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Study of Bone Mineral Density in Transfusion Dependent Thalassemia, its correlation with Biochemical and Hematological parameters: A Cross-Sectional Study

Hegde DG[1*], Ghildiyal R[2], Sharma S[3], Zope S[4], Manavi KM[5], Ramaswamy M[6]

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[1*] Darshan G Hegde, MD, Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra, India.
[2] Radha Ghildiyal, MD, Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra, India.
[3] Sujata Sharma, MD, Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra, India.
[4] Sadhana Zope, MD, Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra, India.
[5] Manavi KM, MD, Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra, India.
[6] Manjunath Ramaswamy, MD, Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra, India.

Background: In thalassemic patients, bone disease is an important cause of morbidity. Patients with transfusion-dependent thalassemia (TDT) are susceptible to osteopenia and osteoporosis, the mechanism being multi-factorial. The present study was undertaken to study the prevalence of osteopenia and osteoporosis in TDT patients and describe its correlation with biochemical, hematological profiles.

Method: A total of 84 patients with TDT on regular PRC transfusion and iron chelation therapy aged between 5 and 18 years were enrolled in the study. Bone mineral densities (BMD) were measured by DXA scan (DXA spine/whole body) and categorized into normal, osteopenia and osteoporosis based on the WHO grading system.

Results: Out of 84 subjects, 57.1% had low BMD with 38(45.2%) having osteopenia and 10(11.9%) of them having osteoporosis. The prevalence of osteoporosis was found to be higher by DXA Spine than by DXA whole body which was found to be statistically significant (P=0.043). A high prevalence of hypoparathyroidism, hypocalcemia, hypovitaminosis D and increased serum phosphorous levels were noted among TDT patients with low BMD. Iron overload in Myocardium by T2*MRI also showed a statistically significant association with low BMD as determined by DXA Spine.

Conclusion: Low bone mass is one of the most prevalent complications among TDT patients. Osteoporosis is a progressive disease with multifactorial etiology. Iron overload status by T2* Cardiac MRI may be used as an early indicator for predicting Osteoporosis along with T-scores from DXA spine for early diagnosis and interventions. Further longitudinal prospective studies are needed to better understand the etiopathogenesis of bone disease in these patients.

Keywords: Transfusion dependant thalassemia, Bone mineral density, Osteoporosis, Osteopenia, DXA scan

Corresponding Author

Darshan G Hegde, MD, Department of Pediatrics, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Maharashtra, India.
Email: darshanhegde06@gmail.com

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Introduction

Beta thalassemia major is an autosomal recessive disease that leads to severe hemolytic anemia, usually in the second half of infancy. [1] Historically, beta thalassemia major was associated with marked osseous changes, particularly facial and limb deformities attributed to bone marrow expansion and cortical thinning caused by ineffective erythropoiesis. [2] The introduction of regular transfusion therapy in the mid-1960s to maintain a near-normal hemoglobin level resulted in the diminution or prevention of bone deformities. Therefore, the detection of low bone mass in many regularly transfused and well-chelated beta thalassemia major patients and other transfusion-dependent thalassemia (TDT) over the last decade was quite unexpected. [2] In thalassemia, marrow expansion causing mechanical interruption of bone formation, leading to cortical thinning, is still considered the main reason for the distortion and fragility of bones in thalassemic patients.

However, the pathogenesis of osteoporosis in thalassemic patients is very complex. The etiology of bone disease in thalassemia is poorly understood and involves multiple factors influencing the reduction in bone mineral density (BMD), mainly but not limited only to genetic factors, endocrine causes like hypoparathyroidism, diabetes mellitus, hypogonadism, iron overload, chelation toxicity, vitamin deficiency (vitamin C and D), and reduced physical activity. [3] The present study aimed to investigate the BMD in pediatric TDT patients and its relationship with mean pre-transfusion Hb, iron overload status, vitamin D and PTH levels, and various other biochemical parameters.

Material and Methods

After obtaining Institutional Ethics Committee and the BORS committee approval, this cross-sectional, observational study was conducted in 84 consecutive patients with TDT between the age group of 8-18 years undergoing regular packed red cell (PRC) transfusion and on iron chelation for a minimum period of two years, attending the Thalassemia daycare Centre in a tertiary care hospital from January 2019 to June 2020 (18 months). Patients having pre-existing bone diseases due to any other causes were excluded from the study.

The diagnosis of thalassemia was confirmed by age of presentation, hemoglobin electrophoresis by High Performance Liquid Chromatography (HPLC). Written informed consent was taken from respective parents or guardians. Demographic details, socio-economic status (modified Kuppuswamy classification), detailed history and clinical examination were noted in a predesigned case record form.

Details of PRC transfusion i.e. age at first transfusion, mean pretransfusion hemoglobin, and annual packed red cell transfusion requirement were noted. The chelation history included the type of drug taken, dose and duration. Also, the details of combination chelation therapy, if received are noted. Complaints about the bone i.e. bone pain, fractures in the past, arthralgia, deformities or any other relevant complaints were recorded.

Examination for hemolytic facies, and enlargement of liver and spleen was checked for and graded as described in the Hutchinson clinical manual. Clinical signs of iron overload in the form of organomegaly, and hyperpigmentation of the skin were looked for. Weight was determined using a digital scale and height was measured using a stadiometer. Iron overload was assessed objectively based on serum ferritin, T2* weighted Magnetic Resonance imaging (MRI) of the liver and heart as a part of routine annual screening.

All patients were tested for blood investigations as part of their routine follow-up: Serum Ferritin, Liver function tests (LFT), Renal function tests (RFT), Calcium profile including serum calcium, phosphorous, alkaline phosphatase, vitamin D3 and serum PTH, Thyroid function (fT4, TSH). All these blood investigations were done during their visits to the Day Care Centre for regular PRC transfusion. Imaging studies including ultrasound of the kidney and urinary bladder for size and echo texture of the kidneys,2D echocardiography for cardiac function (Ejection fraction, pulmonary hypertension, diastolic dysfunction) and DXA-Dual energy X-ray absorptiometry (DXA) (LUNAR DPXMD#7164) scan was done for assessing the density of the bones. [4]

BMD and BMC were measured at the spine, hip and right forearm and reported as DXA whole body T-score. T -score of BMD of the lumbar spine was reported separately. The T-scores thus obtained by DXA Spine and DXA whole body were correlated with the biochemical and hematological parameters.

Osteoporosis was defined as a T score of 2.5 standard deviations below the normal mean BMD for the respective age, whereas a T score between 1.5 and 2.5 standard deviations below normal for the age was defined as osteopenia as per the definition given by WHO. The data collected was analyzed using the SPSS Version 15.0 package. Data was given as Mean ± SD for continuous variables, median and range for non-normal data, and number and percentage for categorical variables. Comparison of mean between 2 groups was carried out by Student's unpaired t-test for numerical normal data. Mann Whitney U test was applied for comparison of non-normal data. Fisher Exact Probability test or Chi-square tests were applied to compare percentages for categorical data between 2 or more groups. Logistic regression analysis was used to identify risk factors related to osteoporosis among thalassemic patients. All statistical tests were two-tailed. Alpha (α) Level of Significance was taken as P ≤0.05.

Results

Amongst the study subjects 49 (58.3%) patients were males and 35 (41.6%) were females with a male: female ratio of 1.4:1 and maximum patients (45.2%) were in the age group of 9-14 years. 92.9% of patients belonged to the lower class and 7.1% upper lower class. 57.2% of patients were stunted, of which 29.8% were moderately stunted and 27.4% were severely stunted. 11.9% of the study group were severely thin and 11.9% had a very low pre-transfusion Hb of less than 7g/dl. Most of the study subjects (72.6%) were on deferasirox and 47.6% were on chelation therapy for 5-8 years. Though the prevalence of low bone mass was high in thalassemias only 7.1% had symptoms of bone disease. 93% of study subjects had hepatomegaly and 91% had splenomegaly. Out of total 84 subjects, 50(59.5%) had a SMR staging of stage 1, 16(19%) had stage 2 and 16(19%) had stage 3, 1(1.2%) had stage 4 and 1(1.2%) had stage 5 SMR staging.

Table 1: Clinico-epidemiological profile

Parameters	Mean (SD)	Range
Age (years)	12.58 (3.12)	5-18
BMI (kg/m2)	15.71 (2.15)	10.7-23.0
Annual PRC requirement (ml/Kg/Year)	175.56 (37.77)	90-300

The mean values of biochemical and hematological parameters are shown in Table 2.

Table 2: Biochemical and hematological profile of study subjects

Parameters	Mean (SD)	Range
Hemoglobin (gm/dL)	7.76 (0.57)	6.3-9.5
Total Bilirubin (g/dl)	1.49 (0.48)	0.3-3.1
AST (IU/dl)	48.72 (20.50)	0.1-124
ALT (IU/dl)	40.95 (22.11)	11-117
Total Protein (g/dl)	7.35 (5.53)	1.6-57.0
Albumin (g/dl)	3.87 (0.50)	2.9-6.8
BUN (mg/dl)	9.03 (3.44)	4.0-19.0
Serum Creatinine (mg/dl)	0.530 (0.142)	0.3-0.9
Blood Ph	7.40 (0.042)	7.34-7.49
Vit D3(ng/ml)	21.06 (13.15)	3.68-83.32
Serum Parathyroid hormone (PTH) (pg/ml)	10.57 (8.18)	1.2-45.1
Serum Calcium (mg/dl)	8.67 (1.42)	5.4-10.8
Serum Phosphorous (mg/dl)	4.50 (0.38)	2.8-5.1
Serum Alkaline phosphatase (U/l)	366.25 (165.76)	121-1035
Sodium (meq/l)	138.83 (2.69)	134-145
Potassium (meq/l)	4.12 (0.25)	3.5-4.5
Serum Ferritin (microgram/l)	2544.44 (1795.20)	524-7329
Whole body T Score	-0.835 (0.796)	-2.6-1.7
Spine T score	-1.363 (1.067)	-4.9-0.9
TSH (µu/ml)	4.029 (1.95)	1.02-11.73

DXA spine revealed that 40(47.6%) had normal BMD, 34(40.5%) had osteopenia and 10(11.9%) had osteoporosis. DXA whole body showed that 49(58.3%) had normal BMD, 33(39.3%) had osteopenia and 2(2.4%) had osteoporosis. However, when either the whole body or Spine T scores were considered, it was found that of the 84 subjects, 36(42.9%) had normal BMD, 38(45.2%) had osteopenia and 10(11.9%) had osteoporosis.

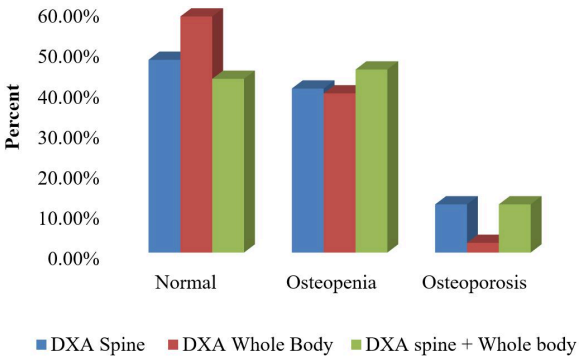

Figure 1: Proportion of Osteopenia and Osteoporosis

There was a statistically significant association between Age and low BMD by DXA whole body (P value 0.021) while no statistically significant association between BMD and gender,

Pre-transfusion Hb, Annual PRC requirement, Iron chelating agents, duration of chelation, serum calcium, phosphorous, alkaline phosphatase, PTH and Vitamin D levels (p>0.05). It was found that there was a high prevalence of hypoparathyroidism, hypocalcemia, hypovitaminosis D and increased levels of serum phosphorus and ferritin among those with low BMD, However, these were not statistically significant. Iron overload by MRI T2* of the Liver had no statistical association with BMD while iron overload in the myocardium by MRI T2* showed a statistically significant association with BMD, (P=0.028) (Table 3).

Table 3: Correlation of BMD by DXA with clinico-epidemiological, biochemical and hematological profile

Parameters		No. of patients (Percentage)							
		DXA (WHOLE BODY)				DXA (SPINE)			
		Normal	Osteopenia	Osteoporosis	P value	Normal	Osteopenia	Osteoporosis	P value
Age (Years)	5-9	15 (83.3%)	03 (16.7%)	00 (0.0%)		10 (55.6%)	07 (38.9%)	01 (5.6%)	
	10-14	23 (60.5%)	15 (39.5%)	00 (0.0%)		21 (55.3%)	13 (34.2%)	04 (10.5%)	
	15-18	11 (39.3%)	15 (53.6%)	02 (7.1%)	0.021	09 (32.1%)	14 (50.0%)	05 (17.9%)	0.398
Sex	Male	29 (59.2%)	18 (36.7%)	02 (4.1%)		25 (51.0%)	20 (40.8%)	04 (8.2%)	
	Female	20 (57.1%)	15 (42.9%)	00 (0.0%)	0.441	15 (42.9%)	14 (40.0%)	06 (17.1%)	0.495
Mean Pretransfusion Hb	<7.0 g/dl	06 (60%)	04 (40%)	00 (0.0%)		05 (50%)	03 (30%)	02 (20%)	
	7.0-9.5 g/dl	43 (58.1%)	29 (39.2%)	02 (2.7%)	0.871	35 (47.3%)	31 (41.9%)	08 (10.8%)	0.623
Annual PRC requirement	<170ml/kg/year	23 (60.5%)	13 (34.2%)	02 (5.3%)		17 (44.7%)	15 (39.5%)	15 (15.8%)	
	170-220ml/kg/year	21 (55.3%)	17 (44.7%)	00 (0.0%)		20 (52.6%)	15 (39.5%)	03 (7.9%)	
	>220ml/kg/year	05 (62.5%)	03 (37.5%)	00 (0.0%)	0.544	03 (37.5%)	04 (50%)	01 (12.5%)	0.803
Sr. Calcium (mg/dl)	<8.4	24 (72.7%)	09 (27.3%)	00 (0.0%)		17 (51.5%)	12 (36.4%)	04 (12.1%)	
	8.4-11	13 (59.1%)	09 (40.9%)	00 (0.0%)		13 (59.1%)	08 (36.4%)	01 (4.5%)	
	>11	12 (41.4%)	15 (51.7%)	02 (6.9%)	0.067	10 (34.5%)	14 (48.3%)	05 (17.2%)	0.389
Sr. Phosphorous (mg/dl)	2.5 – 4.5	24 (61.5%)	14 (35.9%)	01 (2.6%)		18 (46.2%)	17 (43.6%)	04 (10.3%)	
	>4.5	25 (55.6%)	19 (42.2%)	01 (2.2%)	0.839	22 (48.9%)	17 (37.8%)	06 (13.3%)	0.830
ALP IU/dl	100-390	28 (51.9%)	24 (44.4%)	02 (3.7%)		24 (44.4%)	23 (42.6%)	07 (13.0%)	
	>390	21 (70%)	09 (30.0%)	00 (0.0%)	0.199	1 (53.3%)	11 (36.7%)	03 (10.0%)	0.730
VIT D3 (ng/ml)	<20 (Deficient)	24 (49.0%)	24 (49.0%)	01 (2.0%)		20 (40.8%)	21 (42.9%)	08 (16.3%)	
	20-30	14 (70.0%)	06 (30.0%)	00 (0.0%)		10 (50.0%)	09 (45.0%)	01 (5.0%)	
	30-60(Optimal)	11 (73.3%)	03 (20.0%)	01 (6.7%)	0.152	10 (66.7%)	04 (26.7%)	01 (6.7%)	0.327
Sr. PTH	<10pg/mL	28 (53.8%)	22 (42.3%)	02 (3.8%)		21 (40.4%)	24 (46.2%)	07 (13.5%)	
	10-55pg/mL	21 (65.6%)	11 (34.4%)	00 (0.0%)	0.364	19 (59.4%)	10 (31.3%)	03 (9.4%)	0.239
FERRITIN (Microgram/l)	200- 1000mg/l	11 (64.7%)	06 (35.3%)	00 (0.0%)		09 (52.9%)	07 (41.2%)	01 (5.9%)	
	1000-3000	24 (63.2%)	12 (31.6%)	02 (5.3%)		22 (57.9%)	14 (36.8%)	02 (5.2%)	
	3000-5000	10 (52.6%)	09 (47.4%)	00 (0.0%)		06 (31.6%)	10 (52.6%)	03 (15.8%)	
	5000-10000	04 (40.0%)	06 (60.0%)	00 (0.0%)	0.491	03 (30.0%)	03 (30.0%)	04 (40.0%)	0.052
LIVER MRI T2*	ABSENT	03 (75.0%)	01 (25.0%)	00 (0.0%)		03 (75.0%)	01 (25.0%)	00 (0.0%)	
	Mild	04 (80.0%)	01 (20.0%)	00 (0.0%)		03 (60.0%)	02 (40.0%)	00 (0.0%)	
	Moderate	16 (59.3%)	10 (37.0%)	01 (3.7%)		13 (48.1%)	11 (40.7%)	03 (11.1%)	
	Severe	26 (54.2%)	21 (43.8%)	01 (2.1%)	0.819	21 (43.8%)	20 (41.7%)	07 (14.6%)	0.794
CARDIAC MRI T2*	ABSENT	41 (63.15)	23 (35.45)	01 (1.5%)		36 (55.4%)	24 (36.9%)	05 (7.7%)	
	Mild	05 (62.5%)	02 (25.0%)	01 (12.5%)		03 (37.5%)	04 (50.0%)	01 (12.5%)	
	Moderate	00 (0.0%)	03 (100%)	00 (0.0%)		00 (0.0%)	02 (66.7%)	01 (33.3%)	
	Severe	03 (37.5%)	05 (62.5%)	00 (0.0%)	0.308	01 (12.5%)	04 (50.0%)	03 (37.5%)	0.028

Discussion

In the present study, most of the patients (45.2%) were in the age group of 9-14 years with a mean age of 12.58±0.57 years and male to female ratio was 1.4:1, suggesting male preponderance which is similar to the study done by Bejaoui et al [5] and Merchant et al. [6] Majority of patients belonged to lower socioeconomic strata (92.9%) which can be explained by the fact that our centre predominantly caters to the need of this class of society. 57.2% were stunted, of which 29.8% were moderately stunted and 27.4% were severely stunted. Among the severely stunted, 53.6% were in the age group of 14-18years and 21.1% in the age group of 10-14years which is similar to the study of Borgna-Pignatti et al. [7] There was a statistically significant association between height and the duration of the disease process in thalassemia. As age advanced the prevalence of stunting increased, the cause for which was multi-factorial. It is also now proven beyond doubt by various studies that improving calorie take and supplementation of micronutrients like Zinc, Vitamin D and Carnitine is known to have a positive effect on the linear growth in thalassemia patients.11.9% of study subjects were severely thin with a BMI of less than -3SD.15.8% of patient aged between 9-14years were severely thin and 11.9% male and 14.3% were female which is comparable with the study done by Asadi Pooya et al. [8]

This suggests that although height is affected significantly, weight is appropriate for that height hence resulting in a normal BMI in a majority of a patients. 11.9% had a very low pre-transfusion Hb of less than 7g/dl with the mean pre-transfusion hemoglobin being 7.76±0.57 g/dl which is correlated with previous studies. [6],[9],[10] The difference in mean Hb between the current study and the other studies [6][9][10] may be attributed to the differences in the educational level, socioeconomic status and proximity to the health care centre with regular follow-up. The mean annual PRC requirement was 175.56±37.77 ml/kg/year which is comparable with the study conducted by Bejaoui et al [5] and Merchant et al. [6] However, mean pre-transfusion hemoglobin is considered a better indicator of transfusion status and annual PRC requirement is primarily used to decide on the need for splenectomy and to calculate the amount of iron loading that occurs due to blood transfusions.

All the study subjects were on one or a combination of two iron chelation agents. The majority 72.6% were on Deferasirox, 3.6% were on Deferiprone, and 22.6% were on both Deferiprone and Deferasirox. Since the majority of our patients belonged to the age group 9-14 years and considering that the majority of patients were started on chelating agents after 3 years, explains the fact that the majority of patients had a duration between 5-9years. Though the prevalence of low bone mass is high in thalassemia, only 7.1% had symptoms of bone disease. Other studies [6][11] also reported that the symptoms of bone disease are not very prominent hence further highlighting the need for regular screening of BMD by DXA in those who are on regular treatment by blood transfusions and iron chelating agents.

In our study, 93% of study subjects had hepatomegaly and 91% had splenomegaly. Pemde et al [9] study found 30% hepatomegaly and 46.9% splenomegaly, this probably again signifies the extramedullary erythropoiesis which occurs in patients who have low mean pre-transfusion hemoglobin as is seen in the current study as against the high mean pre-transfusion hemoglobin of patients in the study done by Pemde et al [9].20.7% of our patients had delayed puberty, however as high as 60.7% aged above 12 years had delayed puberty attributed to hypogonadotropic hypogonadism due to iron overload.

We found statistical significance suggesting that delayed puberty is predominant as age advances. These findings are comparable with the previous studies [5] [12][13][14]. The higher percentages of delayed puberty seen in other studies may be explained based on the age distribution of the study subjects.

In our study 39.3% had hypocalcemia. There was a significant association with age suggesting that the serum calcium levels improved as age advanced, probably due to routine supplementation of calcium in all thalassemics registered under the tertiary care centre. Out of the total 84 subjects, 45(53.6%) of them had a value of serum phosphorous more than 4.5mg/dl, and 39(46.4%) had a normal value of 2.5-4.5mg/dl. 58.3% of the study group was vitamin D deficient and 61.9% had low serum parathyroid hormone levels. 79.7% had a serum ferritin value of more than 1000 microgram/l. 6(7.1%) patients were hypothyroid.

48(57.2%) of them had a severe iron loading in the liver. 8(9.5%) had severe iron loading in heart while 8(9.5%) patients had mild iron loading. These findings follow the previously conducted studies. [10] [15][16][17][18][19].

Bone strength is determined by bone mineral density (BMD). Biomechanical studies have shown a strong correlation between mechanical strength and BMD measured by DXA. [20] There was a statistically significant association between age and low BMD by DXA whole body (P value 0.021) suggesting that BMD reduces significantly with age which is comparable with the study done by Vogiatzi et al [2] and Pollak et al.[21] However, no statistically significant association was found between BMD and gender, pre-transfusion Hb, annual PRC requirement, iron chelating agents and duration of chelation. Serum calcium, phosphorous, alkaline phosphatase, PTH, and vitamin D levels also did not have any statistically significant association with BMD. There was no statistically significant association between BMD and biochemical parameters like LFT and RFT. These results are similar to the previous studies [6][11][22]. However, it was found that there was a higher prevalence of hypoparathyroidism, hypocalcemia, increased Serum Phosphorous levels and hypovitaminosis D among the thalassemics with low BMD. These findings may be attributed to Iron deposition in the Parathyroid gland, poor dietary intake, reduced outdoor physical activities and inadequate chelation therapy. Although higher ferritin levels were noted in patients with low BMD there was no statistical significance between the two in the present study. Multiple studies from around the globe of varying sample sizes like by Merchant et al, [6] Jensen et al, [11] Saboor et al, [17] Karimi et al [22] and Vogiatzi et al [23] did not find any direct significant correlation between the serum ferritin levels and low BMD.

Iron overload by MRI T2* of the liver had no statistical association with BMD which is correlated with a study conducted by Goh et al [24] and Ebrahimpour et al, [25] however iron overload in the myocardium by MRI T2* showed statistical significant association with BMD which is similar to the study conducted by Ebrahimpour et al, [25] suggesting that severe iron overload in the myocardium was a significant risk factor and associated with low BMD as determined by DXA Spine.

In the present study, it was seen that only 47.6% had normal BMD and the prevalence of low BMD was 57.1% with 45.2% having osteopenia and 11.9% having osteoporosis. These findings of osteopenia are comparable with other studies [6] [17][26] and the difference in the prevalence of osteoporosis in these studies may be due to differences in the age distribution among the study subjects. Also, on comparing the DXA spine and DXA whole body for assessing BMD, it was found that there was a statistical significance with a P value of 0.043, implying that the DXA Spine had a better chance of picking up osteoporosis than the DXA whole body. Melton et al in a study involving an adult group with osteoporosis showed that site-specific regional measurements at the lumbar spine provided comparable overall estimates of osteoporosis prevalence. [27] However, Mohseni et al in a study of 30 thalassemic patients aged 5-19 years of age found the prevalence of low bone mass to be higher in the DXA femur than DXA lumbar spine. [28]

Conclusion

Low bone mass is one of the most prevalent complications among TDT patients. Osteoporosis is a progressive disease and it has a multifactorial pathogenesis in TDT patients. Delayed puberty was a common problem with patients with TDT and attributed to hypogonadotropic hypogonadism. Hypogonadism may also be responsible for reducing BMD in thalassemics. Hence role of Gonadal steroids needs to be rigorously evaluated by prospective longitudinal studies.

Iron overload status by T2* Cardiac MRI may be used as an early indicator for predicting Osteoporosis. Also, T-scores of DXA spine may be used for early diagnosis and management of Osteoporosis.

However, further longitudinal prospective studies encompassing a larger sample size with a wider range of age distribution and a longer follow-up may help determine the exact etiology of bone disease in thalassemia.

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Ethics committee approval: The protocol andinformed consentwere approved by the institute's ethical committee.

Declaration of competing interest: The authors declare no conflict of interest.

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