RESEARCH PAPER

Metabolic Bone Disease in Children With Transfusion-Dependent Thalassemia

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Received: May 13, 2022;
Initial review: May 25, 2022;
Accepted: August 01, 2022.

Objective: This study aimed to detect metabolic bone disease and endocrinopathies in a cohort of patients with transfusion-dependent thalassemia (TDT). **Methods:** This prospective study was conducted between March 2020 - August 2021. Children with TDT older than 5 years, receiving regular blood transfusion, underwent comprehensive endocrine and metabolic bone disease evaluation, which included screening for short stature, delayed puberty, diabetes mellitus, hypothyroidism, adrenal insufficiency and hypoparathyroidism. Children older than 10 years also underwent. *X*-ray of thoracolumbar spine, and dual energy *X*-ray absorptiometry (DXA) scanning. **Results:** Out of 37 patients (19 males), with mean (SD) age 15 (6) years, hypogonadism was the commonest endocrine deficiency seen in 15 (62%), followed by short stature, abnormal glucose metabolism, subclinical adrenal insufficiency, hypothyroidism, and hypoparathyroidism. Vitamin D insufficiency/deficiency was seen in 12 (60%) and hypocalcemia in 2 patients. Low bone mass was seen in 8, and osteoporosis, as evidenced by vertebral fractures, in 4 patients. Of the four patients with vertebral fracture, three were aged ≤18 years, one was symptomatic, two each had grade 1 and grade 2 fractures, one had multiple vertebral fractures, and all four had hypogonadism and multiple endocrine deficiencies. **Conclusion:** Vertebral fractures occur even in the second decade among patients with TDT, and are often associated with endocrinopathies, most commonly hypogonadism. Early screening and prevention of vertebral fractures is necessary.

Keywords: *Bone density, Endocrinopathies, Fracture, Vertebra, Vitamin D deficiency.*

Published online: August 26, 2022; ***PII:*** S097475591600448

Chronic endocrinopathies are one of the commonest comorbidities reported in patients with transfusion-dependent thalassemia (TDT), especially with increasing age. Metabolic bone disease (MBD) is also a major health concern in this group of patients [1,2], with a much higher rate of traumatic and non-traumatic fractures [3,4]. This is due to several factors, many of them preventable, including vitamin D deficiency, inadequate physical activity, and endocrinopathies [1]. While several studies from India have examined other endocrine deficiencies in thalassemia, less attention has been paid to bone health. Prevention is often neglected because of lack of awareness and lack of facilities to test. We undertook this study to examine the burden of poor bone health in our population, and whether the current guidelines for age at complication screening are sufficient.

METHODS

This study was conducted in the Department of Paediatrics, Kasturba Medical College, Manipal, from March, 2020 to August, 2021. Thirty-seven patients, aged more than five years with TDT, who were on regular transfusion were included in the study. Clearance from institutional ethics committee and consent and/ or assent, as applicable, were obtained before recruitment. During admission for blood transfusion, these patients underwent evaluation for underlying endocrine and metabolic bone disease. This included detailed history, and physical examination, particularly looking into growth and puberty.

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The height, weight, and body mass index (BMI) of all participants were measured by standard techniques and were interpreted against Indian standards [5]. All patients underwent screening for underlying delayed puberty, diabetes mellitus, hypothyroidism, adrenal insufficiency, and hypoparathyroidism. Twenty patients, older than 10 years, also underwent screening for metabolic bone disease, which included serum 25(OH) vitamin D, *X*-ray thoraco-lumbar spine, dual energy *X*-ray absorptiometry (DXA) scan of lumbar spine.

Short stature was defined as height <-2SDS (standard deviation score) [1]. Girls with breast stage 1 after 13 years of age, or boys with testicular volume <4 mL after 14 years of age were diagnosed to have delayed puberty. Among children who are already into puberty, failure to progress to the next Tanner stage in 6 months was labelled as arrested puberty. Patients without any sign of puberty beyond 16 years were diagnosed to have hypogonadism [1]. For this report, we used hypogonadism as an umbrella term to represent delayed/arrested puberty and hypogonadism, as all these entities represent the same pathophysiological processes at various ages. Diagnoses of impaired glucose tolerance, impaired fasting glucose, diabetes mellitus, hypothyroidism, adrenal insufficiency, hypoparathyroidism, and vitamin D deficiency were made as per standard guidelines [6-8].

Lateral *X*-ray of the thoracolumbar spine was taken in patients older than 10 years. Anterior, middle and posterior heights of the vertebral bodies from T6-L4 were measured, and whenever the vertebral height ratio was <0.8, a diagnosis of vertebral fracture was entertained, as per Genant semi-quantitative method [9,10]. DXA scan of the lumbar spine was done in the same patients, using the Hologic Horizon W (S/N303088M) machine, and BMD was interpreted as per International Society for Clinical Densitometry (ISCD 2019) criteria, after adjusting for height [11].

Hormonal assays were performed using commercially available electrochemiluminescence immunoassay (ECLIA) kits, while calcium, phosphorous, alkaline phosphatase were tested by spectrophotometric methods and plasma glucose by hexokinase method.

Statistical analysis: EZR software version 3.2 *(http://cran.r-project.org/web/packages/Rcmdr/index.html)* was used for checking normality of data and data analysis.

Table I Baseline Characteristics of Children With Transfusion-Dependent Thalassemia (*N*=37)

Parameter	*Value*
Age at enrollment (y)	15 (6)
Male[a]	19 (51)
Weight SDS	-1.66 (0.94)
Height SDS	-1.28 (1.35)
Body mass index SDS	-1.28 (0.84)
Pre-transfusion hemoglobin (g/dL)	7.05 (0.95)
Transfusion index (mL/kg/y)	137 (34.97)
Deferasirox dose (mg/kg/d)	15.68 (9.1)
Serum ferritin (ng/mL)[b]	2000 (1010, 3237)
<2000[a]	17 (45)

All values in mean (SD), [a]no. (%) or [b]median (IQR). SDS – standard deviation score.

RESULTS

The baseline characteristics of participants (*n*=37) are described in **Table I**. Data of metabolic bone disorder (patients older than 10 years, *n*=20) and endocrinopathies (*n*=37) are given in **Table II**. Backache and bone pain was seen in one patient, and low vitamin D (insufficiency/deficiency) was noted in 12 (60%) patients; two of these had hypocalcemia and one had hypoparathyroidism. Lateral thoracolumbar *X*-ray revealed the presence of vertebral fracture (3 biconcave, 1 crush) in four (20%) patients, two each had grade 1 and 2 fractures. None of the patients with vertebral fractures had a history of significant trauma. Two patients who had vertebral fractures were 16-

Table II Metabolic Bone Disease and Endocrinopathies in Children With Transfusion-Dependent Thalassemia (*N*=37)

Parameter	*Value (%)*
Metabolic bone disease, n=20	
Vitamin D status [a]	
Sufficient	8 (40)
Insufficient	6 (30)
Deficient	6 (30)
Vertebral fractures	4 (20)
Bone mineral density status	
Normal	8 (40)
Low bone mass	8 (40)
Osteoporosis	4 (20)
Endocrine deficiency, n=37	
Hypogonadism, *n*=24	15 (62)
Male	10 (66)
Short stature	12 (32)
Severe short stature	3
Proportionate	3
Disproportionate	9
Abnormal glucose metabolism	10 (27)
Impaired fasting glucose	5 (50)
Impaired glucose tolerance	3 (30)
Diabetes mellitus	2 (20)
Adrenal insufficiency	9 (25)
Primary	1
Secondary	8
Hypothyroidism	5 (13)
Subclinical	3
Overt primary	1
Secondary	1
Hypoparathyroidism	1 (2)
At least one endocrinopathy	25 (67)
Multiple endocrinopathies	13 (35)

[a]serum 25-OH vitamin D: sufficiency, >20ng/mL, insufficiency, 12-20ng/ mL, deficiency, <12ng/ mL.

WHAT THIS STUDY ADDS?

- We report high prevalence of asymptomatic vertebral compression fractures and osteoporosis among adolescents and young adults with transfusion-dependent thalassemia.

year-old with concurrent hypogonadotropic hypogonadism, short stature and IFG. Another 18-year-old with vertebral fracture had DM, hypogonadotropic hypogonadism, and vitamin D insufficiency. A 27-year-old male with hypogonadism, hypocalcemia, hypoparathyroidism and vitamin D insufficiency had multiple biconcave fractures from L4-L5. Among those with vertebral fractures, two each had normal and low BMD *z*-scores. When BMD and vertebral fractures were analyzed together, we observed low bone mass in 8 (40%) children, and osteoporosis in the four (20%) patients who had vertebral fractures, after adjusting for age, sex and height.

Twenty-five (67%) patients had at least one endocrinopathy, and 13 (37%) had multiple deficiencies. A seven-year-old male child, the youngest to have any endocrine deficiency, had impaired fasting glucose and secondary adrenal insufficiency. A 21-year-old male had four endocrine deficiencies (short stature, hypogona-dism, diabetes mellitus, secondary adrenal insufficiency).

Hypogonadism was the commonest endocrinopathy, followed by short stature, impaired glucose metabolism, adrenal insufficiency, impaired thyroid function and hypoparathyroidism. Among the 12 (32%) participants with short stature, 9 (75%) had disproportionate short stature (short upper segment: 8, short lower segment: 1), three had vertebral compression fractures. All the 12 patients with adrenal insufficiency were asymptomatic, with the 8 AM cortisol being significantly low (<5 mcg/dL) in only three patients, and another six patients were diagnosed by a stimulation test.

DISCUSSION

Major findings of our study are the high prevalence of vertebral fragility fractures and low BMD, and early onset and high prevalence of multiple endocrine deficiencies, especially adrenal insufficiency.

Metabolic bone disease in TDT mostly affects vertebral bodies leading to vertebra fractures. However, vertebral fractures are mostly asymptomatic, making active screening the only way for early recognition and treatment [2,10]. The reported prevalence of vertebral fractures ranges from 2-14% in the few studies available, mostly in adults [4,10]. Earlier Indian studies were mostly limited to self-reporting of long bone fractures, and BMD was reported without adjusting for height and vertebral fracture status [2,3]. Recently, a study from Pune [4], which examined 179 children with TDT, found 21% asymptomatic long bone fractures and 4.5% vertebral fractures. However, BMD, pubertal status, or the presence of other endocrinopathies, which can impact bone health, were not reported in this study.

We found the vertebral fracture prevalence (20%) to be higher than in previous reports from India. Three of the four patients were under 18 years of age, unlike previous studies. Except for one, all others with fractures were asymptomatic, reiterating the need for active screening. All four patients had multiple endocrine deficiencies including hypogonadism. In an overburdened system like our country, meeting the ideal transfusion and serum ferritin targets is difficult, thus anemia and poor chelation, with resulting morbidity, including MBD, is likely to be common. As per ISCD guidelines [11], vertebral fractures alone are sufficient to diagnose osteoporosis, in the absence of trauma or local pathology. In our situation, carefully done *X*-rays of the lumbar spine, which are possible to do across the country, can help in early screening (after age 10 years) and detection of vertebral fractures. Where BMD is feasible, it will add to the overall assessment of bone health, but should be interpreted only after correcting for height and considering fracture history. BMD can still be normal in spite of vertebral fracture, as seen in two of our patients. A diagnosis of osteoporosis on uncorrected densitometry criteria alone, in the absence of vertebral or long bone fractures may be inappropriate [11]. Vitamin D deficiency, hypogonadism, and hypothyroidism are all known to have significant deleterious effects on bone health. They all can be easily and conveniently identified and corrected without much expense. Wherever patients with thalassemia are being treated, regular clinical screening at the time of transfusions for growth and pubertal staging must be emphasized. Regular supplementation of vitamin D and timely gonadal replacement would help improve bone mineral accrual.

Another important aspect of our study is early onset and high prevalence of multiple endocrinopathies and adrenal insufficiency compared to earlier reports [13]. Subclinical adrenal insufficiency among TDT patients varies widely (0-45%) [1,14], with very limited data from India. Despite the small sample size and wide age-range, the high prevalence (25%) in our patients is intriguing, and suggests need for routine testing. The incidence of other

endocrine deficiencies in our cohort is comparable with existing literature [13]. Disproportionate short stature was common, perhaps due to vertebral compression fracture, the disease itself, or direct iron toxicity of vertebrae.

Endocrine evaluation from a young age, and comprehensive MBD screening with serum vitamin D, BMD and vertebral fracture assessment are the highlights of our study. Lack of details about dietary intake of calcium-protein, physical activity which and unavailability of growth hormone stimulation test are limitation of our study.

The high and early occurrence of asymptomatic vertebral fractures in TDT underlines the need for early screening for vertebral fractures with at least spine x-rays. Wherever, BMD is estimated, interpretation of data must take into account, height of the patient and history of fracture. The finding of vertebral fractures being usually associated with hypogonadism and other endocrine deficiencies emphasizes the urgent need for greater awareness and timely preventive strategies.

Ethics approval: IEC, Kasturba Medical College and Hospital, Manipal; No. 235/2020, dated March 20, 2020.
Contributors: KH: conceptualized the study design, prepared the manuscript; KH, SA, GS, PK, RBY, SS: recruited patients, conducted endocrine studies; PS,KH: analyzed *X*-ray of spine. All the authors contributed to the final revision and approval of the manuscript.
Funding: Intramural Grants of Manipal Academy of Higher Education (MAHE), Manipal. *Competing interests*: None stated.

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