

Low bone mineral density in thalassemia major: Sanjay Gandhi Post Graduate Institute experience and a brief focus on underlying factors behind the cause

Kritanjali Singh,¹ Sarita Agarwal,¹
Sushil Gupta²

¹Department of Medical Genetics; and
²Department of Endocrinology, Sanjay
Gandhi Post Graduate Institute of
Medical Sciences, India

Abstract

Thalassemia major is a genetic disorder and blood transfusion is critical for survival in these patients. Over the course of the past three decades, hyper transfusion therapy in these patients has shown has dramatically extended life expectancy and improved quality of life. Unfortunately, this type of therapy also increased the incidence of complications due to iron overload. The aim of this study was to assess bone mineral density (BMD) in patients with β -thalassemia major and to determine their biochemical and hormonal profiles that may affect BMD. A cross-sectional study was carried out in Sanjay Gandhi – PGIMS, a tertiary care hospital over period of 3 years on all β -thalassemia major patients above 7 years receiving regular transfusion. Patients with transfusion dependent anaemia other than β thalassemia major were excluded. Physical examination, laboratory tests and bone density measurements were performed. Then, the data were analyzed. The total number of children over 7 years of age with β -thalassemia major receiving regular blood transfusions during the study period was 150. Mean hemoglobin was 7.8 ± 0.6 g/dL and the mean serum ferritin level 5295 ± 2736 ng/mL. Short stature was seen in 54.7% boys and 28.7% of girls. Prevalence of lumbar osteoporosis and osteopenia were 42.5% and 37.5%. Femoral osteoporosis and osteopenia were present in 32.5% and 55% of the patients. Impaired puberty, hypothyroidism, diabetes mellitus, hypoparathyroidism were observed in 26%, 18%, 7%, and 15%, of patients, respectively. Nearly 75% of patients had low bone mineral density. Bone mineral density was significantly associated with short stature ($P=0.002$), hypogonadism ($P=0.006$), hypoparathyroidism ($P=0.038$), hypothyroidism ($P=0.044$) and vitamin D deficiency ($P<0.001$). High prevalence of complications among our thalasseemics signifies the importance of more

detailed studies along with therapeutic interventions.

Introduction

Thalassemia is the most common monogenic disorder in the world.¹ Thalassemia major (β -thalassemia) affects a significant segment of the population in certain areas of the world. Alterations in migration patterns have changed the geographic distribution of this disease and made it a worldwide health problem with a high frequency in Africa, India, Southeast Asia and the Mediterranean area.²

β -thalassemia is a group of recessively inherited disorders of hemoglobin synthesis characterized by reduced synthesis of the β -globin chain caused by a mutation. The homozygous state results in severe anemia which needs regular blood transfusion.³ The advent of safe transfusions and chelation therapy has drastically prolonged the life of these patients, thus transforming thalassemia from a rapidly fatal disease of childhood to a chronic illness compatible with a prolonged life.⁴ However, this hope brought with various complications of repeated transfusions and iron overload.

Thalassemia patients show a variety of bone disorders including bone pain or deformity, bone age delay, growth failure, rickets, scoliosis, spinal deformities, nerve compression, pathologic fracture, osteopenia or osteoporosis.⁵⁻⁷ Despite of regular transfusions and iron chelation therapy in β -thalassemia patient's osteoporosis remains the most prevalent bone complication.⁸ Also, it is supposed that low bone mass in patients with thalassemia is more of a reflection of endocrine abnormalities rather than hematological problems.⁹

Materials and Methods

The subjects were all patients with known β -thalassemia major (TM) with hemoglobin electrophoresis and clinical manifestations who had attended in patient department at Department of Medical Genetics, Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS), Lucknow, India. The diagnosis of thalassemia intermedia was exclusion criteria of the study.

After enrollment, the subject's medical history was documented by a review of previous medical records. The subject interview questionnaire included items on demographics, medical and surgical history (e.g. splenectomy), family history of endocrine complications and medication usage. For female subjects, menstruation history was also abtained. A

Correspondence: Sarita Agarwal, Department of Endocrinology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow-226014, India.
E-mail: skritanjali@gmail.com

Key words: thalassemia, endocrinology, anemia.

Received for publication: 1 November 2013.

Revision received: 28 May 2014.

Accepted for publication: 12 June 2014.

This work is licensed under a Creative Commons Attribution 3.0 License (by-nc 3.0).

©Copyright K. Singh et al., 2014
Licensee PAGEPress, Italy
Thalassemia Reports 2014; 4:2104
doi:10.4081/thal.2014.2104

medical record review was also done by the research coordinator from Hospital Information System and by interviewing patient's, which included documentation of transfusion and chelating history and recent endocrine laboratory values.

The study protocol was approved by the ethics committee of the SGPGIMS. Written informed consent was obtained from parents or legal guardian as age below 18 years and from the subjects themselves over 18 years of age.

Anthropological measurement

Subjects were weighed using a digital scale with light clothing without shoes (accuracy 0.1 kg). Height was measured in an upright position without shoes by a stadiometer (accuracy 0.1 cm). Body mass index (kg/m^2) was calculated by dividing body weight (kg) by the height squared (m^2).

Biochemical analysis

Serum calcium, phosphorus, alkaline phosphatase, albumin, and creatinine were measured by automated analyzer (Randox Ltd., London, UK). Serum calcium was corrected if serum albumin was lower than 4 gm/dL. Vitamin D was measured by enzyme linked immunosorbent assay (IDS UK, Durley, Hampshire, UK). Serum 25OHD3 and intact parathyroid hormone, thyroid stimulating hormone were measured by commercially available kits. Hypovitaminosis D was defined as per Lipps' criteria: sufficiency >30 ng/mL, insufficiency 20-30, deficiency 10-20, severe deficiency <10 ng/mL.

Bone mineral density

Bone mineral density (BMD) of the lumbar spine (L1-L4), total hip and non-dominant forearm was measured on dual X-ray energy absorptiometry (DXA; Hologic, Inc., Bedford, MA, USA) in patients greater than 12 years of

age. Pediatric software was used for children with a weight below 30 kg. The Z-score of BMD at hip, lumbar spine and forearm was categorized in three subgroups: i) normal: Z between > -1 and above; ii) low bone mass: Z between ≤ -1 and -2 ; iii) severely low bone mass: Z score below ≤ -2 .

Statistics

The data were analyzed using SPSS software (IBM Corp., Armonk, NY, USA). Correlation among variables was assessed using chi-square and t-test. The patients experiencing severe low bone mass were categorized in subgroups and comparisons were done among the subgroups by using chi-square of Fisher's exact test. P-value less than 0.05 ($P < 0.05$) was considered significant.

Results

One hundred fifty subjects (7-20 years old) with β -thalassemia major undergoing regular blood transfusion therapy were enrolled in the study. The mean age of subjects was 16.66 ± 5.45 years old. Study comprises of 83 males and 67 female thalassemic patients. Short stature (height $< 5^{\text{th}}$ percentile) was present in 54.7% boys and 28.7% girls while weight less than 5^{th} percentile was present in 41.6% boys and 33.3% girls were found below the 5^{th} percentile. We found that 20% study subjects had normal BMD whereas 37.5% cases had Z score between 1.0 to -2.5 standard deviation (SD) suggesting low BMD (osteopenic). Z score was found below 2.5 SD in 42.5% cases indicating osteoporosis at lumbar spine. An analysis of Spearman's rank correlation coefficient indicated a significant influence of serum vitamin D on Z score of BMD at lumbar spine in the studied group of patients ($r=0.422$, $P=0.031$). Z score of BMD at hips was found as normal, osteopenic and osteoporotic in 12.5%, 55% and 32.5% respectively. The osteopenia/osteoporosis were more prevalent in the spine and there was no significant difference between sexes.

Biochemical hypocalcemia (s. total calcium < 8.5 mg/dL) was present in 27.5% subjects. Hyperphosphatemia (s. $\text{Ip} > 5.5$ mg/dL) was present in 42.5% subjects. Serum creatinine and serum albumin was found normal in all cases. Vitamin D deficiency (s. $25\text{OHD}_3=10-20$ ng/mL) and severe deficiency (< 10 ng/mL) was present in 80.6% and 12.9% subjects respectively. Hypogonadism was the most common endocrine complication observed in 26% patients following short stature (56.6% boys and 27.7% of girls). Hypoparathyroidism was found in 15% patients and hypothyroidism in 18% and 7% had diabetes mellitus of total. Bone density was found to be significantly

associated with hypogonadism ($P=0.006$), hypoparathyroidism ($P=0.038$), short stature ($P=0.002$), hypothyroidism ($P=0.044$) and vitamin D deficiency ($P < 0.001$).

Discussion and Conclusions

Hypertransfusion regimens and early iron-chelating therapy have improved the survival of thalassemia major patients.¹⁰ The marked bone abnormalities previously described¹¹ have been substituted with less severe skeletal lesions. Still, osteopenia with cortical thinning, increased trabeculation of the spine and severe osteoporosis remain serious complications in well-transfused and iron-chelated patients.¹² In particular, osteoporosis and bone fractures tend to be present in a variable percentage of the patients from 20-33%.¹³ Our findings in a group of adult transfusion-dependent patients show that the bone loss is a common feature in well-treated thalassemic patients. Our study found similar results as other previous studies which have reported reduced bone mineral density of spine and hip in over two thirds of the patients with β -thalassemia major and sickle cell disease^{8,14-16} from Israel, Italy, and Egypt. Therefore, bone densitometry should be included in the periodical evaluation of patients with thalassemia in order to help guide proper treatment in appropriate time.¹⁷

Z-score of BMD at the lumbar spine was found to be significantly lower in accordance with previous studies that bone mineral loss is more severe in the spinal column.¹⁸⁻²⁰ The possible explanation behind this is differential bone mineral loss can be the accelerated hematopoiesis with progressive bone marrow expansion, a process which involves the spine more severely.

The etiology of thalassemia major-induced bone mineral loss is multi-factorial and complicated.^{21,22} In concordance with previous studies⁸ present study suggest that there are several significantly associated contributing factors of low bone mass such as a patient's weight, age, duration of the disease, history of hypogonadism or concurrent hypothyroidism and diabetes.

In normal, peak bone mass is attained shortly after completion of puberty and is stable until the third decade of life.^{22,24} Age-related bone mineral loss initiates approximately just after the age of 30 year.²⁴ In contrary, in thalassemics, this 0 starts earlier and with swift progression. BMD Z-score significantly deteriorates with age, based on our study findings and those of others.^{23,25-28} There is possibility of having high prevalence of endocrine complications at an early age due to suboptimal transfusions and chelation therapy in patients with

early age group. Quality of life is more strongly affected in older patients. As it is well known that in those patients whose lifespan is getting longer, osteopenia and osteoporosis are major causes of morbidity.^{29,30} We have not observed significant association between BMD and gender is similar with Chapelon *et al.*³¹ and Shamshirsaz *et al.*³

Patient's weight was a significant predictor of BMD. Similar finding has been reported earlier in various literature,^{23,29} who have shown that body fat and lean mass were positive predictors for BMD Z-scores following adjustment for possible confounding factors such as transfusion status, age, sex, ethnicity, calcium intake, and baseline physical activity. It seems that there is a general consensus regarding the protective effects of maintaining normal body weight for BMD. In accordance with our study findings, most previous reports found that a patient's height is also a significant predictor of BMD.^{23,26,28}

Present study showed that lower BMD values are associated with history of hypothyroidism, gonadal dysfunction or impaired puberty which reflects that low BMD values are found more commonly in the background of endocrinopathies. According to some authors^{25-27,29} gonadal dysfunction probably has the most dominant role in the pathogenesis of bone disease in thalassemia major. So, for normal bone health can be attained by management of endocrine complications. Christoforidis *et al.*³² also stated that management of possible endocrine complications is crucial in order to protect normal bone health during adulthood.

Sex steroid not only plays crucial role in maintaining acquisition of bone mass during adolescence but also for the maintenance of peak bone mass during adulthood.^{24,33} Hypogonadism is mostly observed in thalassemics and therefore they lack sex hormones in critical phases of growth, such as puberty, this hinders in achieving optimal peak bone mass. Short stature seemed to be more prevalent among our patients compared to other studies.³⁴ It has been emphasized that thalassemic patients are often hypogonadal and therefore the lack of sexual hormones in critical periods, such as puberty, contributes to the failure to achieve optimal peak bone mass and to maintain bone mineral density later in life.^{26,34,35}

In an Italian study reported delayed puberty in 47% of females and 51% of males, arrested puberty in 12.6% of females and 15.7% of males, and secondary amenorrhea in 25% of adult females.²³ Short stature (56.6% boys and 27.7% of girls) were also the most prevalent endocrine disorder in our study, which were followed by hypogonadism (26%), hypothyroidism (18%) hypoparathyroidism (15%) and diabetes mellitus (7%).

Vitamin D deficiency may start early in TM even before hypoparathyroidism is estab-

lished. Vitamin D deficiency potentially contributes to low bone mass in thalassemia. Vitamin D deficiency (s.25OHD₃=10-20 ng/mL) and severe deficiency (<10 ng/mL) was present in 80.6% and 12.9% subjects respectively.

In conclusion endocrine evaluation in thalassemic patients must be carried out regularly, especially during adolescence and puberty. As of the improved survival of thalassemic patients, and the high incidence of multiple endocrine complications, it is important to carry out careful follow-up studies for the early detection of any other associated complications to facilitate precise treatment.

The present study showed a high prevalence of low BMD in thalassemia, suggesting that they should be targeted for bone density screening periodically and osteoporosis prevention before permanent end organ bone damage occurs. The disagreements on the possible role of different underlying factors or predictors indicate towards the necessity of further studies in order to unveil the actual pathophysiological brass tacks behind this serious complication of thalassemia major.

References

1. Agarwal MB. Advances in management of thalassemia (Editorial). *Indian Pediatr* 2004;41:989-92.
2. Pearson HA, Cohen AR, Giardina PJ, Kazazian HH. The changing profile of homozygous beta thalassemia: demography, ethnicity, and age distribution of current North American patients and changes in two decades. *Pediatrics* 1996;97:352-6.
3. Shamshirsaz AA, Bekheirnia MR, Kamgar M, et al. Metabolic and endocrinologic complications in beta-thalassemia major: A multicenter study in Tehran. *BMC Endocr Disord* 2003;3:23-34.
4. Fazal-ur-Rahman Khan. Thalassemia: still a challenge. *Gomal J Med Sci* 2006;4:47.
5. Bielinski BK, Darbyshire P, Mathers L, et al. Bone density in the Asian thalassaemic population: a cross-sectional review. *Acta Paediatr* 2001;90:1262-6.
6. Arjmand Rafsanjani Kh, Razzaghy-Azar M, Zahedi-Shoolami L, et al. Bone mineral density in thalassemia major and intermedia, correlation with biochemical and hormonal profiles. *Iran J Blood Cancer* 2009; 1:121-7.
7. Filosa A, Di Maio S, Vocca S, et al. Longitudinal monitoring of bone mineral density in thalassemic patients. Genetic structure and osteoporosis. *Acta Paediatr* 1997;86:342-6.
8. El-Edel RH, Ghonaim MM, Abo-Salem OM, El-Nemr FM. Bone mineral density and vitamin D receptor polymorphism in beta-thalassemia major. *Pak J Pharm Sci* 2010; 23:89-96.
9. Karimi M, Ghiam AF, Hashemi A, et al. Bone mineral density in beta-thalassemia major and intermedia. *Indian Pediatr* 2007;44:29-32.
10. Olivieri NF. The beta-thalassemia. *N Eng J Med* 1999;341:99-109.
11. Cooley TB, Witwer ER, Lee P. Anemia in children with splenomegaly and peculiar changes in bones. *Am J Dis Child* 1927; 34:347-63.
12. Vichinsky EP. The morbidity of bone disease in thalassemia. *Ann N Y Acad Sci* 1998;850:344-60.
13. Giardina PJ, Schneider R, Lesser M, et al. Abnormal bone metabolism in thalassaemia. In: Ando S, et al., eds. *Endocrine disorders in thalassemia*. Berlin; Springer; 1995. pp 39-46.
14. Dresner Pollak R, Rachmilewitz E, Blumenfeld A, et al. Bone mineral metabolism in adults with beta-thalassaemia major and intermedia. *Br J Haematol* 2000;111:902-7.
15. Ferrara M, Matarese SM, Francese M, et al. Effect of VDR polymorphisms on growth and bone mineral density in homozygous beta thalassaemia. *Br J Haematol* 2002; 117:436-40.
16. Hamed HM, Galal A, El Ghamrawy M, et al. Vitamin D receptor polymorphisms and indices of bone turnover and bone mass in egyptian children with sickle cell disease. *Res J Med Med Sci* 2010;5:1-7.
17. Orvieto R, Leichter I, Rachmilewitz EA, Margulies JY. Bone density, mineral content, and cortical index in patients with thalassemia major and the correlation to their bone fractures, blood transfusions, and treatment with desferrioxamine. *Calcif Tissue Int* 1992;50:397-9.
18. Tantawy AA, El Kholly M, Moustafa T, Elsedfy HH. Bone mineral density and calcium metabolism in adolescents with beta-thalassemia major. *Pediatr Endocrinol Rev* 2008;6:132-5.
19. Shamshirsaz AA, Bekheirnia MR, Kamgar M, et al. Bone mineral density in Iranian adolescents and young adults with beta-thalassemia major. *Pediatr Hematol Oncol* 2007;24:469-79.
20. Lasco A, Morabito N, Gaudio A, et al. Effects of hormonal replacement therapy on bone metabolism in young adults with beta-thalassemia major. *Osteoporos Int* 2001;12:570-5.
21. Kyriakou A, Savva SC, Savvides I, et al. Gender differences in the prevalence and severity of bone disease in thalassaemia. *Pediatr Endocrinol Rev* 2008;6:116-22.
22. D'Eufemia P, Finocchiaro R, Celli M, et al. Taurine deficiency in thalassemia major-induced osteoporosis treated with neridronate. *Biomed Pharmacother* 2010;64: 271-4.
23. Vogiatzi MG, Autio KA, Mait JE, Schneider R, Lesser M, Giardina PJ. Low bone mineral density in adolescents with beta-thalassemia. *Ann NY Acad Sci* 2005;1054:462-6.
24. Skordis N, Ioannou YS, Kyriakou A, et al. Effect of bisphosphonate treatment on bone mineral density in patients with thalassaemia major. *Pediatr Endocrinol Rev* 2008;6:144-8.
25. Mylona M, Leotsinides M, Alexandrides T, et al. Comparison of DXA, QCT and trabecular structure in beta thalassaemia. *Eur J Haematol* 2005;74:430-7.
26. Vogiatzi MG, Autio KA, Schneider R, Giardina PJ. Low bone mass in prepubertal children with thalassemia major: insights into the pathogenesis of low bone mass in thalassemia. *J Pediatr Endocrinol Metab* 2004;17:1415-21.
27. Pafumi C, Roccalvalva L, Pernicone G, et al. Osteopenia in female beta-thalassemic patients. *J Pediatr Endocrinol Metab* 1998; 11:989-91.
28. Lala R, Chiabotto P, Di Stefano M, et al. Bone density and metabolism in thalassaemia. *J Pediatr Endocrinol Metab* 1998;11:785-90.
29. Vogiatzi MG, Macklin EA, Fung EB, et al. Bone disease in thalassemia: a frequent and still unresolved problem. *J Bone Miner Res* 2009;24:543-57.
30. Di Matteo R, Liuzza F, Manicone PF, et al. Bone and maxillofacial abnormalities in thalassemia: a review of the literature. *J Biol Regul Homeost Agents* 2008;22:211-6.
31. Chapelon E, Garabedian M, Brousse V, et al. Osteopenia and vitamin D deficiency in children with sickle cell disease. *Eur J Haematol* 2009;83:572-8.
32. Christoforidis A, Kazantzidou E, Tsatra I, et al. Normal lumbar bone mineral density in optimally treated children and young adolescents with beta-thalassaemia major. *Hormones (Athens)* 2007;6:334-40.
33. Carmina E, Di Fede G, Napoli N, et al. Hypogonadism and hormone replacement therapy on bone mass of adult women with thalassemia major. *Calcif Tissue Int* 2004;74:68-71.
34. Doxiadis S, Georgaki E, Papamichael D, et al. Bone density in thalassemic children during the course of the disease. *Pediatr Res* 1978;12:811-5.
35. Molyvda-Athanasopoulou E, Sioundas A, Karatzas N, et al. Bone mineral density of patients with thalassemia major: four-year follow-up. *Calcif Tissue Int* 1999;64:481-4.