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Bone mineral density in a cohort of transfusion-dependent β-thalassemia (TDT) patients

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Abstract

Background and objective: β-Thalassemia is a common inherited disease in this region. A considerable number of transfusion-dependent β-thalassemia (TDT) patients suffer bone problems. The objective of this study was to evaluate bone mineral density in TDT patients using dual-energy X-ray absorptiometry (DEXA) scan.

Methods: In this study, 53 TDT patients aged ≥10 years, together with 25 normal healthy individuals were enrolled. Their bone status was assessed using DEXA scan at lumber spine (L1-L4) and femoral neck. The effect of physical, biochemical, and hormonal characteristics on the bone mineral density (BMD) parameters were evaluated. BMD-Z score was used to assess the magnitude of bone disease.

Results: The mean age of the patients was 21.3±7.8 years with male to female ratio 1.4:1. The values BMD parameters were significantly lower in the patients compared to the normal group. The mean values of BMD Z-core among the patients at lumber spine and femoral neck were -2.95±1.07 and -1.51±1.02 respectively. Among the patients, osteoporosis was detected in 69.8% and 13.2% in lumber spine and femoral neck respectively. None of the normal individuals had osteoporosis. Patients' age. body mass index (BMI) and parathyroid hormone level had a significant association with BMD Z-score (P <0.05).

Conclusion: Osteoporosis and osteopenia are extremely prevalent among our TDT patients. DEXA scan is an effective, non-invasive, and relatively inexpensive procedure for assessing bone status.

Keywords: BMD; TDT; Z-score; Osteoporosis.

Introduction

Thalassemias are a group of inherited abnormalities of hemoglobin synthesis caused by a deficiency in the formation of one or more of the globin chains of the hemoglobin. It is a major health burden in many parts of the world, particularly in the Mediterranean basin and the Middle East. It is the most common monogenic disease worldwide.[1] Usually, the diagnosis of TDT becomes evident by the second year of life with patients having significant anemia and failure to thrive. The life expectancies and standard of life of these patients have increased significantly in to their fourth and fifth decade of life due to blood transfusion and iron chelation therapy such as Deferoxamine, Deferiprone, Deferasirox.[2]

It has been observed that when TDT patients' age progress, bone diseases like deformities, fractures, nerve compression, pain, osteopenia, and osteoporosis are a major source of morbidity and the long-term complications.[3]

Osteoporosis is a reduction of bone mass due to increased bone resorption with an increased risk of fractures. Reduced bone mass in TDT patients occur due to a variety of reasons such as increased

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marrow erythropoiesis, marrow expansion,[4] genetic factors,[5] extensive iron overload,[6] iron chelators,[7] hormonal deficit like hypothyroidism, hypoparathyroidism and hypogonadism,[8] nutritional and vitamin deficiency,[9] and decreased level of physical activity.[10]

DEXA scan remains to be a convenient tool to assess bone mineral density (BMD) to detect osteopenia and osteoporosis at the lumber spine and femoral neck as it is quite accurate, non-invasive, and relatively safe. β-Thalassemia is common in the northern Iraqi Kurdistan region.[11,12] Erbil is the capital city of the region; according to the regional statistics office, the population of Erbil province is estimated around 2.25 million. Currently, more than 750 TDT cases are documented and registered at Erbil thalassemia care center.

A considerable number of thalassemic patients attending the care center are complaining of diffuse bone pain and problems mainly in the lower back. The main objective of the present study was to assess the BMD in TDT patients and to correlate the rate of osteoporosis and osteopenia with the patients' clinical, biochemical and hormonal parameters.

Methods

This cross-sectional comparative study included 53 TDT patients and 25 healthy, age and gender matched individuals. TDT patients aged 10 years and above were conveniently enrolled to this study while visiting the local thalassemia care center in Erbil. Written consent was obtained from the included patients and healthy subjects after explaining the objective of the work. The study was approved by the ethical committee of Hawler Medical University. Patients <10 years, and those who had bone marrow transplantation were not included. Patients receiving drugs affecting BMD like antiepileptic drugs, oral calcium, vitamin D and corticosteroids were also excluded.

Patients were directly interviewed and clinically examined prior blood transfusion. Sociodemographic and clinical data were recorded; body mass index (BMI) was calculated. History of transfusion and chelation therapy, splenectomy, bone pain, and fractures were specifically scrutinized. Pre-transfusion Hb was recorded. Serum sample was obtained from the patients as well as the normal control individuals and levels of calcium, vitamin D, ferritin, phosphorus, alkaline phosphatase (ALP), and parathyroid hormone (PTH) were measured using automated analyser (Cobas 6000 modular system, Roche Germany). BMD was performed using Hologic QDR DEXA scan device to evaluate the BMD (g/cm2) and bone mineral concentration (BMC) at lumbar spine (L1-L4) and the femoral neck. DEXA scan was performed for the enrolled patients and normal control subjects at Physiotherapy and Rehabilitation Centre of Erbil Teaching Hospital. After performing DEXA scan, Z-score was also automatically generated at the two measuring sites, lumber spine and femoral neck. As per the WHO criteria for the diagnosis of osteoporosis, a BMD Z-score of ≥ −1 was considered normal, Z-score between −1 and −2.5 was considered as osteopenia, and Z-score of ≤ −2.5 was considered as osteoporosis. The BMD Z-score was correlated with the clinical and lab data in the patients and normal control groups.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 25). Chi square test and Fisher's exact test were used to compare proportions. Student's t test (unpaired t test) of two independent samples was used to compare means of two samples. ANOVA was employed to compare between more than two means. Bivariate linear correlations for continuous variables was used. A *P* value of ≤0.05 was considered statistically significant.

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Results

In this study, the bone mineral density of 53 TDT patients and 25 normal healthy individuals was assessed. The thalassemic group included 31 (58.5%) males and 22 (41.5%) females. Their age ranged between 11-41 years with a mean of 21.3±7.8 years. The mean age of the control group was 24.5±9.3 years, ranged between 11-40 years. The means of BMI, Hb, serum calcium, vitamin D and PTH were significantly lower in the TDT group comparing to the controls (*P* <0.05). The mean serum level of phosphorus did not show any significant difference in the two groups; while serum ferritin and ALP levels were significantly higher in the TDT patients (Table 1).

Table 1 Demographic and lab characteristics of the TDT patients and control groups

Characteristics	**TDT patients**	**Control groups**	***P*-value***
	Mean±SD (Range)	**Mean ± SD (Range)**	
Age (year)	21.3±7.8 (11-41)	24.5±9.3 (11-40)	0.115
Gender**			
Male	31 (58.5%)	12 (48.0%)	0.755
Female	22 (41.5%)	13 (52.0%)	
BMI (kg/m^2)	20.8±3.1 (14.2-28)	24.8±7.3 (13.5-46.3)	<0.001
Hb (g/dl)	8.5±0.9 (6.4-10.9)	12.9±1.7 (10.2-16.8)	<0.001
Calcium (mg/dl)	9.5±0.8 (6.8-11.0)	10.0±0.6 (8.5-11.2)	0.001
Vitamin D (ng/ml)	18.6±6.8 (4.0-33.7)	26.9±19.1 (10.1-95.0)	0.003
Ferritin (µg/L)	3701±2737 (431-11880)	80.6±96.7 (10.1-404.9)	<0.001
Phosphorus (mg/dl)	4.7±0.9 (2.3-7.6)	4.5±0.9 (2.9-7.5)	0.200
ALP (U/L)	162.9±55.8 (61.6-304.0)	104.4±73.6 (49-342)	<0.001
PTH (pg/ml)	5.6±4.0 (1.2-17.4)	24.2±13.3 (5.0-59.1)	<0.001

* By unpaired t test, ** By Chi square test

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Table 2 shows BMD parameters of the TDT patients and control groups. The mean values of all BMD parameters were significantly lower in the thalassemic group compared to the normal control group (*P* <0.05) at lumber spine and femoral neck.

Table 3 reveals the rates of osteopenia and osteoporosis at both lumber spine and neck of femur. The proportion of bone disease was significantly higher in the thalassemic patients' group (*P* <0.001). The BMD Z-score at lumber spine showed that 69.8% of the TDT patients have osteoporosis and 24.5% others have osteopenia. None of the normal controls had osteoporosis. The BMD Z-score values at neck of femur showed less prevalence of bone disease in both groups.

Table 2 BMD parameters of the TDT patients and control groups

BMD Parameters	TDT patients Mean±SD	Controls group Mean±SD	*P*-value*
Spine BMD (g/cm^2)	0.71±0.13	0.94±0.17	<0.001
Spine BMD Z-score	-2.95 ±1.07	-0.77±0.94	<0.001
Spine BMC (g)	33.73±10.01	51.02±9.91	<0.001
Femoral Neck BMD (g/cm^2)	0.76±0.13	0.87±0.14	<0.001
Femoral Neck BMD Z-score	-1.51±1.02	-0.39±0.92	<0.001
Femoral Neck BMC (g)	3.71±0.84	4.60±0.94	<0.001

* By unpaired t test

Table 3 Prevalence of osteoporosis and osteopenia in the TDT and control groups

BMD Z-score parameters	TDT patients No. (%)	Controls No. (%)	P-value
BMD Z-score, spine (L1-L4)			<0.001
Osteoporosis (<-2.5)	37 (69.8)	0 (0.0)	
Osteopenia (-1 to -2.5)	13 (24.5)	7 (28.0)	
Normal (<-1)	3 (5.7)	18 (72.0)	
BMD Z-score, femoral neck			<0.001
Osteoporosis (<-2.5)	7 (13.2)	0 (0.0)	
Osteopenia (-1 to -2.5)	30 (56.6)	5 (20.0)	
Normal (<-1)	16 (30.2)	20 (80.0)	
Total	**53 (100.0)**	**25 (100.0)**	

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Table 4 shows the relation between patients' clinical and lab characteristics and BMD Z-score. The age and gender did not significantly vary between patients with normal BMD Z-score and those with osteoporosis and/or osteopenia. The BMI related significantly with the BMD Z-score at lumber spine. Most of the lab parameters showed no significant relation with BMD Z-score except PTH which revealed strong relation at both scanned sites.

Table 4 Relation between TDT patients' characteristics and BMD Z-score

Overall	BMD Z-score	Spine	*P**	Neck Femur	*P**
Age (year)	Osteoporosis	20.19 ± 8.40	0.283	19.29 ± 6.95	0.600
	Osteopenia	23.85 ± 6.20		22.23 ± 8.59	
	Normal	24.33 ± 4.62		20.50 ± 6.88	
Gender**	Osteoporosis	23 (74.2%)	0.636	3 (9.7%)	0.486
Male	Osteopenia	7 (22.6%)		17 (54.8%)	
	Normal	1 (3.2%)		11(35.5%)	
Female	Osteoporosis	14 (63.6%)		4 (18.2%)	
	Osteopenia	6 (27.3%)		13 (59.1%)	
	Normal	2 (9.1%)		5 (22.7%)	
BMI (kg/m^2)	Osteoporosis	19.77 ± 2.57	0.001	19.15 ± 3.59	0.295
	Osteopenia	22.97 ± 2.83		20.79 ± 3.23	
	Normal	23.19 ± 5.39		21.38 ± 2.65	
Hb (g/dl)	Osteoporosis	8.30 ± 0.83	0.068	8.56 ± 0.39	0.430
	Osteopenia	8.82 ± 0.91		8.58 ± 0.94	
	Normal	9.13 ± 0.45		8.24 ± 0.87	
Calcium (mg/dl)	Osteoporosis	9.60 ± 0.72	0.088	9.43 ± 0.62	0.585
	Osteopenia	9.06 ± 0.80		9.39 ± 0.89	
	Normal	9.57 ± 0.68		9.63 ± 0.56	
Vitamin D (ng/ml)	Osteoporosis	17.97 ± 7.31	0.529	21.16 ± 0.76	0.158
	Osteopenia	19.50 ± 5.56		17.02 ± 9.85	
	Normal	22.00 ± 3.61		20.35 ± 6.93	
Ferritin (ng/ml)	Osteoporosis	4014.62 ± 2677.98	0.227	5249.43 ± 2062.21	0.268
	Osteopenia	3363.15 ± 2998.07		3553.97 ± 3010.94	
	Normal	1300.33 ± 798.14		3299.88 ± 2329.14	
Phosphorous (mg/dl)	Osteoporosis	4.73 ± 0.73	0.975	4.57 ± 0.81	0.975
	Osteopenia	4.68 ± 1.26		4.74 ± 0.95	
	Normal	4.63 ± 0.32		4.71 ± 0.86	
ALP (mg/dl)	Osteoporosis	165.12 ± 54.69	0.305	169.79 ± 43.14	0.683
	Osteopenia	167.59 ± 61.72		166.69 ± 57.28	
	Normal	114.47 ± 22.81		152.64 ± 59.54	
PTH (pg/ml)	Osteoporosis	4.70 ± 3.61	0.029	2.20 ± 1.65	0.035
	Osteopenia	8.05 ± 4.40		5.81 ± 3.57	
	Normal	6.53 ± 3.39		6.79 ± 4.80	

* By ANOVA, ** By Fisher's exact test

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Splenectomy was encountered in 27 (50.9%) patients. There was no difference in the BMD Z-score between the splenectomized and not splenectomized TDT patients. Chelation therapy was regularly received by 35 (66%) patients with no variation in the prevalence of bone disease between TDT patients receiving regular chelation therapy and those not regularly chelated (Table 5).

Bivariate linear correlation was used to determine the correlation between BMD Z-score at both scanned sites with the age, BMI, Hb, calcium, phosphorous, ALP, ferritin and PTH. The age and BMI correlated significantly with BMD Z-score at lumbar spine (rho= 0.334, *P* = 0.01; rho= 0.341, *P* = 0.012) Figure 1 (A and B). PTH correlated significantly with BMD Z-score at both scanned sites (rho= 0.331, *P* = 0.015; rho= 0.352, *P* = 0.012) Figure 1 (C and D). There was no significant correlation between the BMD Z-score with the other variables (*P* >0.05). Figure 1 (E) shows a significant negative correlation between vitamin D and ferritin levels (rho= -0.362, *P* = 0.008).

Table 5 Relation of BMD with splenectomy and chelation therapy in TDT patients

Splenectomy	**BMD Z- score**	**Yes (27)**	**No (26)**	***P*-value***
Lumber spine	Osteoporosis	16	19	0.55
	Osteopenia	9	6	
	Normal	2	1	
Femoral neck	Osteoporosis	3	2	0.08
	Osteopenia	20	17	
	Normal	1	7	
Chelation therapy	**BMD Z- score**	**Regular (35)**	**Irregular (18)**	***P*-value***
Lumber spine	Osteoporosis	23	12	0.89
	Osteopenia	10	6	
	Normal	2	0	
Femoral neck	Osteoporosis	2	3	0.40
	Osteopenia	26	11	
	Normal	7	4	

* Fisher's exact test

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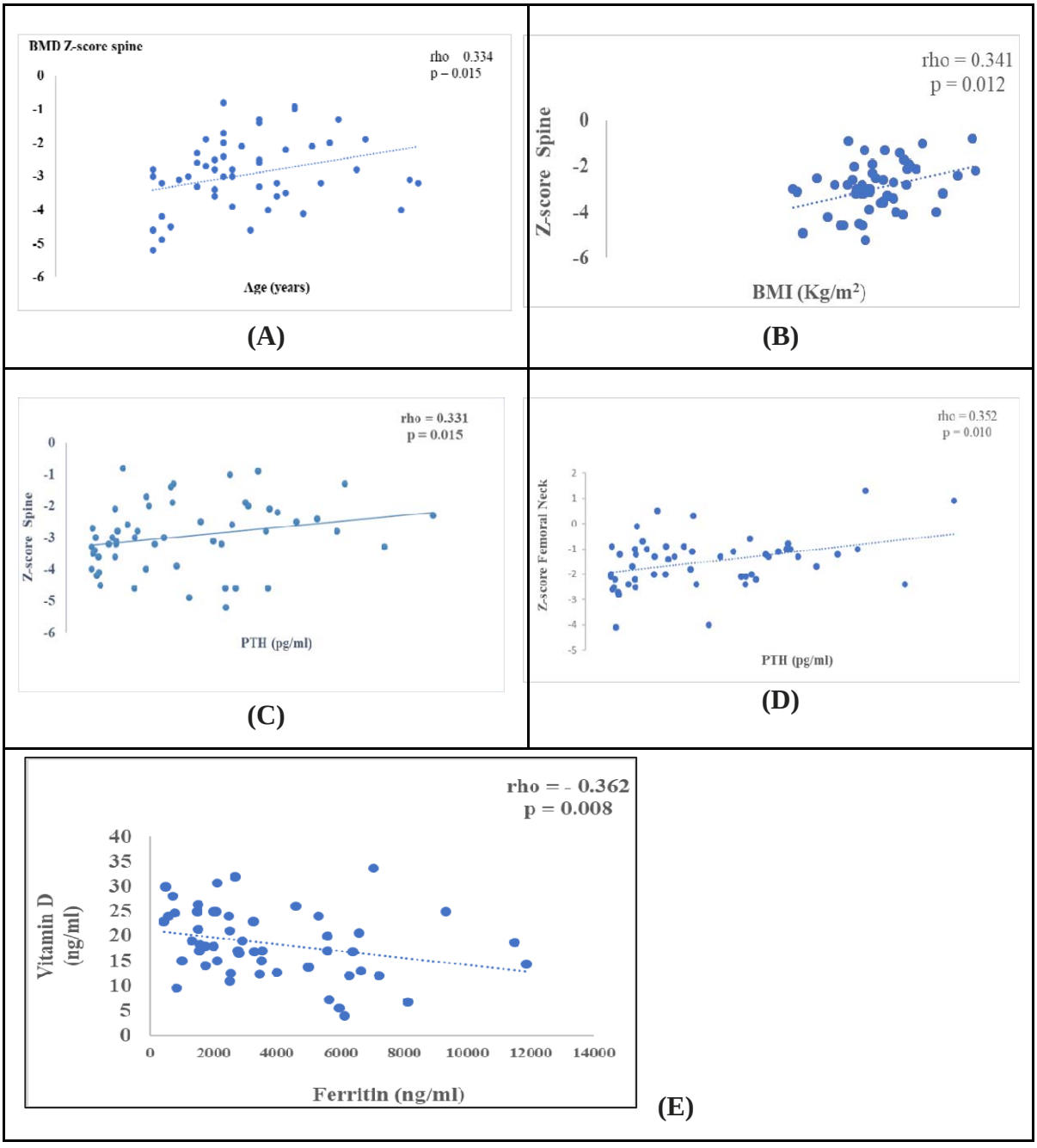

Figure 1 Correlation between the BMD Z-score with age(A), BMI(B), PTH (C) at lumbar spine, and PTH (D) at femoral neck. (E) Correlation between vitamin D and ferritin.

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Discussion

Osteoporosis and osteopenia in patients with TDT patients are very prevalent; they are frequently occurring manifestations even in well treated thalassemia patients. Bone loss in thalassemia involves complex interactions of various factors affecting the growing bones. Manifestations of defected BMD in β-thalassemia are still not very well understood in spite of the progress that has been made in the understanding of the natural history and pathogenesis of the disease.[13]

The current study showed significant bone disease among TDT patients. The mean values of the BMD parameters among TDT patients were significantly lower compared to the normal control group at both lumber spine and femoral neck. These findings are comparable to previous study.[14]

DEXA scan device is programmed to calculate BMD scores. The BMD Z-score compares one's bone density to the average value for a person of the same age and gender. BMD T-score is a standard deviation that calculates how much a result varies from the average. The latter is recommended to be used for adults. In our cohort, majority of the enrolled were children and adolescents; therefore, we adopted the BMD Z-score as the main parameter of bone density. Out of 53 enrolled TDT patients, 50 (94.3%) found to have defected by abnormal BMD Z-score at lumber spine while 37 (69.8%) patients had abnormal Z-score at femoral neck. Unexpectedly, a considerable number of the control individuals found to have osteopenia at the scanned sites, most of them were adults.

The rate of osteoporosis and osteopenia among our TDT cohort were very comparable to what have been reported in Iraqi thalassemic patients, the prevalence of osteoporosis was 67.5%.[15] In Iranian study the prevalence of osteoporosis was 62%,[16] but higher than the figure of Izdyar et al among 40 patients in Turkey, where 37.5% and 12.5% of the patients have spinal and femur neck osteoporosis.[17]

In our thalassemic patients many factors such as increasing age, low BMI, endocrine disorders such as hypoparathyroidism are responsible for bone loss with the subsequent morbidity of osteopenia and osteoporosis.[16,17]

It is clear that our data shows significantly lower bone density parameters at lumber spine compared to femoral neck. Similar finding was observed in the previous study which showed that the bone mineral loss is more severe in the spinal column than femoral neck.[18] The explanation of this differential bone mineral loss is attributed to the fact that lumber spine consists of trabecular bone and wide marrow space, and the accelerated hematopoiesis and progressive bone expansion, which is part of thalassemia pathology, affects the spine more severely than the proximal femur.[18]

Growth impedance is a complication in patients with thalassemia. In the current study, the mean BMI of TDT patients was significantly lower compared to the control group. This finding is consistent with some previous studies who concluded that low BMI is a significant predictor of impaired BMD.[14,19] The patients' Hb and ferritin levels did not reveal any significant correlation with the BMD. The normalization of hemoglobin levels does not affect the unbalanced bone turnover in thalassemia patients.[20] Zadeh et al found a significant correlation between the Hb and BMD Z-score.[21]

It is well-known that the pathological changes of thalassemia have cumulative effects and therefore complications become more apparent with age. We found a significant correlation between the value of BMD Z-score and patients' age. Some studies reported similar findings.[14,20]

We noted a higher frequency of spinal osteoporosis in male patients comparing to females (74.2% vs. 63.6%), while at femoral neck osteoporosis was more in female. However, no significant differences were noted between patients' gender and BMD Z-score values at the both scanned sites. This finding is in agreement with

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Zadeh et al.[21]

Serum levels of calcium, vitamin D, and PTH were significantly lower in the TDT patients comparing to normal control group; whereas the ALP level was higher. Phosphorus did not vary between the patients and control individuals. Despite their lower levels, calcium and vitamin D did not reveal significant correlations with BMD values. Same findings were reported by Zadeh et al.[21] In our study, we observed a significant negative correlation between vitamin D level and ferritin level (rho= - 0.362, *P* = 0.008). Low vitamin D level in thalassemia is mainly attributed to high ferritin level which in turn effects on the hydroxylation of vitamin D in the liver.[22] Other study showed that regular intake of calcium and vitamin D can be important for bone formation and preventing osteoporosis.[22]

Increased level of ALP in thalassemia is multifactorial; renal failure, hyperthyroidism, high intake of phosphate, and hypoparathyroidism are possible contributors. No significant correlation between BMD values and levels of ALP and phosphorus was detected in TDT patients at both scanned sites. These finding are comparable to that of Izadyar et al, though Ansari-Moghadam et al found a significant difference between BMD Z-score and phosphorous level in their TDT cohort.[23] Serum PTH level was significantly lower in the patients compared to the control group; El-Nasharet al reported no difference in PTH between their thalassemia and control cohorts.[24]

Effective iron chelation in addition to the provision of regular care to TDT patients in the developed part of the world is mostly the reason for maintaining PTH levels near the optimal levels. We observed significant relation between BMD values and PTH in the TDT patients at both scanned sites. The main cause of hypoparathyroidism in thalassemia is accumulation of iron in the parathyroid gland. We explored the incidence of osteoporosis and osteopenia among TDT patients in relation with splenectomy and chelation therapy. The proportion of the splenectomized and non-splenectomized patients were nearly equal. No variation in the rate of bone disease was observed between the two groups at both scanned sites. Similarly, we observed no difference between the regularly chelated patients with those who received irregular chelation therapy. Salih and Al-Khero observed significantly higher incidence of osteoporosis among the non-splenectomized TDT patients.[19]

Conclusion

A high proportion of the enrolled TDT patients found to have variable degree of bone loss. Osteoporosis and osteopenia correlated significantly with patients' age, BMI and PTH level. No significant relations between calcium, vitamin D, phosphorus, and ALP with bone disease were noted.

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Competing interests

The authors declare that they have no competing interests.

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