Bone Mineral Density and Calcium Status in Children with β-Thalassemia

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Abstract: Background: Thalasssmia is one of the most common single gene disorders. It is widely distributed in the Mediterranean region .In spite of the improved treatment of the hematologic disorder and its complications, β-thalassemia patients exhibit an unbalance in bone mineral turnover with increased resorptive rates and suppression of osteoblast activity, resulting in diminished bone mineral density (BMD) more evident in the lumbar spine. **Objectives:** In this work we attempted to delineate calcium status and bone mineral density in a group of transfusion dependent Egyptian β-thalassemic patients of both sexes. **Patients and methods:** This study was cross sectional study. It included 50 cases diagnosed as ß- thalassemia major. The patients were selected by simple randomization from the pediatric hematology units of Al Azhar University Hospitals, as well as 15 healthy children included as a control group. For each (patients and control) bone mineral density (BMD) had been measured by the Dual Energy X-ray Absorption (DEXA) method for total body and lumber spines. Serum calcium, phosphorous and alkaline phosphatase were measured. **Results:** Serum Calcium was lower (P<0.001), the alkaline phosphatase was higher (P 0.000) when compared to controls. The Mean Total BMD values in patients with thalassemia were significantly reduced in comparison with that of controls (Z- score: -1.5 ± 1.2 and -0.2 ± 0.9) respectively P <0.001.. In patients with thalassemia LBD were significantly reduced in comparison with that of control (Z-score: -2.4 ±1.7and -0.1 ±1) respectively P <0.001; **Conclusion:** Decreased mineral density is frequent in β-Thalassemic patients. The sequalae of osteoporosis, especially vertebral and long bone fractures, represent a major cause of morbidity in these patients. Bone mineral density should be done annually for follow up and early detection of bone status in patients with thalassemia.

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1. Introduction:

Thalasssmia is one of the most common single gene disorders; it is inherited as an autosomal recessive disorder. It is widely distributed in the Mediterranean region [1].

The thalassemia syndromes are a heterogeneous group of inherited anemias characterized by defects in the synthesis of one or more globin chain subunits of the adult hemoglobin tetramer (HbA), this leads to deficient hemoglobin resulting in hypochromic microcytic red cells, ineffective erythroposiesis and hemolytic anemia [2].

The incidence of α- thalassemia is higher in South East Asia, China and certain areas of Africa, while β-thalassemia syndromes are more common in Mediterranean countries as Greece and Italy [3].

In spite of the improved treatment of the hematologic disorder and its complications, β-thalassemia patients exhibit an unbalance in bone mineral turnover with increased resorptive rates and suppression of osteoblast activity, resulting in diminished bone mineral density (BMD) more evident in the lumbar spine [4].

During chronic anemia stage, increased Erythropiosis in bone marrow may result in decreased proliferation of osteogenic progenitors, including both osteoblast and osteoclast cells which consequently reduced both bone formation and resorption, respectively. Chronic anemia causes tissue hypoxia which in turn may reduce both circulating and local insulin-like growth factor-1 (IGF-1) and subsequent reduction of bone formation. Blood transfusion with inadequate iron chelation results in an accumulation of iron in the pituitary causing impaired growth hormone (GH)-IGF-1 axis function. Low IGF-1 reduces bone formation and resorption resulting in osteoporosis. Hemosiderosis of liver may cause defective vitamin D synthesis. Iron accumulation in bone and vitamin D deficiency can impair bone mineralization causing osteomalacia[5].

Besides impairments in osteoblast activity, which are thought to be a major cause of osteopenia/osteoporosis in βTM, an enhanced activation of osteoclasts is also invoked as a contributing factor. This provides the rationale for the use of bisphosphonates, which are potent inhibitors of

osteoclast function, for the management of βTM-induced osteoporosis [6].

An association between increased circulating levels of proresorptive cytokines and altered bone turnover has been detected in βTM patients [7]. The receptor activator of nuclear factor-kappa B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) pathway has recently been recognized as the final, dominant mediator of osteoclast proliferation and activation [8]. The OPG/RANKL system acts as an important paracrine mediator of bone metabolism also in thalassemic patients. Indeed, these patients showed no differences in plasma levels of OPG in the presence of higher circulating levels of RANKL, with consequent lower OPG/RANKL ratio and increased osteoclastic activity [7].

Aim of the Work:

In this work we attempted to delineate calcium status and bone mineral density in a group of transfusion dependent Egyptian β-thalassemic patients of both sexes.

2.Patients and Methods:

This study was cross sectional study carried out from February 2012 to October 2012. It was conducted according to the ethical guidelines of Al Azhar Ethical Committee. It included 50 cases diagnosed as ß-thalassemia major. The patient were selected by simple randomization from the pediatric hematology units at Al Hussein and Bab Al Shareyea Hospitals; Al Azhar University, as well as 15 healthy age and sex matched children included as a control group.

Inclusion criteria:

- Ages between 5- 18 years.
- Children on regular blood transfusion therapy.
- Children on iron chelation therapy, whether oral or subcutaneous.

Exclusion criteria:

- Thalassemic children not receiving regular transfusion therapy.
- Patients not on iron chelation therapy
- Patients with other hemoglobinopathies

A written consent from one of the parents after explanation of the study was taken.

*All the patients were subjected to the following:

1-History taking stressing upon the following:

Demographic data; Age (in years), sex, age at onset of diagnosis.

Transfusion history; Frequency/year, amount and transfusion index (ml/kg/yr).

Chelating history; Onset of chelation, type, dose and compliance.

Complications; Cardiac, hepatic or endocrinal complications.

Bony symptoms including history of bone pain, pathological fractures and deformities.

Operations; Splenectomy and Cholecystectomy.

Drug intake including Calcium and vitamin D supplements

2- Complete blood count (CBC), serum calcium, phosphorus and alkaline phosphatase.

3- Estimation of Bone Mineral Density (BMD):

Bone Mineral Density had been measured by the Dual Energy X-ray Absorption (DEXA) method. DEXA were done for the both groups (patients and control) on total body and lumber spines.

Technique:

All DXA measurements were done on Lunar GE prodigy medical system, USA. This technology uses a combination of a narrow angle fan beam with rectilinear scanning to give fast scan times with low radiation doses.

Statistical analysis:

Statistical analysis was performed with Epi - info software, version 6.04 which in public domain. Descriptive statistics including the mean and standard deviation for each group were calculated. Descriptive analysis of the presented data was used through tables. For comparing categorical data, Chi square (χ^2) test was performed. Comparison between pre- and post-splenectomy values was done using paired *t* test. Correlation between various variables was done using Pearson moment correlation equation for linear relation in normally distributed variables and Spearman rank correlation equation for non-linear relations. The minimum significant level adopted was 5% (0.05).

3.Results

The demographic data of the cases and control are presented in (Table1& Fig 1). Both the weight and height of the cases were significantly lower than that of control with *p* value = 0.005.

Serum calcium was lower ($P<0.001$), the serum phosphorous was higher (P □0.000) and serum alkaline phosphate was higher (P <0.000) when compared to controls (Table 2 & Fig 2).

The mean total bone mineral density (TBMD) and lumber (LMBD) values in patients with thalassemia were significantly reduced in comparison with that of controls (Z-score: -1.5 ± 1.2 and -0.2 ± 0.9) respectively P <0.001(Table 3 & Fig 3).

Low BMD was detected in (80%) in female patients and (89%) in male patients with no statistically significant difference between both sexes regarding bone mineral values either total or lumber density with *p* value = 0.912 & 0.834 respectively (Table 4).

There was no correlation between biochemical parameters (calcium, phosphorous and alkaline phosphatase) values and bone mineral density in thalassemic patients (Table 5& Figs 4, 5).

Table 1: Clinical data of cases and control.

	Cases		Control		*p*-value
	Mean	± SD	Mean	± SD	
Age	11.90	3.50	11.60	3.40	0.876
Height (cm)	136.0	16.50	142.1	13.3	0.166
Mean Z-score (Height)	1.340		0.687		0.172
Weight (kg)	32.70	11.0	38.40	13.60	0.152
Mean Z-score (Weight)	1.042		0.353		0.005
BMI	17.01	2.70	18.500	4.1	0.256
Mean Z-score (BMI)	0.600		0.280		0.102

- *P*- value is significant if <0.05

Table2: Comparison between cases and control regarding laboratory results.

Parameter	Cases (n=50)	Control (n=15)	*p*-value
Hemoglobin (g/dl) Mean ± S.D	**7 ± 1.1**	**13.2 ± 1**	**0.000**
Platelets (c/uL) Mean ± S.D	**604 ± 321**	**345 ± 43.7**	**0.003**
TLC (c/uL) Mean ± S.D	**45.5 ± 42.4**	**8.7 ± 1.2**	**0.000**
Calcium (mg/dl) Mean ± S.D	**8.4 ± 0.9**	**9.6 ± 0.7**	**0.001**
Phosphorus(mg/dl) Mean ± S.D	**5.1 ± 1.1**	**3 ± 0.4**	**0.000**
Alkaline phoshatase (U/L) Mean ± S.D	**241 ± 102**	**61.8 ± 23.7**	**0.000**

Table 3: Comparison between cases and control regarding Total and Lumber bone density.

	Cases	Control	*P*-value
TBD Mean ± SD Range	-1.5 ± 1.2 -4.1 _ 1.5	-0.2 ± 0.9 -1.7 _ 0.9	0.000
LBD Mean ± SD Range	-2.4 ± 1.7 -5.7 _ -0.1	-0.1 ± 1 -2.1 _ 0.9	0.000

Table 4: Correlation between total bone density (TBD) and lumber bone density (LBD) and sex of the studied cases.

Parameter	Male (n=19)	Female (n=31)	Total (n=50)	*P* value
TBD Mean ± SD Range	-1.53 ± 1.17 -4.0 - 0.7	-1.55 ± 1.29 -4.1 - 1.5	-1.54 ± 1.23 -4.1 - 1.5	0.912
LBD Mean ± SD Range	-2.46 ± 1.62 -5.7 - -0.3	-2.44 ± 1.75 -5.7 - -0.1	-2.44 ± 1.68 -5.7 - - 0.1	0.834

Table 5: Correlation between TBD and LBD and laboratory results in the studied cases.

Parameters	TBD		LBD	
	Correlation coefficient	*p*-value	Correlation coefficient	*p*-value
Hb	-0.172	0.779	-0.062	0.450
Hct	0.330	0.231	0.125	0.668
Calcium	0.306	0.019	0.162	0.389
Phosphorus	-0.672	0.031	-0.685	0.262
Alkaline Phosphatase	-0.647	0.000	0.847	0.000

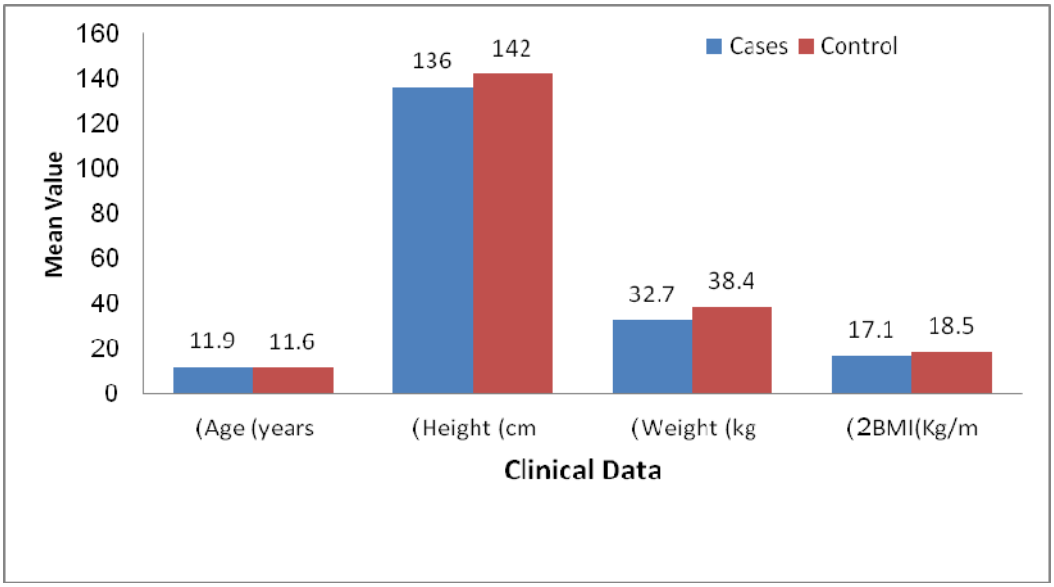

Figure 1: Clinical data of cases and control

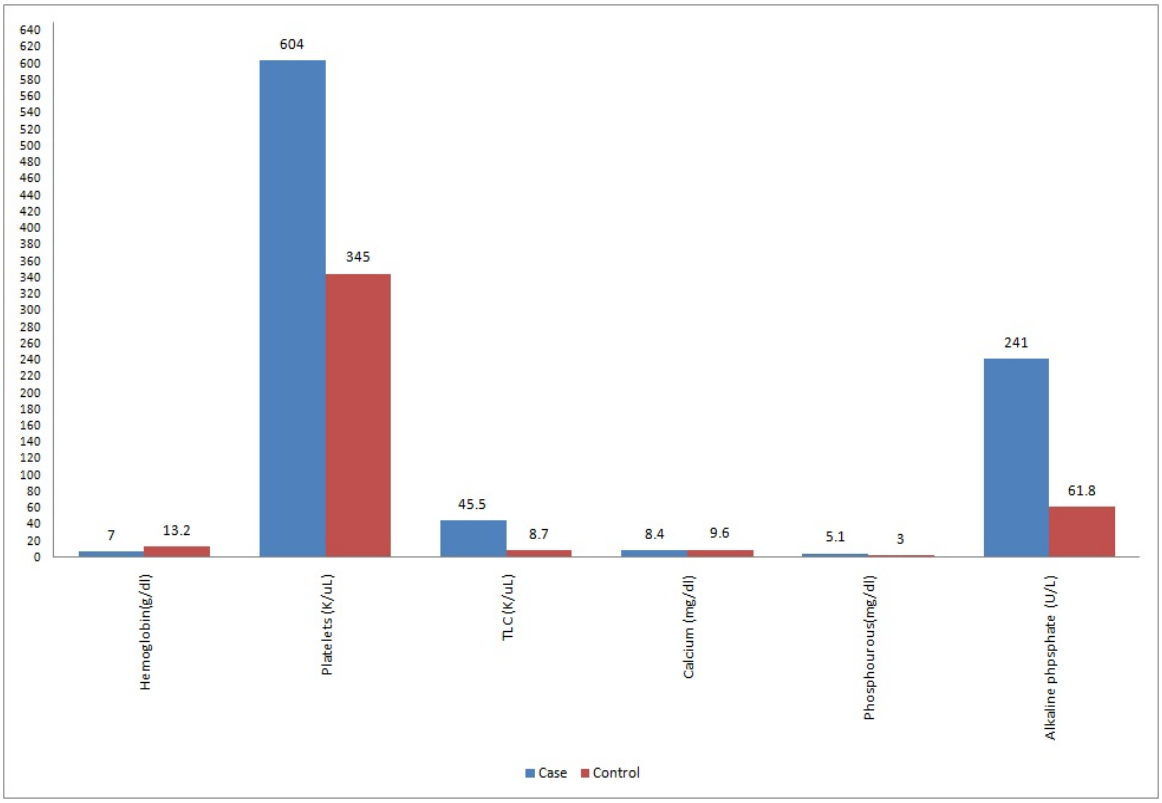

Fig. 2: Comparison between cases and control regarding laboratory results

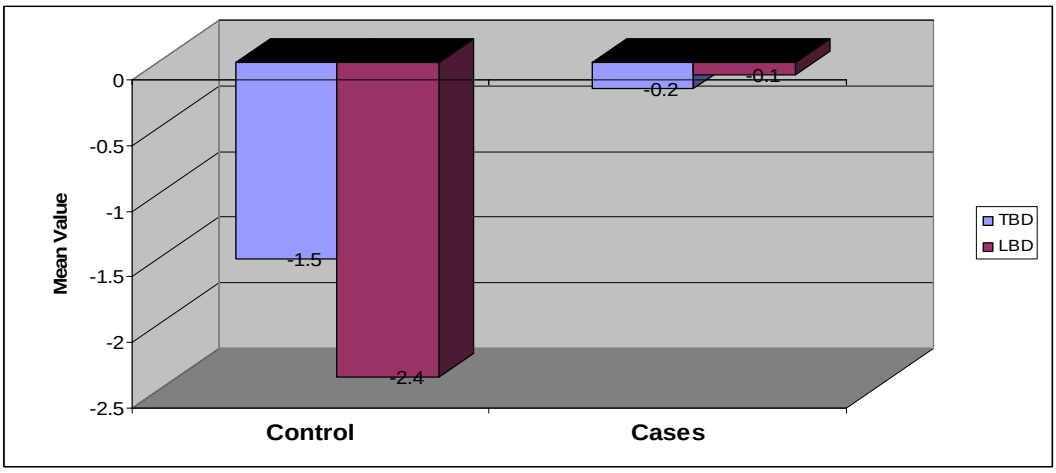

Fig. 3: Comparison between cases and control regarding Total and Lumber bone density

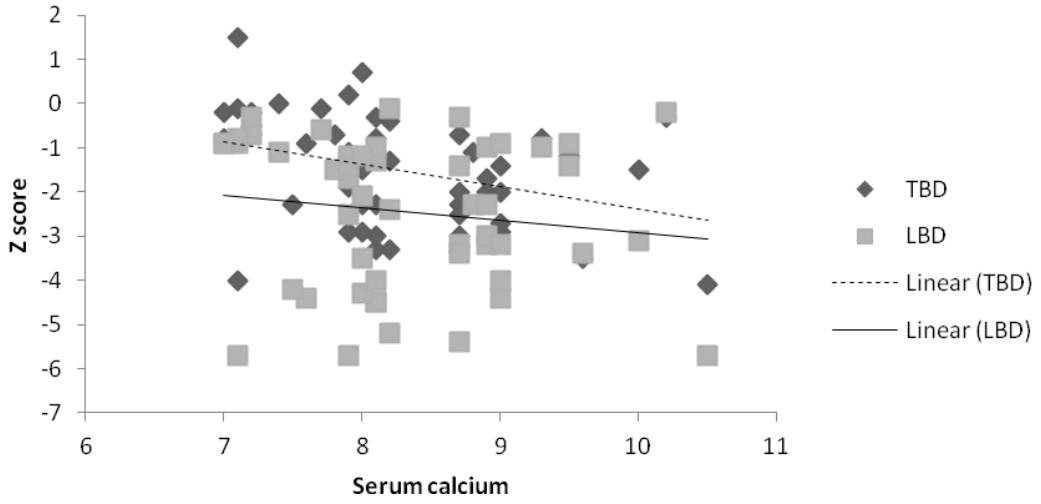

Fig. 4: Correlation between serum calcium (mg/dl) and TBD and LBD in the study cases.

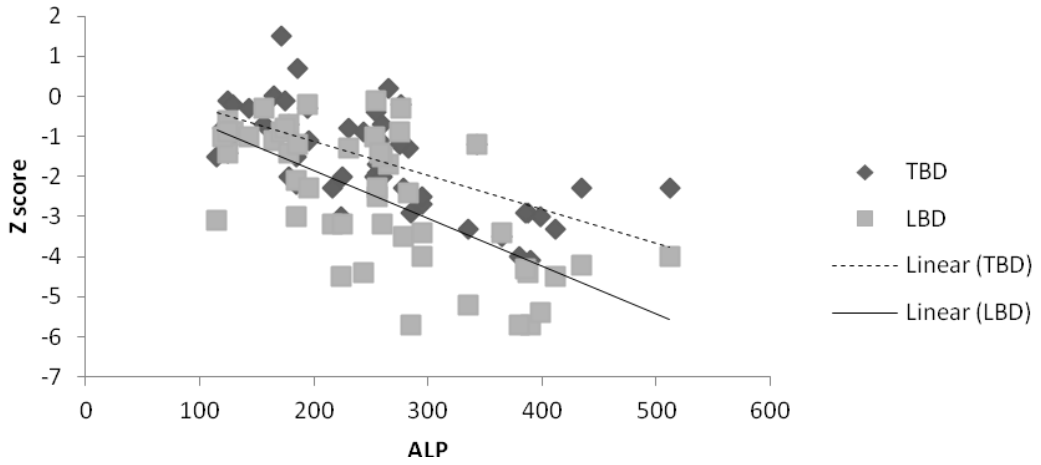

Fig. 5: Correlation between Alkaline Phosphatase (ALP, IU/L) and TBD and LBD in the study cases.

4. Discussion:

The results of this study were based on data obtained from 50 thalassemic patients, 19 males (38 %) and 31 females (62%) and 15 sex and age matched controls.

The mean age of the studied cases was 11.8 ± 3.5 years (range: 6-18 years). The mean weight was 32.7 ±11 kg and mean height was 136 ± 6.5 cm. (Table 1 & Fig.1). Both the weight and height of the cases was significantly lower than the control as the thalassemia is a chronic disease. Many studies have shown that although conventional therapy allows children to grow normally during the first decade of life, growth retardation is observed in a significant proportion during adolescence. **Raiola *et al.*, in 2003** found that growth retardation (weight and height) among thalassemic patients with age progression [9].

As regards the biochemistry results (Table 2 & Fig.2); Serum Calcium was lower (P<0.001), the serum phosphorous was higher (P 0.000) and serum alkaline phosphate was higher (p<0.000) when compared to controls. This highlights the biochemical results reflected the state of chronic vitamin D deficiency among cases with Thalassemia. This confirms the data reported in the majority of published literatures [10]. ***Autio et al***. observed that 61% of their patients with β-thalassemia had hypocalcemia [11].

In the contrary, a study was done by ***Soliman , and his collegues 2008*** documented that out of 40 thalassemic patients only 2 had hypoparathyroidism and low 25-OH D, and 2 had hypocalcemia with high alkaline phosphatase (ALP), high PTH and serum 25-OH D below ng/ml. The rest of the patients (n=36) had low circulating 25-OH D concentrations with normal serum Ca and PO4 concentrations [12].

After assessment of bone mineral density we noticed that; 9 patients (18%) have normal BMD (Z score >-1), 41 patients (82%) have low BMD. Three patients (7%) with only low TBD and eight patients (20%) with only low LBD and thirty cases(73%) have both low TBD and LBD. The mean total BMD values in patients with thalassemia were significantly reduced in comparison with that of controls (Z-score: -1.5 ±1.2 and -0.2 ±0.9) respectively p <0.001(Table 3 & Fig.3).

The same finding in mean lumber BMD values was detected. In patients with thalassemia LBD were significantly reduced in comparison with that of the control (Z-score: -2.4 ±1.7, -0.1 ±1) respectively p <0.001;

High prevalence of osteoporosis and osteopenia in thalassemic patients is in gross agreement with those reported in the earlier literature; similar results from other studies have also been reported [8,13, 14].

The lumbar spine, consisting mainly of trabecular bone,is mostly affected by bone marrow expansion due to increased and ineffective haemopoiesis occurring in patients with β-thalassaemia. In addition, as axial BMD increases more rapidly than peripheral BMD during puberty, pubertal disorders, frequently reported in thalassaemic patients, affect the lumbar spine to a higher degree than other sites. In a study performed by **Mahachoklertwattana *et al.***, BMD was evaluated in several sites in thalassaemic patients. Lumbar spine values were the lower ones, particularly in transfusion-dependent patients [4].

Low BMD was detected in 80% in female patients and 89% in male patients with no statistically significant difference between the sexes. There was no significant difference between genders regarding bone mineral values (table 4).This finding was in agreement with the some previous reports [13, 15, 16,17]. However in contrary to these findings; **Jensen *et al.*** in **1998** reported that the bone lesions in thalassemic patients are more frequent and more prominent in males [18].

There was no correlation between BMD (TBD and LBD) and hemoglobin or hematocrite level at the time of the study which in agreement with ***Vogiatzi, and his colleagues 2004*** which suggested a weak contribution of anaemia in early bone derangement in thalassemic patients [19].

A study done by ***Mehrnoush Kosaryan and his collegues 2010*** found that a negative significant correlation was detected between BMD and the mean of hematocrit (P<0.005) [20].

Other biochemical parameters (calcium, phosphorous and alkaline phosphatase) and hematological parameters (Table 5) had no statistical significance with BMD values [21].

Conclusion:

Low mineral density and bone changes are frequent in β-Thalassemic patients and occur as a consequence of the hematological disorder and its complications as well as nutritional deficits (especially vit D). The sequalae of osteoporosis, especially vertebral and long bone fractures, represent a major cause of morbidity in these patients. Bone mineral density is a good index of bone status in patients with β-thalassemia.

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