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Original Article

How Age, Sex and Transfusion Affects the Incidence of Endocrine and Bone Density Disorders in Major Thalassemic Patients

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Abstract

Background: Beta-thalassemia major patients frequently have endocrinopathies. We tried to determine relation between demographic and transfusion factor and endocrinopathies.

Methods: Major beta-thalassemia patients (n=114 cases), 3–38 yr of age, entered this study. Female to male ratio was 51/63. Children (less than 20 yr) formed 57% of participants. Information about bone mineral density (BMD) and hormonal and biochemistry blood evaluation including fasting blood sugar (FBS), ferritin, triiodothyronine (T3), thyroxine (T4) and thyroid-stimulating hormone (TSH), luteinizing hormone (LH) and follicle-stimulating hormone (FSH), testosterone (males), and estradiol (females) entered data sheet.

Results: Sex and ferritin level showed no significant correlation with above disorders. Age significantly correlated to short stature, diabetes, low BMD at femur and neck (*P*, 0.031, 0.008, 0.009 and <0.001, respectively) . The risk of short stature had increased in 12 yr and older patients 7.71 times than younger patients (*P*= 0.008). The risk of diabetes had increased in 35 yr and older patients 26.25 times than younger patients (*P*= 0.03). The risk of Z-score ≤ -2 in femoral region has increased in 19 yr and older patients 5.84 times than younger patients (*P*= 0.002). The risk of Z-score ≤ -2 in spinal region has increased in 14 yr and older patients 17 times than younger patients (*P*= 0.007).

Conclusion: The main factor related with endocrinopathies was age. The correlation between age and short stature, diabetes and low BMD was positive. Therefore, we recommend early monitoring of thalassemia patients (in their late childhood and early teenage) for these complications.

Keywords: Thalassemia; Endocrine; Bone; Thyroid; Blood sugar

Introduction

Thalassemia, is inherited blood disorder with abnormal hemoglobin structure, divided to different types. In beta-thalassemia major (TM) patients with severe and fatal anemia and need to life-long hyper-transfusion, endocrine disorders are common. Growth retardation as one of most common complications (1) may be seen in the whole stature, or any of shoulder width, hip breadth or sitting height or combination of them (2).

In this article when we mention thalassemia, we talk about beta-thalassemia major.

Abnormalities in pituitary structure and problematic growth hormone secretion and Insulin-like growth factor 1 (IGF-I) synthesis due to liver dysfunction -secondary to siderosis and/or chronic viral hepatitis-, whole growth hormone-Insulin-like growth factor- IGF Binding Protein-3 (GH–IGF-I–IGFBP-3) axis malfunction, and other endocrine disorders suggested as the underlying factors (3, 4). No doubt, malnutrition and the hyper metabolism are important (5). The increase of caloric intake; increases IGF-I in thalassemic children (2).

Cut-off age for growth retardation is under investigation. Growth retardation appears by 8 years of age (6) and Soliman et al indicate the age of 4 as the cut-off point (2). Higher growth retardation cut-off ages also was reported (6).

Another frequent endocrine complication (and as some believe the most frequent disorder (7)) in is hypogonadism. Usually the main form of hypogonadotropic hypogonadism results from iron deposition in the hypothalamus and pituitary, but sometimes it occurs due to iron induced primary gonadal failure (5) Chronic hypoxia, zinc deficiency, free radical oxidative stresses, liver disorder and diabetes mellitus, also have contributions. Some patients lose their initial capacity for spermatogenesis in older ages. This phenomenon is called late onset hypogonadism. In these patients, exogenous gonadotrophins may be induce or restore spermatogenesis, so finding cut-off age of onset of hypogonadism seems very crucial. Some authors think late onset male hypogonadism occurs in second and third decades of life (8). For covering the early onset and late onset of hypogonadism, Perera et al. recommend patient monitoring begin from 10-12 years (9).

Disorders of glucose metabolism with different severity and different onset time are reported in different studies. Impaired glucose tolerance prevalence is up to 26% and diabetes is detectable in about 8% of patients (10). Of course higher rates are reported (11). Diabetes is related to viral infections and mainly iron overload of liver. Iron deposition in pancreas is another factor and autoimmune reaction against beta cells destructs these cells. Family history also plays an important role (9).

Hypothyroidism in thalassemia is a common finding. Reports of the severity and prevalence are different. Prevalence of hypothyroidism reported up to 20% and 40%.(12, 13). In older reports 13 to 60 percent are also mentioned (14).

Another complication is low bone mass that reported as high as 36% in thalassemic patients (15). Vogiatzi et al (16) believe getting close to puberty has a negative effect on consuming bone density in thalassemic patients. It means low BMD is not common in pediatric children (16, 17). Endcrinopathies (18) liver disease (19) and even short stature may have roles in thalassemia induced osteoporosis (20). Though the results may be different from one ethnicity to another (21) osteoporosis is so important problem in these patients that International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A) recommends Dual-energy X-ray absorptiometry (DXA) BMD tests repeat every year at age 0-12 years and every 2 years afterward (22).

As some of above thalassemia endocrine disorders defined as treatable in early periods (8), it seems very desirable if we find cut-off age for their incidence.

Materials and Methods

Sample size

According type 1 error= 0.05, type 2 error=0.2 and correlation age and hypothyroidism =0.3, sample size determined as 114 cases.

Study protocol

In this cross-sectional study, 114 Major beta-thalassemia patients entered this study from 2004-2013. Locations were thalassemia clinics of Endocrinology and Metabolism Research Center as well as Special Medical Center of Charity Foundation for Special Diseases**.** Age of participants was 3–38 yr. Female to male ratio was 51/63. Children (less than 20 yr) formed 57% of participants.

Inclusion criteria included at least one BMD by DXA and hormone assessment in above centers. Exclusion criteria was current use of bisphosphonate or chronic use of systemic steroids. A medical and drug history was obtained by face-to-face interview. Information about BMD and hormonal and biochemistry blood evaluation including FBS, ferritin, T3, T4 and thyroid-stimulating hormone (TSH), luteinizing hormone (LH) and follicle-stimulating hormone (FSH), testosterone (males), and estradiol (females), obtained from review of patients records.

The procedures approved with code "00307" by the Ethics Committee of the Endocrinology and Metabolism Research Institute of Tehran University of Medical Sciences (EMRI of TUM) and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Diagnosis Criteria for endocrine disorders

1) Hypogonadotropic hypogonadism defined as Low FSH, LH and estradiol (among females) and testosterone (among males), according to lab normal data.
2) Short stature in children was defined by height percentile less than 3%.
3) Hypothyroidism defined as sub-clinical hypothyroidism defined as TSH between "5-10 MIu/ml" and TSH more than 10 defined as clinical hypothyroidism.
4) Impaired fasting glucose: fasting blood glucose >100 mg/dL<126 mg/dL
5) Diabetes mellitus: fasting blood glucose ≥126
6) Low bone mass: Z scores ≤−2 BMD Z relative to age and sex specific norms.

As some patients did measurement BMD by a Hologic (Discovery) device and some did it by a Norland (XR-46) device, in analysis of BMD measurement, we used only final Z-score values (and their diagnosis threshold (refer to above)) for finding relation of other parameters and BMD measurement. In less than 20 year-old patients, the results were analyzed by using pediatric specific software.

Statistical analysis

Analyses Continuous variables were summarized as means, standard deviations (SDs), and ranges. Categorical variables were summarized as simple percentages. The Independent-Samples *t* Test procedure was used for comparison of means of the two groups.

We used logistic regression analysis to assess association of age category with endocrine and bone disorders. The results of logistic regression was reported as odd ratio (OR). 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. Therefore, 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 do not 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 and BMD complication in thalassemic patients. We tried to find being "which age (and older)", significantly raises the risk of any complication (at first we tested these correlation).
All comparisons were made two-tailed, and statistical significance was set at 0.05.

Results

Participant characteristics and prevalence of disorders

Medical records of 114 TM patients were used for this study. Mean age of the participants was 18.47± 7.58 years (3–38 yr). Mean ages of boys and girls was 18.16 and 19.45 years, respectively (no significant difference, *P* value= 0.368). Short stature found to be most prevalent disorders (36%). Impaired fasting glucose (IFG) found in 26% and diabetes found in 4%. Hypothyroidism was found in 8% of cases. Hypogonadism was found in 6% of cases. Low BMD of neck found in 18% and low BMD of spine found in 25% of cases.
Characteristics of patients of patients can be seen in Table 1.

Table 1: Endocrine characteristics of patients

Amounts Parameters	*Mean*	*Standard Deviation*	*Maximum*	*Minimum*
Age(yr)	18.7	7.5	3.0	38.0
TSH	3.0	2.0	0.4	13.9
FSH	3.6	2.6	0.1	15.0
LH	3.5	3.1	0.1	12.7
Femur BMD	0.730	0.126	0.362	0.992
Spine BMD	0.682	0.149	0.333	1.000

Associations

Correlation was measured between age, sex, ferritin level and the spine and femur low BMD and other endocrinological diseases. Sex and ferritin level showed no significant correlation with above disorders. Youngest patients with IFG, hypothyroidism and hypogonadism were at age, 5 yr, 10 yr and 13 yr respectively, but age showed no significant correlation with IFG, hypothyroidism and hypogonadism. Age significantly correlated to short stature, diabetes, low BMD at femur and spine (*P*, 0.031, 0.008, 0.009 and <0.001, respectively) and youngest patients with short stature, diabetes, low BMD at femur and spine were at age 7 yr, 20 yr, 14 yr and 11 yr respectively. The risk of short stature has increased in 12 yr and older patients 7.71 times than younger patients (*P*= 0.008). The risk of diabetes has increased in 35 yr and older patients 26.25 times than younger patients (*P*= 0.03). The risk of Z-score ≤ -2 in femoral region has increased in 19 yr and older patients 5.84 times than younger patients (*P*= 0.002). The risk of Z-score ≤ -2 in spinal region has increased in 14 yr and older patients 17 times than younger patients (*P*= 0.007).
We stated only age level as cut-off point (for any complication) that showed higher chance of observing complication. However, in Table 2 and Fig. 1, we showed other significant cut-offs.

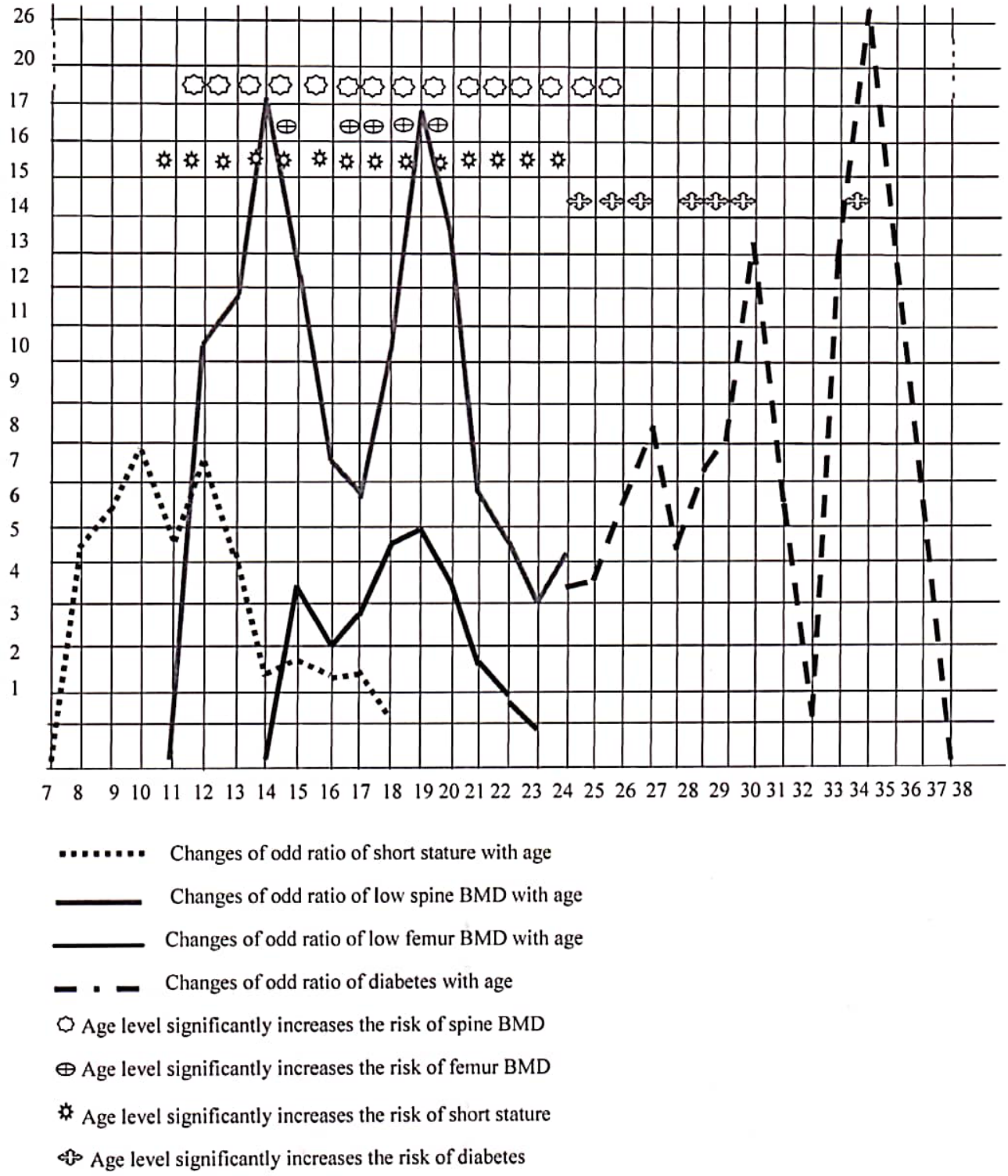

Fig. 1: Schematic increased risks of different endocrinological problems in specific age ranges

Table 2: Age levels and increased risks of different endocrinological problems

Complications Age-cutoff	*Short Stature*	*Low femur BMD*	*Low Spine BMD*	*Diabetes*
11 yr and older	* † 5.6(1.2-26.0)	0.00000005 (0--)	0.00000008 (0--)	0.0000009 (0--)
12 yr and older	*7.7(1.6-35.1)	0.00000005 (0--)	*10.3(1.3-81.3)	0.0000009 (0--)
13 yr and older	*5.3(1.4-19.5)	0.00000005 (0--)	*11.8(1.5-92.5)	0.0000009 (0--)
14 yr and older	2.3(0.9- 6.2)	0.00000006 (0--)	*17.0(2.1-132.2)	0.00000001 (0--)
15 yr and older	*2.5(1.05-6.1)	* 4.2(1.1-15.5)	*12.1(2.6-54.6)	0.00000001 (0--)
16 yr and older	2.2(0.9- 5.2)	3.0(0.9- 9.7)	*7.7(2.1-27.9)	0.00000001 (0--)
17 yr and older	*2.3(1.01-5.4)	* 3.6(1.1-11.8)	*9.6(2.6-34.7)	0.00000001 (0--)
18 yr and older	1.3(0.6- 3.0)	* 5.4(1.6-17.5)	* 10.2(3.2-32.6)	0.00000001 (0--)
19 yr and older	1.7(0.7- 3.7)	* 5.8(1.9-17.5)	*16.8(5.2-54.5)	0.00000001 (0--)
20 yr and older	1.8(0.8- 4.0)	* 4.5(1.6-12.6)	* 13.8(4.8-39.9)	0.00000001 (0--)
21 yr and older	1.4(0.6- 3.2)	2.6(0.9- 7.0)	*6.8(2.6-17.7)	6.6(0.7-61.1)
22 yr and older	1.3(0.5-3.0)	1.9(0.7-5.1)	* 5.5(2.1-14.1)	7.7(0.8- 72.1)
23 yr and older	1.5(0.6- 3.5)	1.0(0.3- 3.1)	* 4.0(1.5-10.1)	3.3(0.5- 20.8)
24 yr and older	1.9(0.7- 4.7)	1.5(0.5- 4.5)	* 5.2(1.9-13.9)	4.3(0.6- 27.6)
25 yr and older	1.8(0.7- 4.7)	1.6(0.5- 4.9)	*5.8(2.1-16.1)	4.8(0.7-30.7)
26 yr and older	1.8(0.6- 4.8)	0.7(0.1- 2.8)	*4.3(1.5-12.5)	*6.4(1.01-41.1)
27 yr and older	0.9(0.3- 2.9)	0.2(0.0- 2.1)	2.1(0.6- 6.8)	*8.4(1.3-54.5)
28 yr and older	1.2(0.4- 3.9)	0.3(0.0- 2.6)	1.9(0.5- 6.8)	5.2(0.7- 34.4)
29 yr and older	1.4(0.4- 4.9)	0.4(0.0- 3.9)	1.3(0.3- 5.6)	*7.1(1.05-48.7)
30 yr and older	1.7(0.4- 6.3)	0.5(0.0- 4.6)	1.5(0.3- 7.1)	*8.1(1.1-56.2)
31 yr and older	1.2(0.2- 5.8)	0.0 (0--)	1.2(0.2- 7.4)	*13.4(1.8-99.6)
32 yr and older	2.5(0.4- 16.0)	0.0 (0--)	2.6(0.3- 19.8)	6.3(0.5- 70.8)
33 yr and older	5.2(0.5- 51.8)	0.0 (0--)	1.2(0.1- 14.7)	8.5(0.7- 101.8)
34 yr and older	3.3(0.2- 38.5)	0.0 (0--)	2.6(0.1- 43.1)	13.0(0.9-175.0)
35 yr and older	1.6(0.1- 27.1)	0.0 (0--)	2.6(0.1- 43.1)	*26.2(1.3-499.6)
38 yr and older	0.000000002 (0--)	0.0 (0--)	0.000000004 (0--)	0.0000000004(0--)

* $P < 0.05$

† Results of odds ratio (odds ratio range)

Discussion

In this study, we found the prevalence of endocrine disorders much higher than age matched normal persons (mean age of 18.2 yr). We observed spinal Z-score <-2 in 25%, femoral z score <-2 in 18%, Impaired fasting glucose in 26%, diabetes in 4%, short stature in 36%, hypothyroidism in 8% and hypogonadism in 6% of thalassemic patients.

Hypogonadotropic hypogonadism found much less prevalent than other studies. This may be due to common use of hormone replacement therapy (HRT) in older patients. However, it was not practical for us to exclude patients consuming supplement and replacement therapies, because it contains large portion of our adult patients. On the other hand, we could not recommend patients not to use them because it was unethical. Despite the observation that HRT consumption decreased the hypogonadism prevalence but it was not affective in decreasing short stature prevalence. This may be due to delay in diagnosis or start of hormone replacement therapy. However in the previous study we found prevalence of hypogonadotropic hypogonadism as much as 18% (23).

In our previous study, all of our hypogonadism patients were male (24). In the present study, gender had no correlation with hypogonado-

tropic hypogonadism. As prevalence of this disorder is confounded by HRT use in our patients, may be finding no relation between sex and hypogonadotropic hypogonadism; is confounded. There is also such confounding effect of use of Levothyroxine on hypothyroidism in our study.

About higher low BMD and diabetes, prevalence in comparison with previous project results (24) is higher. We now have larger sample size and higher mean age. Apart from the larger number of samples, it seems that increasing age played a role in increasing the prevalence of these complications. At the same time, the prevalence of short stature and IFG is similar to that study. Perhaps, in general, these complications are stabilized at a younger age.

However prevalence of short stature, in other articles was reported from to 35% (25) to 45% (2) and even as high as 67% (1). It seems that growth of Iranian thalassemics is better than some countries and worse than some other countries.

It is also the same about the prevalence of IFG and diabetes. Some studies reported prevalence of IFG, 18%, 20% and 30% respectively. Diabetes found in 0%, 5% and 2%, of their patients, respectively (26-28).

We found reports of 13.6-50% (29) and 55.84% (30) of low BMD prevalence in other studies. Low BMD prevalence in our study, is lower in comparison with them (spinal Z-score <-2 in 25% and femoral z score <-2 in 18% of our patients).

Our analysis show no association between many of endocrine and BMD parameters and ferritin level. May be ferritin level is not a very good criterion for iron overload (17).

The risk of Z-score ≤ -2 in femoral region has increased in 19 yr and older patients 5.84 times than younger patients. In our previous study, being 21 yr and 22 yr considered as the cut-off point of age for Z-score ≤ -2 (31).

We think our new findings seems more logical because there was no case of Z-score ≤ -2 in children in that study (patients less than 20 yr) and now our sample size is also larger. In that study (24) we could not find cut-off point for low BMD in spine -may be due to lower sample size- but now we found that the risk of Z-score ≤ -2 in spinal region has increased in 14 yr and older patients 17 times than younger patients. May be our finding is in agreement by Vogiatzi et al. study, that found adolescence is a critical period for bone loss development (16) , and our new cut-off points are set around puberty.

In our previous study, we could not determine a specific age range which increases the risk of short stature among our patient (24). The risk of short stature has increased in 12 yr and older patients 7.71 times than younger patients. There is different report about the cut-off age that growth retardation begins. Growth retardation appears by 8 years of age (6) . In another study, age of 4 years was that cut-off point (2). But their findings were only based on pediatric studies, and had lesser sample size. In addition, no evidence found that they reported such cut-off point based on statistical analysis.

Our present study shows the risk of diabetes has increased in 35 yr and older patients 26.25 times than younger patients; that is in coordination with other authors' suggestions. They suggested that before 16 yr, diabetes mellitus is unusual (32) and by exposure to hyper-transfusion; incidence of diabetes may increase 2.5 times per decade. Unfolding of diabetes in thalassemic patients in their third or four decades of age, may be explainable by this assumption (6).

When we reviewed guidelines for monitoring endocrine disorders in thalassemia major patients, we found Perera et al. (9) recommend monitoring of patients in 10-12 years age, for puberty changes and consultation with endocrine experts if signs of delayed puberty are seen. About adults, they also recommend annual clinical survey and assessment of the gonadotropins and sex hormones and start of HRT if it is useful. ICET-A recommends diabetes screening from age of 10 years (22). ICET-A guideline, also recommended endocrine screening to start at the age of 9 years (or earlier at any age that clinical manifestations like short stature or decreased growth velocity/year; appear) and continuing it annually. About bone densitometry, ICET-A recommends

bone mineral densitometry (BMD) to measure every year at age 0-12 years and every 2 years afterward.

We are agree with lower age for monitoring as ICET-A, especially when we watch the graph of our analysis and find that age like 15; is the age that 3 disorders like "low BMD in spine and femur and short stature" increase significantly. We also know that the process of unfolding these disorders begins years earlier. On the other hand, the development of pituitary iron overload in beta-thalassemic patients occurs as young as 4 years of age. Of course, initially, iron is safely buffered in the cells and glandular volume is maintained, producing a gland that is dark on MRI but functions normally. As at this point, aggressive chelation may remove glandular iron with no long-term squeals (33). Therefore, monitoring patients as early as possible and before it become untreatable, is logical.

Overall, the cross-sectional design of this study and using medical records in some patients, constitute limiting factors in our ability to explain the etiology of endocrine complications in thalassemia. This limitation, as well as sample size considerations, may also explain the lack of association between different factors and endocrine parameters. In addition, because there was no control group, our data were compared with standard databases, and consequently it affects the interpretation of our results (24).

Conclusion

We used statistical method to find cut-off age of endocrinological disorders. No evidence found that previous studies report such cut-off points using statistical analysis. We recommend early monitoring of thalassemia patients (in their late childhood and early teenage) for these complications.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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