Low bone mineral density and high bone turnover in adult subjects with thalassemia major

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Summary

In this study we evaluated 38 TM patients (recruited from the Thalassemia centre of Palermo), 14 male and 24 female. We obtained the BMD of the lumbar spine (L1 L4), femoral neck (DEXA; Lunar DPX plus), serum levels of PTH, osteocalcin, C-telopeptide and bone alkaline phosphatase.
Patients with TM presented low bone mass at lumbar spine (Z score: L1-L4 -2.23 ± 1.25 SD), and femoral neck (Z-score -1.52 ± 1.14 SD): 50% of subjects were osteoporotic; 36% osteopenics and 13.1% were normal. Were presented normal serum levels of osteocalcin (19.1 ± 8 ng/ml), but hight level of bone alkaline phosphatase (24.2 ± 9.1 µg/L), and C-telopeptide (452 ± 221 pmol/L). Patients with TM presented BMD reduction more marked at lumbar spine than femur; increased C telopeptides and alkaline phosphatase were observed, although osteocalcin was normal. Patients with TM presented low bone mineral density and high bone turnover. It's possible that subjects with increased reabsorbtion, have a marked bone loss and a progressive increased fracture risk.

KEY WORDS: thalassemia major, bone mineral density, bone turnover, osteoporosis.

Introduction

Beta Thalassemia Major (TM) affects a significant number of the population in certain areas of the world (1).
TM is an inherited blood disorder in which the body is unable to make adequate hemoglobin. This is due to an inborn error of metabolism that leads to absence or reduced synthesis of one or more types of globin polypeptide chains of the hemoglobin molecule; is a hereditary disorder of haemoglobin synthesis resulting in severe anemia. Treatment consists of multiple blood transfusions, a complication of which is iron overload. Excessive iron is then deposited in almost all tissues but primarily in the liver, heart and the endocrine glands (2).
The bone marrow expands to compensate for anemia and as a result there occur marked skeletal changes leading to frontal and parietal bossing, malar prominence, protrusion of upper jaw leading to malocclusion of teeth, distortion of ribs, vertebrae and weakening of long bones, low bone mass.

Patients and methods

38 TM patients (recruited from the thalassemia centre of Palermo) were studied (14 male and 24 female), age range 20-40 years old. Osteoporosis was defined using the standard World Health Organization criteria (z-score of BMD lower than 2·5). The BMD of the lumbar spine (L1-L4), the femoral neck and the forearm was determined by Dual Energy X-Ray Absorptiometry (DEXA; Lunar DPX plus). The PTH was studied by ELISA (Biosource, Belgium), osteocalcin, C-telopeptide and bone alkaline phosphatase by Elisa (Beckmann-Coulter USA). Analisys of variance and t-test of Mann-Whitney were used for TM patients and controls. The correlation was obtained with Pearson index. P value < 0.05 was considered statistically significant. The calculated Z-scores for males and females were evaluated by normal ranges.

Results

Patients with TM presented low bone mass at lumbar spine (Z score: L1-L4 -2.23 ± 1.25 SD) (Fig. 1), and femoral neck (Z-score -1.52 ± 1.14 SD) (Fig. 2): 50% of subjects were osteoporotic; 36% osteopenics and 13.1% were normal (Fig. 3).

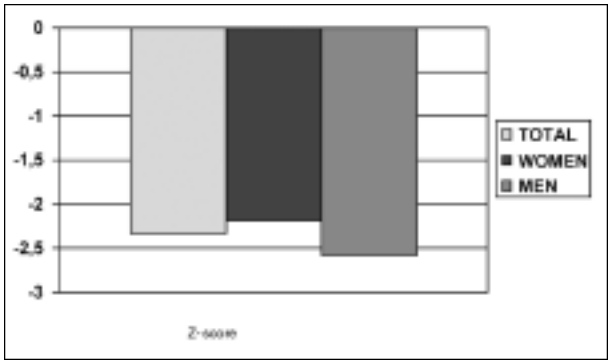

Figure 1 - Z-score lumbar spine. Low bone mass at lumbar spine in TM women and men (Z-score: L1-L4 -2.23 ± 1.25).

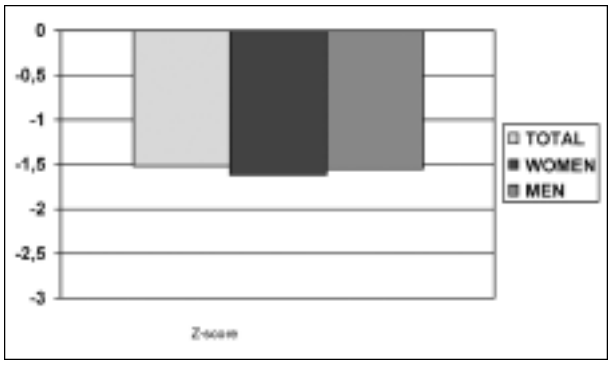

Figure 2 - Z-score femoral neck. T-score femoral neck: patients with TM presented low bone mass at femoral neck (Z-score -1.52 ± 1.14).

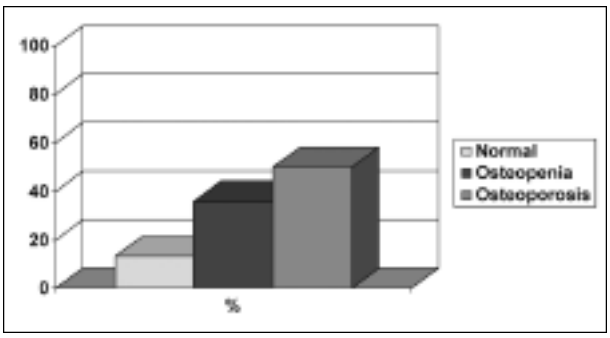

Figure 3 - Prevalence of osteopenia and osteoporosis inTM patients. Prevalence of osteoporosis and osteopenia inTM patients: 50% of subjects were osteoporotic; 36% osteopenic and 13.1% were normal.

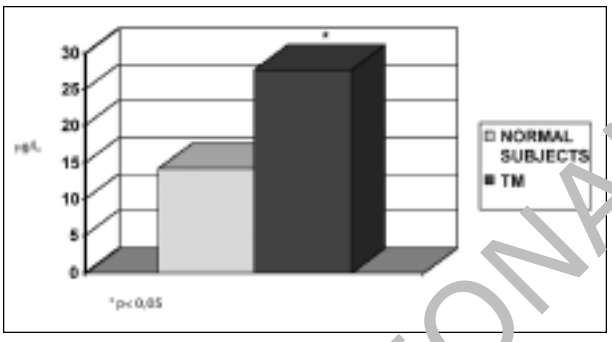

Figure 5 - Serum levels of bone alkaline phosphatase. High serum levels of bone alkaline phosphatase in TM (24.2 ± 9.1 µg/L).

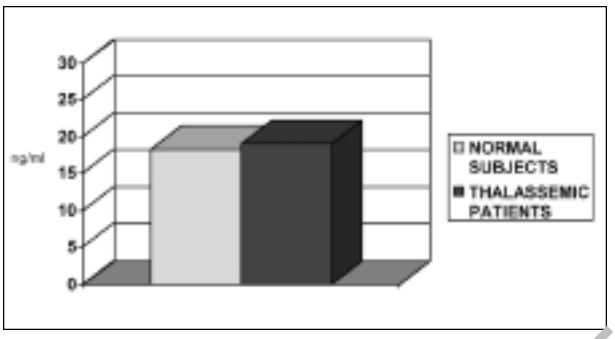

Figure 4 - Serum levels of osteocalcin. Normal serum levels of osteocalcin in TM (19.1 ± 8 ng/ml).

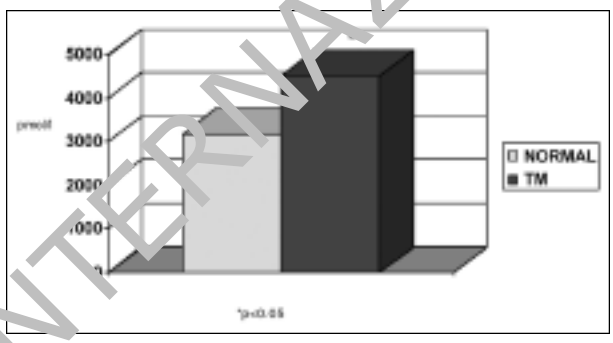

Figure 6 - Serum level of C-telopeptide. High serum levels of C-telopeptide inTM (4528 ± 2821 pmol/L).

Compared to normal subjects, thalassemic patients presented normal levels of blood and urinary calcemia and phosphoremia. Normal level of osteocalcin (19.1 ± 8 ng/ml) (Fig. 4), but hight level of bone alkaline phosphatase (24.2 ± 9.1 µg/L) (Fig. 5), and C- telopeptide (4528 ± 2821 pmol/L) (Fig. 6).

Discussion

In the general population osteoporosis is less common in men than in women, with the incidence of vertebral fractures being one sixth of that in women (3).
However, the sex difference was reversed in the thalassemia patients studied here, with men being both more commonly and more severely affected with low bone mass. This striking observation is difficult to explain. Clinical experience indicates that male thalassemia patients, particularly during their adolescent years, are less compliant than females with DFX therapy. The impact of this on peak bone mass, even with subsequent improvement in chelation compliance as they improve chelation therapy, may contribute to the sex difference in observed bone mineral density. However, we could find no significant correlation between severely low bone mass and serum ferritin levels, measured at the time of this study. In a study of 17 transfusion-dependent children with thalassemia also no apparent association between iron overload and vitamin D deficiency and bone disease was found (4).
The most common endocrine disorder among our patients is hypogonadotrophic hypogonadism. In the general population hypogonadism is a well-recognized cause of overt osteoporosis and of asymptomatic osteopenia. Oestrogen replacement therapy for women is the most effective preventative measure against postmenopausal osteoporosis. The exact mechanism of action of oestrogen on bone, calcium and phosphorus metabolism has not been determined, but oestrogens appear primarily to inhibit osteoclastic activity and bone resorption (5).
It is important to note that therapeutic correction of hypogonadism with appropriate HRT in these thalassemia patients has failed to protect them from low bone mass.
In spite of regular blood transfusions the ineffective erythropoiesis is not fully suppressed in thalassemia major. Expansion of the marrow may contribute to the decreased bone mineral density. It is also possible that excess iron in the bone may influence osteoblast number and activity and lead to the development of osteoporosis (6).
In the general population, osteoporosis is associated with a sedentary lifestyle, but no association with current exercise habits was apparent in this study. However, parental anxiety may have limited participation in sporting activities during childhood and it is possible that this contributed to the development of severely low bone mass.
As the longevity of patients with TM increases, osteoporosis will become an increasingly prominent problem (7, 8). Osteoporosis is a progressive disease, so prevention and early diagnosis are important, as well as treatment of the established disease. The prevalence of clinical features of severely low bone mass and results of its treatment in our patients will form the basis of further investigations (9).
The average of bone density, that indicates an osteopenia, doesn't fully account for the real clinical state. The analysis of individual values shows that the 50% of the TM patients is affected with osteoporosis (defined as a reduction of the bone mass > 2.5 DS), osteopenia in the 36% of the subjects, while the 13% had a normal bone mass.
There is a difference between men and women BMD, likely due to the low compliance to the treatment in male subjects. In

fact, the anamnestic study showed that almost none of the male TM patients was on hormonal therapy.
The BMD reduction is more marked at lumbar spine than femur. It may be caused by the age: the reduction of the bone mass starts at the beginning in the spine and just lately the femur.
Analysis of bone remodelling has shown, through the dosage of bone markers that in thalassemic patients is very increased, suggesting that both reabsorption and neoformation processes are accelerated.
Particularly, increased C telopeptides and alkaline phosphatase were observed, although osteocalcin is normal.
It's possible that subjects with increased reabsorbtion, have a marked bone loss and a progressive increased fracture risk.
Bone remodelling is an evolutionary process, so that the BMD, considering the high reabsorption markers, may be further reduced, with a consequential progressive increase of the fracture risk.
The mechanisms influencing negatively the risk fractures enclode the increase of the rate of bone loss, the impairment of skeletal microarchitecture, trabeculae perforation and loss of structural elements of the bone.
It's necessary to prevent a further loss of bone, in order to avoid the risk of fractures.
TM patients need to be treated because of the progressive osteoporosis. For this reason is not necessary just the HRT, but specific antireabsorbitive drugs, able to improve bone turn over and reduce the reabsorption.
Likely, biphosphonates, blocking the bone reabsorption, are the most indicated drugs for the treatment of osteoporosis in TM patients.
Nevertheless, we don't know yet the long term efficacy and safety of these drugs in TM patients, further studies are needed.

References

1. Mohammadian S, Bazrafshan HR, Sadeghi-Nejad A. Endocrine gland abnormalities in thalassemia major: a brief review. J Pediatr Endocrinol Metab. 2003 Sep;16(7):957-64.
2. Al-Elq AH, Al-Saeed HH. Endocrinopathies in patients with thalassemias. Saudi Med J. 2004 Oct;25(10):1347-51. Review.
3. Riggs BL, Melton LJ 3rd. Evidence for two distinct syndromes of involutional osteoporosis. Am J Med. 1983 Dec;75(6):899-901.
4. Rioja L, Girot R, Garabedian M, Cournot-Witmer G. Bone disease in children with homozygous beta-thalassemia. Bone Miner. 1990 Jan;8(1):69-86.
5. Riggs BL, Jowsey J, Kelly PJ, Jones JD, Mahoney FT. Effect of sex hormones on bone in primary osteoporosis. J Clin Invest. 1969 Jun;48(6):1065-72.
6. Gratwick GM, Bullough PG, Johnes WH, Markenson AL, Peterson CM. Thalassemic osteoarthropathy. Ann Intern Med. 1978 Apr; 88(4):494-501.
7. Dresner Pollak R, Rachmilewitz E, Blumenfeld A, Idelson M, Goldfarb AW. Bone mineral metabolism in adults with β-thalassaemia major and intermedia. Br J Haematol. 2000;111:902 7.
8. Voskaridou E, Kyrtsonis MC, Terpos E et al. Bone resorption is increased in young adults with thalassaemia major. Br J Haematol. 2004;126:36 41.
9. Jensen CE, Tuck SM, Agnew JE et al. High prevalence of low bone mass in thalassaemia major. Br J Haematol. 1998;103:911-5.