardation, because we found ages of 7y/o and 11 y/o and 18 y/o as cut-off points. However, according to our findings we think growth retardation in thalassemic patients is a continuous phenomenon. May be the reason behind this, is incident of deformities due to micro compression fractures of vertebrae that is a continuous problem. In this cross-section we

found 4 percent deformity in spine and 1 percent deformity in femur and 30% of low BMD. However the results may be different from one ethnicity to another **(29).**

Male to female difference in short stature prevalence is significant and males have more short stature than females. This is in agreement with Nokeaingtong et al.study. They found that children's height-for-age Z-scores decreased up to the age of 14 (from the age of 5). But at 14, females showed growth spurt, whereas growth in male children continued to decline. May be females show a better response to hormones or less detrimental reactions to iron overload. Even some investigators suggested that they have lesser sensitivity to chronic oxidative stress **(19).** But there are studies in disagreement **(25-27).** In Altincik and al. study, short stature was present in 42% and in men and women the prevalence was almost the same **(25).** In nother population of 40 female and 40 male beta thalassemia patient, number of short stature patients was almost the same (33 male, 32 female) **(26).** Rathaur et al. found that 14/24 female and 32/46 male were short, but no significant association found between sex and short stature **(27).** Diabetes found to have a direct correlation with short stature and hypothyroidism not. We found no scientific reason for these correlations but late peak of increased risk of short stature in 27 and 30 y/o may be due to increase of diabetes risk in these ages in thalassemic patients **(30).**

Our study has some limitation. The lack of information about hypogonadism and delayed puberty in patients is a limitation (data about females is consistent but no question about males' age of puberty or hypogonadism asked, so we ignored all data about hypogonadism and delayed puberty). Also a DXA scan is not gold standard for diagnosis of spinal or femoral deformity, but if we don't find any deformity is spinal region in a DXA scan, it is confirmatory. Another limitation of our study is no data about hormonal lab tests in our questionnaire. Although there are some limitations, this study has strong aspects such as high number of patients and measurement in a referral center, by one device, and one operator (95% measurement done by one operator). Other novelty of this study is using statistical tools for finding cut-off point of short stature, that didn't use or not referred in previous studies. The statistical test that we used for defining cut-off points in this study is also important, because with using it, we could determine the odd ratio between short stature and age cut-off points that we determined

Conclusion:

We suggest that awareness about short stature and monitoring for it in thalassemics, should be done in their childhood. As we found being 7 y/o increases of risk of short stature, we suggest start of monitoring as early as 5 y/o.

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At the end, we hope that with these studies we aid in the improvement of thalassemic patients management and enabling a better quality of life for them.

Declarations of interest: none.

Financial Disclosure Statement: none.

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