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Original Research Article

Biochemical indices and radiological examination to evaluate bone health in children with β-thalassemia major

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ABSTRACT

Background: β-Thalassemia major is a serious hematological problem requiring regular blood transfusions. In regularly transfused thalassemic patients, metabolic bone disease is an important cause of morbidity. Problems include bone pain, deformities, short stature, osteopenia/osteoporosis, rickets, osteomalacia, spinal deformities, nerve compression and fractures. This study was undertaken to evaluate the status of bone health in children with β-thalassemia major by selected biochemical indices and radiological examination.
Methods: Fifty children with β- thalassemia major were enrolled. Detailed history, examination and anthropometry were done. Serum calcium, phosphorus, magnesium, alkaline phosphatase, and vitamin D levels were measured. X-ray of skull, wrist, and knee were studied for radiological changes. Biochemical indices were analysed with appropriate statistical tests.
Results: Stunting and wasting was observed in 58% and 44% children respectively. Hypocalcaemia was seen in 22%, hyperphosphatemia in 56% and 24% children had raised alkaline phosphatase levels. Vitamin D levels were severely deficient in 12%, deficient in 50%, and insufficient in 38% of children. There was no significant difference between vitamin D levels of cases and controls. Radiologically almost all children had a range of osteopathy, like thinned out cortex (96%), medullary expansion (54%), loss of density (40%), diffuse osteoporosis (18%) and growth arrest lines were seen in 8% children.
Conclusions: Vitamin D abnormalities and radiological features suggestive of decreased bone mineralization are seen in all the children with β-thalassemia major treated with periodic blood transfusion at this institute. No biochemical predictors of bone disease in these children were identified.

Keywords: Beta-thalassemia, Bone disease, Children, Stunting, Serum calcium, Vitamin D

INTRODUCTION

β-Thalassemia major (β-TM) is a fairly common and serious haematological problem that causes life threatening anaemia by three to six months of life. Regular blood transfusions and chelation therapy have considerably prolonged survival in thalassemic patients.[1] It has been estimated that about 1.5% of the global population (80 to 90 million people) are carriers of β-TM, with about 60,000 symptomatic individuals born annually, the great majority in the developing world. The total annual incidence of symptomatic individuals is estimated to be 1 in 100,000 worldwide.[2] Earlier studies have shown that the overall prevalence of β-TM is 3-4 % with an estimate of around 8,000 to 10,000 new births with major disease each year in India.[3] There is not much information on the distribution of β-thalassemia in Karnataka.

In regularly transfused thalassemic patients, metabolic bone disease becomes an important cause of morbidity. Problems include bone pain, deformities, short stature osteopenia/osteoporosis, rickets, osteomalacia, spinal deformities, nerve compression and fractures. Impaired calcium homeostasis is thought to be a consequence of iron overload seen in β-TM patients receiving regular blood transfusions.

Defective synthesis of 25 OH vitamin D and/or hypoparathyroidism have been described in these patients. Both of these negatively affect bone metabolism.[4] A report from North India showed prevalence of Vitamin D deficiency to be 80% in thalassemic patients.[5]

In a developing country like India with huge population and poor healthcare facilities, it is important to know the prevalence of bone disease in different populations of thalassemic children and to elucidate the underlying pathogenic mechanisms of bone mineral loss in these patients. This will help in designing optimal therapeutic and preventive measures for these patients.

METHODS

A cross sectional descriptive study was conducted from January 2016 to December 2016, in children aged between 1 and 15 years with confirmed diagnosis of β-thalassemia major, admitted for periodic blood transfusion in paediatric ward, Karnataka Institute of Medical Sciences, Hubli. β-thalassemia major patients who had received vitamin D3 and/or calcium within the last 6 months were excluded.

An informed consent was obtained from the parents. Detailed history which included complaints pertaining to bone disease, treatment history (chelation therapy and folic acid supplements), age at diagnosis, transfusion history, surgical history, family history and history of consanguinity were taken and recorded on structured proforma.

Detailed physical examination was performed, which included measurement of patient's height/length and weight. Height was measured using a metal stadiometer to the nearest 1 mm and length was measured using infantometer. Height/length, weight and body mass index z scores were compared with WHO growth charts for evaluation of stunting and wasting.[6]

Venous blood, 5ml each from all β- thalassemia major children included in the study, and also of 20 age and sex matched healthy children as controls were collected in plain bottles, centrifuged and serum was separated.

Biochemical analysis for Calcium (Ca), phosphorus (P), and alkaline phosphatase (ALP) were done using fully auto-analyzer XL 300. Calcium levels were estimated by ARSENAZO method by using Erba kits. Phosphorus levels were estimated by ammonium molybdate kit method. Alkaline phosphatase levels were estimated by 4-nitrophenol by using kits. Vitamin D (25-OH Vitamin D) levels were measured by VITROS ECi/ECiQ Immunodiagnostic system 3600 and 5600 using intellicheck technology.

X-ray of skull, right wrist, right knee of all children included in the study were taken by ALLENGERS–HF 300 MA or SIEMENS-300 MA X-ray machines to study radiological features. X-ray findings were reported by a single experienced radiologist. Studied radiological findings included features such as widening of diploic space, marrow expansion, coarsened trabeculae, thinned out cortex, loss of bone density, diffuse osteoporosis and growth arrest lines.

Hypocalcaemia and hypercalcemia were defined as serum calcium level <8.5mg/dl, and >10.5mg/dl respectively. Hypophosphatemia was defined as serum phosphorus level <4.5mg/dl, and hyperphosphatemia as >5.5mg/dl. Alkaline phosphatase >150IU/L was considered as significantly increased. Serum Vitamin D (25-OH Vitamin D) levels were classified as severe deficiency (<10ng/ml), deficiency (10-20ng/ml), insufficiency (20-30ng/ml) and sufficient (>30ng/ml).[7]

Demographic, anthropometric, clinical, biochemical, and radiological results were tabulated in Microsoft Excel sheet and statistical analysis was done using SPSS 22 software. Results were analyzed by median, mean, standard deviation, t-tests or ANOVA for normally distributed data, and for non-normal distribution data appropriate non-parametric tests were used. Chi-squared test was used for analysing categorical data.

Comparison of serum vitamin D levels was done between different subsets of patients for age, sex, number of blood transfusions, chelation therapy and anthropometric indices. P value <0.05 was taken as statistically significant.

RESULTS

A total of 50 children admitted to pediatric medical ward at Karnataka Institute of Medical Sciences, Hubli, with β -thalassemia major were included in the study. Age of the children included in the study ranged from 1 year to 13 years. Median age was 5.5 years. Number of children less than 5 years were 25(50%) and 25 (50%) were more than 5 years. Males were 31(62%), and 19(38%) patients were females, with a male to female ratio of 1.6:1 (Table 1).

Table 1: Age and sex distribution (n=50).

Age	Male	Female	Total
<5 years	16	9	25
>5 years	15	10	25
Total	31 (62%)	19 (38%)	50

Cases included in the study received periodic blood transfusions ranging from a minimum of 6 to maximum of 88. Children have been receiving transfusions once in 15 days to 2 months. Thirty-five (70%) children were receiving oral chelation therapy (Deferasirox-30 to 50 mg/kg/day) (Table 2).

Table 2: Blood transfusion and chelation therapy (n=50).

	Number of children
Number of transfusions	
≤20	16 (32%)
21-40	10 (20%)
41-60	16 (32%)
≥60	8 (16%)
Chelation therapy	
Yes	35 (70%)
No	15 (30%)

Wasting or severe wasting as per WHO definitions was noted in 13 (52%) of children aged less than five years and 9 (36%) of children aged more than 5 years. In total 22(44%) of 50 children were malnourished. Stunting or severe stunting was observed in 29 (58%) children (Table 3).

Table 3: Anthropometric indices (n=50).

	Number of children
Nutritional Status	
Severe wasting	5 (10%)
Wasting	17 (34%)
Normal	28 (56%)
Stature	
Severe stunting	11 (22%)
Stunting	18 (36%)
Normal	21 (42%)

Hypocalcaemia was noted in 11(22%) and 3(6%) had hypercalcemia, 12(24%) children had hypophosphatemia, 28(56%) had hyperphosphatemia, whereas 12(24%) children had increased alkaline phosphatase level. Vitamin D levels ranged from a minimum of 8 ng/ml to 30 ng/ml, with a mean of 17.91±6.06 ng/ml.

Table 4. Biochemical markers of bone metabolism.

	Reference range	Study group (n=50) Mean±SD	Controls (n=20) Mean±SD	p value
Calcium	8.5-10.5mg/dl	9.03±0.83mg/dl	9.74±0.06mg/dl	0.0001*
Phosphorous	4.5-5.5mg/dl	6.38±2.19mg/dl	3.50±0.07mg/dl	0.0001*
Alkaline phosphatase	20-150IU/L	128.22±41.92IU/L	84.87±3.87IU/L	0.0001*
Vitamin D		17.91±6.06ng/ml	17.65±4.71ng/ml	0.8640

*p<0.05

The mean difference between the biochemical indices measured in 50 children of study group and 20 age and sex matched children were statistically significant for calcium, phosphorous and alkaline phosphatase levels, whereas difference in vitamin D levels did not show any statistical significance (p=0.8640) (Table 4).

Table 5. Vitamin D status.

Vitamin D levels	Study population (n=50)	Controls (n=20)
Severe Deficiency <10ng/ml	6 (12%)	2 (10%)
Deficiency 10 to 20ng/ml	25 (50%)	13 (65%)
Insufficiency 20 to 30ng/ml	19 (38%)	5 (25%)
Chi-square=1.7321;P=0.4212		

Deficient Vitamin D levels were observed in 25(50%) children with thalassemia major, 6 (12%) had severe deficiency and 19 (38%) children had insufficient Vitamin D levels. These proportions were comparable to control group (Table 5).

Table 6. Comparison of vitamin D levels with various patient profiles: n=50.

Variable		No.	Mean±SD (ng/ml)	p value
Age	<5 years	25	19.92±6.21	0.0176*
	>5 years	25	15.91±5.29	
Sex	Male	31	18.23±5.64	0.6406
	Female	19	17.40±6.82	
Chelation therapy	Yes	35	17.20±5.73	0.2027
	No	15	19.59±6.67	
Wasting	Wasted	22	18.77±5.58	0.3827
	Not wasted	28	17.24±6.43	
Stunting	Stunted	29	16.78±4.98	0.1217
	Normal	21	19.48±7.12	
No. of transfusion	≤20	16	20.39±6.62	0.2544
	21-40	10	17.43±6.50	
	41-60	16	16.41±6.05	
	≥60	8	16.59±2.91	

*p<0.05

To know the effect of increasing numbers of transfusion on Vitamin D levels using ANOVA, p value was found to be 0.2544 which was not significant, though a decreasing trend of Vitamin D was observed with increasing number of transfusions.

Vitamin D levels were compared between different subsets of study population to know any significant differences.

Mean Vitamin D levels in children less than 5 years of age was 19.92±6.21 ng/ml and in those more than 5years was15.91 ±5.29ng/ml. This difference was statistically significant (p=0.0176) by t test. (Table 6)

Radiologically almost all children had a range of osteopathy like thinned out cortex (96%), medullary expansion (54%), loss of density (40%), diffuse osteoporosis (18%) and growth arrest lines (8%).

No child had radiological feature suggestive of rickets (Table 7) (Figure 1) (Figure 2) (Figure 3).

Table 7. Radiological features.

Features	No.	%
Skull X-ray		
Prominent convolutional markings	8	16
Widened diploic space	34	68
Normal study	8	16
Wrist X-ray		
Medullary expansion	27	54
Coarsened trabeculae	13	26
Thinned out cortex	48	96
Loss of density	20	40
Diffuse osteoporosis	9	18
Knee X-ray		
Coarsened trabeculae	26	52
Loss of density	19	38
Diffuse osteoporosis	7	14
Growth arrest lines	4	8
Normal	13	26

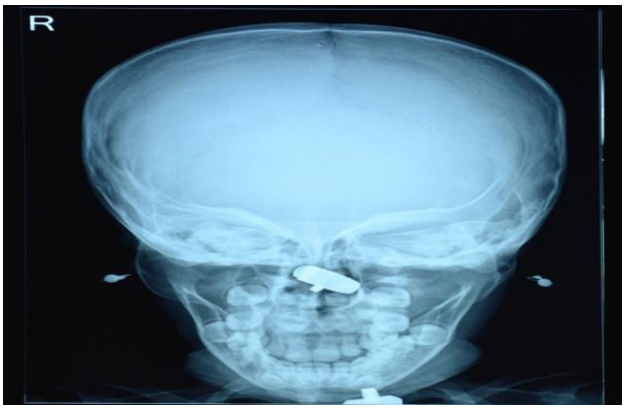

Figure 1: X-ray skull showing widened diploic spaces and prominent convolutional markings.

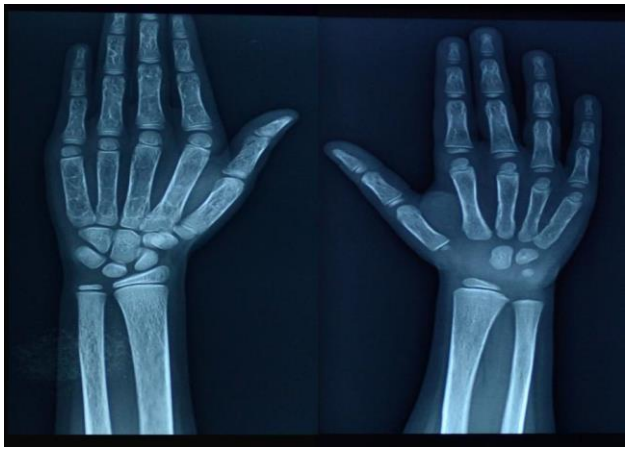

Figure 2: X-ray wrist showing coarsened trabeculae, thinned out cortex, loss of density and diffuse osteoporotic changes in a thalassemic child.

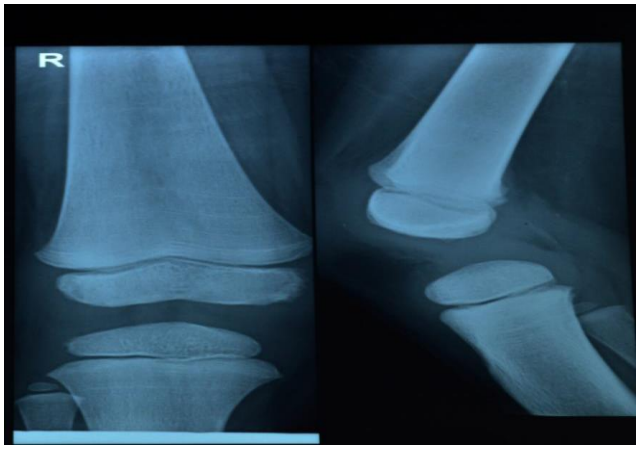

Figure 3: X-ray lower limb showing coarsened trabeculae, loss of density, diffuse osteoporosis and growth arrest lines.

DISCUSSION

Survival of β-thalassemia major patients has improved over the years with regular blood transfusions and the availability of novel iron chelating drugs.[1] Several studies in the past have shown development of bone disorders ranging from bone pain, deformity, bone age delay, growth failure, pathological fractures, rickets and osteopenia/osteoporosis.[4]

Growth failure in thalassemia patients is multifactorial.[8,9] It is related to chronic anaemia, undernutrition, chelation therapy, iron overload and associated endocrinopathies. Short stature (height/length for age <-2 SD) was observed in 29(58%) of children in this study. Similar observations were made by Fahim et al.[10] In their study, 49% of the children aged between 4 to 15 years had short stature. Hashemi et al found 65.71% of thalassemic patients had height less than fifth percentile.[11] In studies by Pamir et al and Vogiatzi et al, growth retardation was reported to be 25.5% and 25% respectively.[9,12]

In children with β-thalassemia major there are alterations in levels of Calcium, Phosphorus and alkaline phosphatase levels. These alterations are attributed to repeated blood transfusions resulting in iron overload and hypoparathyroidism resulting in hypocalcemia. Alterations in serum Phosphorus levels may be due to higher Phosphate loading in more frequently transfused patients. Biochemical evidences of suboptimal bone health are elevated alkaline phosphatase, a surrogate marker for increased bone turnover, and elevated PTH levels.[13]

In the present study 22% of the children had hypocalcemia. Anuj et al Fazlul et al reported lower calcium levels in thalassemic children than controls.[14,15] Their results were explained by endocrinopathies secondary to iron overload. Endocrinopathies resulting in biochemical imbalance are common with advancing age in children with beta thalassemia major. In the present study mean calcium level was 9.03±0.83 mg/dl. This value falls within the normal range for age, but it was significantly lesser than the controls. Fahim et al and Vernejoul et al, in their studies found no significant difference in Calcium levels between study and control groups.[10,16]

Authors found significant increase in Phosphorus levels (6.38±2.19 mg/dl) in present study. 56% of children in present study had hyperphosphatemia. Fatemah et al reported hyperphosphatemia in 18.18% of β-thalassemia major children.[17] In a study by Osama et al serum Phosphorus levels were significantly higher than control groups.[18] Similarly Soliman et al and Mahchoclowattana et al found Phosphorus levels to be slightly higher in transfusion dependent thalassemic children than transfusion independent patients and this can be referred to the associated hypocalcaemia and hypoparathyroidism.[4,19]

In present study 24% of children had increased serum alkaline phosphatase levels. Mean ALP level was 128.22±41.92IU/L. Though mean ALP level being within normal range, it was significantly higher than controls. Increased serum ALP levels in children with β-thalassemia major have been reported by Fazlul et al.[15] Osama et al, Vernejoul et al and Soliman et al found that there was no significant difference in ALP levels between patients and controls.[18,16,19] They attributed normal ALP levels to maintenance of normal haemoglobin levels in their patients.

Vitamin D is an important hormone in bone metabolism involved regulation of Calcium and Phosphorus balance for bone mineralization and remodelling.[20] Deficiency of Vitamin D in growing age causes rickets, where as in adults it causes osteopenia, osteoporosis, and osteomalacia.[21] Vitamin D deficiency in thalassemia major children is attributed to poor intake, defective absorption, defective hydroxylation in liver due to hemosiderosis, secondary to hypoparathyroidism and increased excretion due to chelation therapy. Deficiency is also attributed to geographical altitude, air quality, cloud cover, clothing, time of the day and sun screen use. Mean Vitamin D levels in Thalassemic children in present study was 17.91±6.06ng/ml and control group had mean levels of 17.65±4.71ng/ml, which showed no significant statistical difference. Similar reports were found in studies conducted by Fahim et al Sadia et al and Mahesh et al.[10,22,23] In present study 12% children had severe deficient, 50% children had deficient and 38% children had insufficient levels of vitamin D. No child in the study group had sufficient levels of vitamin D. In present study, it was found that children <5 years of age had higher level of Vitamin D (19.92±6.21ng/ml)) as compared to age >5 years (15.91±5.29ng/ml), which is statistically significant. This could be explained by the fact that with advancing age number of transfusions would have increased, leading to iron overload and resulting in endocrinopathies, and also may be secondary to chelation toxicity.[8] In this study authors observed declining trend of vitamin D levels with increasing number of transfusions, though this observation was not statistically significant.

In wrist X-rays, thinned out cortex was seen in 48 (96%) children, followed by medullary expansion 27 (54%), loss of density in 20 (40%), coarsened trabaculae in 13 (26%) and diffuse osteoporosis in 9 (18%) children. No child in the study population had features of rickets. Similar results were found in a study by Patt M et al conducted in Bangkok, Thailand over 48 children and adolescents with thalassemia major. They reported radiological changes to be more evident in under transfused children than well transfused children. Similar observations were made by Vernejoul et al in children aged 3-18 years.[4,16]

X-ray findings of knee in present study group were coarsened trabaculae 26 (52%), loss of density 19 (38%), diffuse osteoporosis 7 (14%) and growth arrest lines 4 (8%). Thirteen (26%) children had normal findings. Similar observations were made in a study conducted by Chan et al in Hong Kong. They found osteoporosis in 91% and cortical thinning in 70% children. Sharma et al reported similar radiological features in their study.[24,25]

Radiological changes in thalassemia are usually evident by 1 year of age, these changes do occur at an earlier age with severe form in under transfused or non-transfused thalassemic children. Radiological changes are due to ineffective erythropoiesis, anaemia and hypoxia resulting in increased erythropoietin. This results in marrow hyperplasia, decreased trabecular bone mass and widening of diploic space leading to typical hemolytic faces.[26-28] Radiological changes are also attributed to defect in bone metabolism due to endocrinopathies secondary to iron overload in older optimally transfused children.[29,30] Lastly chelating drugs can cause hypercalciuria, direct toxic effect and dysplastic changes.[24,31] Estimation of Bone Mineral Density (BMD)

by DEXA, which is a gold standard investigation for assessing bone mass was not done in this study. Endocrinopathies and other markers of bone metabolism like PTH, osteocalcin levels were not assessed in this study.

CONCLUSION

Stunting, Vitamin D abnormalities and radiological features suggestive of decreased bone mineralization are seen in all the children with β-thalassemia major treated with periodic blood transfusion at this institute. No biochemical predictors of bone disease in these children were identified. As thalassemia has become a chronic manageable disease due to free availability of regular blood transfusion and novel chelating drugs, periodic monitoring of biochemical indices and radiological evaluation for early identification and management of bone related complications is recommended in these patients.

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