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Original Article

Osteopenia and Osteoporosis in Children and Adolescents with Beta Thalassemia Major

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Abstract

Background: Osteopenia and osteoporosis in beta thalassemia major cases start early in life and increases the risk of fractures. It enhances morbidity, adds to the injury of patients and parents/ caregivers and burdens the health care system.
Objective: To assess prevalence of decreased bone mineral density (osteopenia and osteoporosis) in children and adolescents with beta thalassemia major.
Study type, settings & duration: This cross-sectional study was carried out at DHQ Hospital Zhob from May 2021 to December 2021.
Methodology: The Children and adolescents (5-18 years of age) with beta thalassemia major were included. Bone mineral density was measured using Z-score by Dual Energy X-ray Absorptiometry (DEXA-Scan). Z-Scores results were categorized into normal (Z-score <-1), osteopenia (Z score -1 to -2.5) and osteoporosis (Z-score >-2.5). Hemoglobin levels (g/dL), serum calcium (mmol/L), vitamin D levels (ng/mL) and ferritin levels (ng/dL) were carried out for all the participants. The data was entered in Statistical Package for Social Sciences (SPSS. 21) and analyzed.
Results: Out of 82 patients, there were 44 (53.7%) males and 38 (46.3%) females. Mean age was 11.5±4.24 years. The DEXA-Scan results identify; all had decreased bone mineral density, 42.7% were having osteopenia and 57.3% were having osteoporosis. There was a significant decrease in bone mineral density in higher age group (p <0.001) and in children with higher serum ferritin level (p =0.042).
Conclusion: Beta thalassemia major patients start developing bone demineralization in young age and progresses with age. The decrease in bone mineral density was significantly related to higher serum ferritin levels.
Key words: Bone mineral density, osteopenia, osteoporosis, beta thalassemia major.

Introduction

Thalassemia is the commonest hemoglobinopathy worldwide.[1] It is a preventable genetic disorder.[2] Hemoglobin is the oxygen transporting component of red blood cells and is made up of two alpha and two beta proteins. These proteins are synthesized by globin genes. Thalassemias are caused by mutations in globin genes. Beta thalassemias occur due to mutations in one or both beta-globin genes situated on chromosome 11. Beta-thalassemia has peak prevalence in Middle-East, Mediterranean and Asian descent.[3] Beta-thalassemia is classified into beta-thalassemia minor, beta-thalassemia intermedia and beta-thalassemia major. Beta-thalassemia minor (beta-plus thalassemia) is the mildest form that is commonly asymptomatic. Beta-thalassemia major (beta-zero thalassemia) is the most severe clinical form that requires life-long transfusions. These cases have severe anemia, jaundice, hepatosplenomegaly and growth failure. Thalassemia intermedia is between beta thalassemia minor and major with mild to moderate symptoms[4]. Recently, thalassemias have been classified clinically on the requirement of blood transfusion or otherwise into transfusion dependent and non-transfusion dependent thalassemia.[5]

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Authors Contribution

SA conceptualized the project. SA, MAK & NH did the data collection. AR & NH performed the statistical analysis. AZR, IAB & FR did the data collection. Literature search, drafting, revision & writing of manuscript were done by MAK & AR.

Beta thalassemia patients have anemia because of decrease in hemoglobin synthesis and an increase in HbA2 and HbF formation owing to less beta chains. In beta thalassemia major and intermedia, excess alpha chains form alpha chain inclusions leading to intramedullary hemolysis. In addition to ineffective erythropoesis, there is bone marrow expansion and extramedullary-hematopoesis.[6] These pathologic mechanisms cause characteristic bone damage and bony deformities, including frontal bossing, maxillary protrusions etc. Bone marrow expansion signals increased iron absorption. Beta thalassemia major requires multiple blood transfusions leading to iron overload. Significant iron overload causes multiple organ damage. Notable complications of iron overload are cardiac siderosis, heart failure, hepatic and endocrine dysfunction.[7]

The progressive aging of bones begins early in childhood in cases of beta thalassemia major. It is caused by accelerated osteoclastic activity and insufficient osteoblastic activity owing to chronic anemia, iron overload, chelating agents, endocrine dysfunction etc. Hypogonadism, delayed puberty, anemia, vitamin D deficiency, hypothyroidism, diabetes and growth hormone dysfunction lead to osteopenia and osteoporosis.[8] Osteopenia is a medical term used to describe a decrease in bone mineral density (BMD) below normal reference values, but not low enough to meet the criteria to be diagnosed as osteoprosis. BMD can be diagnosed by dual-energy x-ray absorptiometry (DXA) bone scans. Osteopenia, as defined by the World Health Organization (WHO), is a t-score between -1 to -2.5, while values less than -2.5 are diagnostic for osteoporosis. Decreasing BMD values are reflective of an underlying disruption in the microarchitecture of bone and osteopenia, and osteoporosis is considered quantitative, not qualitative, disorders of bone mineralization.[9] The role of chronic anemia, iron overload and chelation therapy in osteoporosis in cases of thalassmeia major is of much interest. Iron deposition in bone hinders osteoid maturation and decrease bone mineralization. Iron chelators are of vital significance to decrease iron overload. They include deferoxamine (DFO), deferiprone (DFP) and deferasirox (DFX). These chelators reduce osteoblast activity and enhance apoptosis of osteoclasts.[8] Decreased bone mineralization leads to osteopenia which progresses to osteoporosis. Osteopenia and osteoporosis can lead to multiple fractures, add to the morbidity in affected cases and adversely affect the patients, parents/care givers and health care system. Thalassemia patients experience fracture rates as high as 71%. Other skeletal complications include thalassemic osteoarthropathy, premature epiphyseal closure and fractures to minor trauma.[10]

There is a need to address osteoporosis and osteopenia in children with beta thalassemia major and prevent it from the beginning to decrease the burden of morbidities and complications in this chronic disease. We have carried out this study to assess decreased bone mineral density in children and adolescents (aged 5-18 years) with thalassemia major cases and study its relationship with anemia, iron overload and chelation therapy. It will help clinicians to better manage and prevent osteoporosis in thalassemia major.

Balochistan has very scarce population with around 90% population residing in rural (far flung and scattered) areas with no treatment or transfusion facility except few district headquarter hospitals.[11] The study has been carried out to assess frequency of osteopenia and osteoporosis in beta thalassemia major children and emphasize upon its importance to the clinicians treating such cases in peripheries where facilities like bone scans are not available. This study was conducted in DHQ Hospital Zhob provides the only health facility for a large encatchment area for district Zhob and Sheerani.

Methodology

The cross-sectional study was carried out at District Headquarter Hospital Zhob from May 2021 to December 2021 after acquiring permission from Ethical review Board of hospital. Total 90 cases of beta thalassemia major fulfilling the inclusion exclusion criteria were included in the study. Informed consent was obtained from all participants. Sample size was calculated taking prevalence of hemoglobinopathies as 0.79% according to study by Akram et al., and beta thalassemia major constituted 29.4% of hemoglobinopathies[1] and that turned to be 73 cases as calculated via online Rao soft calculator. We increased it to 90 cases to cater for any patients loss to follow up etc.

The cases who were taking corticosteroids, anti-epileptic drugs, vitamin D, bisphosphonates or hormone replacement therapy and those with chronic liver disease, hepatitis B virus, hepatitis C virus, cardiomyopathy, diabetes mellitus, hypoparathyroidism, and thyroid illness were excluded. Bone mineral density of all cases was measured by Dual Energy X-ray Absorptiometry (DEXA-Scan) using Z-score of femoral neck and lumber vertebra.[12] The Z-score describes the number of standard deviations by which bone mineral density of a patient varies from a mean

value of a healthy individual of the same age and gender[9]. Since there is no DEXA-scan available in Zhob, so the participants were sent to tertiary care set-ups for DEXA-scans. Following blood parameters were recorded for all the participants; Hemoglobin levels (g/dL), serum calcium (mmol/L), vitamin D levels (ng/mL) and ferritin levels (ng/dL). Venous blood samples were drawn and sent to laboratories before correcting anemia by blood transfusions.

Beta thalassemia children and adolescents were divided into three categories of age; from 5-10 years, 11-14 years and 15-18 years. Anemia was defined as a hemoglobin level less than 11 gm/dL.[1] The cases were categorized into mild anemia, moderate anemia and severe anemia. Mild anemia corresponds to hemoglobin level 10-10.9 g/dL, moderate anemia corresponds to hemoglobin level 7-9.9 g/dL, and severe anemia corresponds to hemoglobin level <7 g/dL.[11] Ferritin levels were divided into three categories; <1000 ng/dL, 1000-2500 ng/dL and > 2500 ng/dL. In beta thalassemia major cases, the desired ferritin levels should be less than ≤1000ng/dL. The normal serum calcium level is 2.1-2.6 mmol/L, a value less than 2.1 mmol/L was termed hypocalcaemia. The main circulating form of vitamin D in the blood is 25 hydroxyvitamin D {25(OH)D} and shows reliably body's vitamin D level. Its levels are classified into following.[13] Vitamin D deficiency is labeled when patient has serum 25 (OH) D level <20 ng/mL. Vitamin D insufficiency is labeled when serum 25 (OH) D level 20-29 ng/mL and it is said to be sufficient when 25 (OH) D level > 30 ng/mL and toxicity develops after 25 (OH) D levels increase >150 ng/mL. Bone mineral density report was categorized as: Z-Scores normal (z-score <-1), osteopenia (Z score -1 to -2.5) and osteoporosis (Z-score >-2.5).[14]

Data including age, gender, hemoglobin level, bone mineral density (Z-score) results, serum ferritin levels, serum calcium and serum vitamin D level status were entered in Statistical package for social sciences 21 and analyzed. Simple percentages were used to express frequencies. Chi square was used to analyze qualitative variables. *p* value <0.05 was considered significant.

The ethical approval was obtained from DHQ Teaching Hospital, Zhob vide reference No. 722/23.

Results

A total of 90 patients with beta thalassemia major were selected from the outpatient department of DHQ hospital, Zhob. Eight cases were lost on follow-up and were excluded. Out of these 82 patients, there were 44 (53.7%) males and 38 (46.3%) females. The age range was between 5 years to 18 years with mean age of 11.5±4.24 years. DEXA-Scan results identify, 35 (42.7%) cases of beta thalassemia major having osteopenia (Z-score between -1 to -2.5), 47 (57.3%) cases had osteoporosis (Z-score<-2.5). All the cases of beta thalassemia major were anemic. Out of these, 1 (1.2%) had mild anemia, 60 (73.2%) had moderate anemia, and 21(25.6%) had severe anemia. Mean hemoglobin was 7.7±1.10 gm/dL. All the cases except 3, had less than normal serum vitamin D levels; 3 (3.7%) were Vitamin D sufficient, 36 (43.9%) were deficient and rest 43 (52.4%) were Vitamin D insufficient (Table-1). The mean serum vitamin D level was 20.3± 6.93ng/ml. Serum calcium was reported normal for 12 (14.6%) patients and 70 (85.4%) were hypocalcemic. Mean serum calcium level was 1.8±0.23 mmol/L varying between 1.5 mmol/L to 2.6 mmol/L**.** Mean serum ferritin level was 2734.2±1927.7 ng/dL. Eleven (13.4%) cases had serum ferritin levels in desired range (<1000 ng/dL), 42 (51.2%) cases had iron overload between 1000-2500 ng/dL and rest 29 (35.4%) had ferritin levels > 2500 ng/dL. The minimum ferritin level noted was 357 ng/dL and the maximum was 9206 ng/dL.

Bone mineral density was compared to other parameters like age group, anemia, serum ferritin status, serum calcium and vitamin D. There was significant inverse relation between age group and bone mineral density i.e osteoporosis increased (bone density decreased) with age in cases of beta thalassemia major (*p* <0.001) as shown in Table-2. Similarly, serum ferritin levels were significantly higher in the cases with osteoporosis versus those with osteopenia (*p* =0.042). But, there was no significant association between anemia, vitamin D levels and serum calcium with bone mineral density.

Discussion

Frequency of osteoporosis in beta thalassemia major cases have been reported in more than 50% of cases.[12] In our study, we have seen osteoporosis in 47 (57.3%) of beta thalassemia cases and osteopenia in 35 (42.7%) of cases. These findings match those from other researches. Al-Khairo et al., reported osteoporosis in 50% and osteopenia in 36.5% cases while 13.4% cases were normal.[12] Abbasi S et al., found 82% of beta thalassemia major cases to have decreased BMD (osteoporosis and osteopenia), and 18% had normal BMD.[15] Benigno V et al., also found 84% cases of beta thalassemia major with poor bone mineral density (60% had osteoporosis and 24% osteopenia).[14] Vogiatzi et al., have reported

Table 1: Characteristics of beta thalassemia major cases.

S.No.	*Characteristic*	*Value*	*N (%)*
1	Gender	Males	44 (53.7)
		Females	38 (46.3)
2	Age Group	5-10 years	37 (45.1)
		11-14years	20 (24.4)
		15-18 years	25 (30.5)
3	DEXA-Scan Results	Normal (Z-score > -1)	0
		Osteopenia (Z-score -1 to -2.5)	35 (42.7)
		Osteoporosis (Z-score<-2.5)	47 (57.3)
4	Hemoglobin (g/dL)	7.7 ± 1.10 gm/dL	
5	Anemia categories	Mild Anemia (hb 10-10.9 g/dL)	1 (1.2)
		Moderate Anemia (hb 7-9.9 g/dL)	60(73.2)
		Severe Anemia (hb<7.0g/dL)	21(25.6)
6	S. Vitamin D	Mean 20.3 ± 6.93 ng/mL	
7	Vitamin D Status	Vit D Insufficiency (level 20-29 ng/mL)	43 (52.4)
		Vit D Deficiency (level <20 ng/mL)	36 (43.9)
		Vitamin D sufficiency (level >30 ng/mL)	3 (3.7)
8	S. Calcium	1.8± 0.23 mmol/L	
9	S. Calcium Status	Normal (2.1-2.6 mmol/L)	12 (14.6)
		Hypocalcemia (<2.1 mmol/L)	70 (85.4)
10	S. Ferritin	2734.2 ± 1927.7 ng/dL	
11	S. Ferritin Status	Desired level (<1000 ng/dL)	11(13.4)
		Iron overload (1000-2500 ng/dL)	42 (51.2)
		Increased iron overload (>2500 ng/dL)	29 (35.4)

Table 2: Association between bone mineral density with clinical and biochemical parameters.

S/No	Parameter	Category	Osteopenia N (%)	Osteoporosis N (%)	Total N (%)	P value
1	Age groups	5-10 years	26 (70.3)	11 (29.7)	37 (45.1)	>0.001
		11-14 years	7 (35)	13 (65)	20 (24.4)	
		15-18 years	2 (8)	23 (92)	25 (30.5)	
		Total	35 (42.7)	47 (57.3)	82 (100)	
2	Anemia Status	Mild Anemia (hb 10-10.9 g/dL)	1 (100)	0	1 (1.2)	
		Moderate Anemia (hb 7-9.9 g/dL)	26 (43.3)	34 (56.7)	60 (73.2)	0.464
		Severe Anemia (hb<7.0g/dL)	8 (38.1)	13 (61.9)	21 (25.6)	
		total	35 (42.7)	47 (57.3)	82 (100)	
3	Vitamin D Status	Vit d sufficient (level >30 ng/mL)	3 (100)	0	3 (3.7)	
		Vit D Insufficiency (level 20-29 ng/mL)	16 (37.2)	27 (62.8)	43 (52.4)	0.100
		Vit D Deficiency (level <20 ng/mL)	16 (44.4)	20 (46.5)	36 (43.9)	
		total	35 (42.7)	47 (57.3)	82 (100)	
4	S. Calcium Status	Normal (2.1-2.6 mmol/L)	4 (33.3)	8 (66.7)	12 (14.6)	
		Hypocalcemia (<2.1 mmol/L)	31 (44.3)	39 (55.7)	70 (85.4)	0.479
		Total	35 (42.7)	47 (57.3)	82 (100)	
5	S. Ferritin Levels	Desired level (<1000 ng/dL)	6 (54.5)	5 (45.5)	11 (13.4)	0.042
		Iron overload (1000-2500 ng/dL)	22 (52.4)	20 (47.6)	42 (51.2)	
		Marked iron overload (>2500 ng/dL)	7 (24.1)	22 (75.9)	29 (35.4)	
		Total	35 (42.7)	47 (57.3)	82 (100)	

osteoporosis in 61.3% and osteopenia in 22.6% of cases of thalassemia major, similar to our study.[16] Izadyar S et al., reported relatively low frequency of low bone mineral density (37.5% osteoporosis and 12.5% osteopenia).[17] This might be attributed to comparatively small sample size of 40 cases of beta thalassemia major. Overall, the prevalence of low mineral density ranges till 90% of thalassemia major patients.[18]

Anemia is a characteristic hallmark in beta thalassemia major patients, because of ineffective erythropoesis and the short life of RBCs.[1] Patients require lifelong transfusions to make up for this deficiency. Desired hemoglobin level is more than 10 g/dL in thalassemia cases. Anemia has been suggested to be associated with osteoporosis in adult non-thalassemia patients.[19] Low hemoglobin enhances the osteoclastic activity and bone resorption leading to bone loss.[20] As all the cases of beta thalassemia major were anemic, no significant association was found in our study.

All the cases had low serum vitamin D levels. Even healthy children are deficient in serum Vitamin D levels in our country. According to Akram

et al., 30.8% of healthy children were vitamin D deficient and 32.5% were vitamin D insufficient (total 63.3% had low vitamin D).[13] In our study, 36 (43.9%) were Vitamin D deficient and the rest 43 (52.4%) were Vitamin D insufficient. Fahim et al., have reported 91% of thalassemia cases with vitamin D deficiency and insufficiency.[21] Similarly Yu et al., also showed decreased mean serum vitamin D level in thalassemia cases[22]. The main cause of this reduction has been attributed to liver iron deposition.[21,22]

The majority of cases in our study had low serum calcium (85.4%), which is in accordance with other studies.[21,23] Hypocalcemia is caused by endocrinopathies, iron overload, chelation therapies etc in thalassemia patients.[21] Normal serum ferritin levels are 20-350 ng/dL.[12] We found serum ferritin levels were high in all patients. It was in accordance with all other researches.[12,22,23] In our resource constrained area of study, people cannot afford regular chelation therapy to maintain it within the desired range. That is why most cases (86.6%) had iron overload and marked overload in present study. Best management strategy for beta thalassemia major patients is prevention, as bone demineralization begins early in life. Calcium supplements, vitamin D intake and physical activity to prevent dreadful complications of osteoporosis i.e fractures which adds to misery and burden to patients and parents.[9]

Beta thalassemia major is a chronic life-long illness. All these cases develop decreased bone mineral density (osteopenia and osteoporosis). DEXA-scan facility is not available except few major cities in our country to ascertain bone mineral density. We recommend early and timely management of impending osteoporosis and fractures through prevention, i.e calcium supplements, vitamin D intake and physical activity.

Beta thalassemia major patients start developing bone demineralization in young age and progresses with age. The decrease in bone mineral density was significantly related to higher serum ferritin levels.

Conflict of interest: None declared.

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