



Osteoporosis in Thalassemia Major

Talasemi Majorde Osteoporoz

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Summary

Thalassemia Major is an inherited blood disorder which leads to ineffective erythropoiesis, bone marrow expansion, and skeletal deformity. In the last two decades the survival of the patients has improved considerably and osteoporosis has become a serious burden. Genetic and acquired factors play role in bone demineralization and osteoporosis is the most common involvement in the skeletal system. It is seen in %40-50 of Thalassemia major patients, even in well-treated ones. Therefore regular screening and preventive interventions are important in these patients. In addition to blood transfusions and iron chelation therapy; hormonal replacement therapy, calcium and vitamin D supplementation; antiresorptive drugs like bisphosphonates are used to inhibit osteoclast function. In this review, an overview of osteoporosis and its treatment modalities in patients with Thalassemia major are presented. (Turkish Journal of Osteoporosis 2012;18: 89-91)

Key words: Thalassemia, osteoporosis

Özet

Talasemi Major inefektif eritropoez, kemik iliği ekspansiyonu ve iskelet deformitelerine neden olan kalıtsal bir kan hastalığıdır. Son yirmi yılda hastaların sağ kalımının belirgin şekilde uzamasıyla, osteoporoz ciddi bir sorun haline gelmiştir. Kemik demineralizasyonunda genetik ve kazanılmış faktörler rol oynar. İskelet sisteminde en sık osteoporoz görülür ve iyi tedavi edilmiş olan Talasemi Major hastalarında bile %40-50 oranında mevcuttur. Bu açıdan düzenli tarama ve önleyici müdahaleler önemlidir. Kan transfüzyonları ve demir şelasyonu, hormon replasman tedavisi, kalsiyum ve Vitamin D desteğine ek olarak antirezorptif ilaçlar olan bisfosfonatlar osteoklast fonksiyonunu inhibe etmek için kullanılırlar. Bu derlemede, Talasemi Major hastalarındaki osteoporoz ve tedavi modaliteleri gözden geçirilmiştir. (Türk Osteoporoz Dergisi 2012;18: 89-91)

Anahtar kelimeler: Talasemi, osteoporoz

Introduction

Thalassemia major (TM) is an inherited blood disorder which is characterized by reduced synthesis of one or more of the globins that form the hemoglobin tetramer. The disease leads to ineffective erythropoiesis, severe anemia, bone marrow expansion, skeletal deformity, increased gastrointestinal iron absorption and the patient requires regular blood transfusion and iron-chelating therapy throughout life from early childhood (1-3).

In the last two decades, transfusional and iron-chelation therapies have improved the survival of TM patients. A common group of morbidities associated with TM includes diabetes mellitus, hypothyroidism, hypogonadism, hepatic cirrhosis and cardiac complications, including arrhythmias and congestive heart failure.

Osteoporosis is the most common involvement of the skeletal system and represents an important cause of morbidity in adult patients (2,4-6). It is characterized by reduced bone mass, disruption of bone architecture and increased risk of bone fragility and fractures (4,7,8). In this review, we present an overview of osteoporosis and its treatment modalities in patients with TM.

Etiopathogenesis

The etiopathogenesis of TM-induced osteoporosis is multifactorial. Genetic and acquired factors play role in demineralization of bone in thalassemia.

Acquired factors include bone marrow expansion secondary to ineffective erythropoiesis with cortical thinning, hypogonadotropic

hypogonadism, hypothyroidism, hypoparathyroidism, diabetes mellitus, direct toxic effects of iron overload on osteoblast number and activity, deleterious effects of desferrioxamine on the bone metabolism, the negative impact of chelation therapy on fibroblast proliferation and collagen synthesis, calcium and zinc deficiencies, low vitamin D levels due to aberrant vitamin D–parathyroid hormone axis and reduced physical activity (8-13). In thalassemia, anemia, hypoxaemia and impaired GH/IGF-1 axis disturb growth and puberty (10). In a study of Scacchi et al. (9), it is suggested that defective GH secretion and diminished serum IGF-I levels may contribute to femoral demineralization in thalassemia patients.

Genetic factors also play an important role in the pathogenesis of osteoporosis in children and young adults with TM. One of the most important candidate genes for predisposition to osteoporosis is the collagen type Ia1 (COLIA1) gene, which encodes type I collagen, the major protein of bone. The polymorphism at the Sp1 site of the COLIA 1 gene has been associated with severe osteoporosis and pathologic fractures of the spine and the hip in TM patients. Early detection of this mutation is important to start the treatment before fractures occur (7,13,14). The vitamin D receptor (VDR) polymorphism is also a risk factor for bone mineral damage and low bone mineral density (BMD) (8,13).

The diminished osteoblast function leads to decreased bone formation with reduced osteocalcin which is a protein produced by osteoblasts. This is accompanied by increase in osteoclast activity, increased bone resorption through the RANK/RANKL/OPG pathway (3,8,13).

In a study by Salah et al. (15), it was found that thalassemia patients with osteopenia and/or osteoporosis have significantly low levels of OPG and OPG/RANKL ratio when compared with thalassemia patients with normal BMD. The RANK/RANKL/OPG system is important for the activation and proliferation of osteoclast precursors. In this study, the most specific marker for detecting osteoporosis was the OPG/RANKL ratio.

Endocrine abnormalities caused by iron overload in various endocrine organs despite chelation therapy are other important causal factors. Jensen et al. (1) showed that in TM the degree of low bone mass was significantly associated with male sex, diabetes and the lack of spontaneous puberty. Nevertheless, in untreated thalassemics, the severity of the disease appears to be a primary factor for low BMD (1,10).

Epidemiology

Bone loss is a common feature even in well-treated thalassemia patients in spite of adequate transfusion and iron chelation. In well treated TM patients, the reported frequency of osteoporosis is approximately 40-50% with an additional 45% affected by osteopenia (3,6,13). In a study of Chinese TM children, BMD deficit was detected in 62% at the spine and in 35% at the hip (12). In TM, peak bone mass is also adversely affected since there is low BMD at ages as young as 12 years (1).

Although in the general population, osteoporosis is more common in women than in men, in thalassemia patients, men are more commonly and more severely affected. It is presumed that this fact

is due to lower compliance of male patients with desferrioxamine therapy during their adolescent years than females (1).

Diagnosis

The most reliable and widely used method for measuring BMD is Dual Energy X-ray Absorptiometry (DEXA) which assesses bone mass at the lumbar spine and proximal femur (12). True bone density, which is volumetric BMD, can be assessed only by quantitative computed tomography. This technique involves high radiation exposure, so studies use mostly areal BMD which does not measure true bone density (5).

Recent evidence indicates that individual values of BMD measured by traditional DEXA are lower than those determined by quantitative computed tomography in thalassemic patients (9).

Patients with TM and osteoporosis have elevated markers of bone resorption, such as N-telopeptides of collagen type I in urine, tartrate resistant acid phosphatase isoform 5b in serum, pyridinoline and deoxypyridinoline (13).

Management

Adequate iron chelation may prevent iron toxicity in the bone and sufficient blood transfusions may inhibit uncontrolled bone marrow expansion (13).

Continuous hormonal replacement therapy with transdermal estrogen for females or human chorionic gonadotrophin for males help to improve bone density parameters (3,9,13,16).

Physical activity must always be encouraged and smoking should be discouraged.

Adequate calcium (500 mg–1 g/day orally) and zinc intake in combination with of low doses of vitamin D (1000–1500 IU/day orally) should be recommended (3,13,16). To decrease the risk of kidney stones in thalassemia patients, it is recommended to use calcium citrate instead of calcium carbonate, add magnesium citrate and monitor urinary calcium excretion (3).

Even if the patients with TM receive hormonal replacement therapy, calcium, vitamin D and effective iron chelation and have normalized hemoglobin levels, they continue to lose bone mass because of increased resorptive phase (5,13). Therefore, annual follow-up of BMD, starting in adolescence, is considered crucial (12,13).

The reduced osteoblast function, which is thought to be the major cause of osteopenia/osteoporosis in TM, is accompanied by a comparable or even greater increase in osteoclast activity. The increased bone resorption observed in thalassemic patients justifies the use of powerful antiresorptive drugs, such as bisphosphonates, which are potent inhibitors of osteoclast function (5,15).

To date, alendronate, pamidronate, and zoledronate seem to be effective in increasing BMD and normalizing bone turnover (3,5,16). Zoledronate dosages can be arranged at the same time with transfusion sessions. This advantage makes zoledronate the most promising candidate bisphosphonate (6).

Otrock et al. (17) assessed whether the polymorphisms of VDR gene influence the response to zoledronic acid treatment. They found that in thalassemic osteoporotic patients, none of the VDR genotypes influenced the efficacy of zoledronic acid.

In a study of Chatterjee et al. (8), the effect of pamidronate infusion on bone quality was assessed by histomorphometry, on quantity by DEXA, and on dynamics by a bone turnover marker, type 1 collagen. Patients with TM responded favorably with improvement in bone volume, whereas patients with thalassemia intermedia responded poorly to pamidronate.

In another study, 39 TM patients were followed over a 3 year period and BMD values were significantly improved only in those treated with monthly pamidronate in addition to standard treatments with calcium and vitamin D (12). Thus, these observations justify the use of powerful antiresorptive drugs, such as bisphosphonates, in improving BMD and normalizing bone turnover in TM (12).

Marabito et al. (18) compared the effects of 10 mg daily oral aledronate and 100 mg clodronate (infusion in every 10 days) treatments for two years. Although there were significant increases in hip and vertebral BMD in alendronate group, there was no improvement in clodronate group.

In a study done by Patiroglu et al. (19), the treatment group received 15 mg pamidronate infusion every 3 months for one year. The next year all patients received only calcium and vitamin D supplements. After two years, femoral neck and lumbar spine BMD had increased significantly compared to baseline.

Gilfillan et al. (20) gave 4 mg i.v. zoledronate every 4 months, for 24 months. When compared with placebo both lumbar and femoral BMD increased significantly. In a study done at Cukurova region, in thalassemia patients having normal levels of 1,25-dihydroxyvitamin D, the effects of zoledronate (once in every 6 months, 4 mg i.v.) and calcitriol (0.25 mcg/day) treatments were compared. In zoledronate arm, lumbar BMD; and in calcitriol arm femur neck BMD improved significantly. The difference for BMD and T scores in lumbar and femoral neck was not significant between groups (21). In a report by Yigitoglu et al. (22), 4 mg i.v. zoledronate treatment were given intermittently for 6 years to two TM sisters, one of whose having many major fractures. Lumbar BMD measurements improved and there was no new fracture in the long term.

Conclusion

Osteopenia and osteoporosis are common complications seen in patients with TM. Even if they receive adequate transfusion and iron chelation therapy, bone loss is an important cause of morbidity. Regular screening, preventive intervention and early management of possible endocrine complications starting from infancy are important to prevent severe BMD deficit in TM patients.

References

1. Jensen CE, Tuck SM, Agnew JE, Koneru S, Morris RW, Yardumian A et al. High prevalence of low bone mass in thalassaemia major. *Br J Haematol* 1998;103:911-5.
2. Kidson-Gerber GL, Francis S, Lindeman R. Management and clinical outcomes of transfusion-dependent thalassaemia major in an Australian tertiary referral clinic. *Med J Aust* 2008;188:72-5.
3. Borgna-Pignatti C, Gamberini MR. Complications of thalassemia major and their treatment. *Expert Rev Hematol* 2011;4:353-66.
4. Perrotta S, Cappellini MD, Bertoldo F, Servedio V, Iolascon G, D'Agruma L et al. Osteoporosis in beta-thalassaemia major patients: analysis of the genetic background. *Br J Haematol* 2000;111:461-6.
5. Gaudio A, Morabito N, Xourafa A, Macri I, Meo A, Morgante S et al. Bisphosphonates in the treatment of thalassemia-associated osteoporosis. *J Endocrinol Invest* 2008;31:181-4.
6. Mamtani M, Kulkarni H. Bone recovery after zoledronate therapy in thalassemia-induced osteoporosis: a meta-analysis and systematic review. *OsteoporosInt* 2010;21:183-7.
7. Hamed HM, Galal A, Ghamrawy ME, Abd El Azeem K, Hussein IR, Abd-Elgawad MF. An SP1-binding site polymorphism in the COL1A1 gene and osteoporosis in Egyptian patients with thalassemia major. *Blood Coagul Fibrinolysis* 2011;22:81-5.
8. Chatterjee R, Bajoria R. Osteopenia-osteoporosis syndrome in patients with thalassemia: understanding of type of bone disease and response to treatment. *Hemoglobin* 2009;33(Suppl 1):136-8.
9. Scacchi M, Danesi L, Cattaneo A, Valassi E, PecoriGiraldi F, Argento C et al. Bone demineralization in adult thalassaemic patients: contribution of GH and IGF-I at different skeletal sites. *ClinEndocrinol (Oxf)* 2008;69:202-7.
10. Mahachoklertwattana P, Chuansumrit A, Sirisriro R, Choubtum L, Sriprapradang A, Rajatanavin R. Bone mineral density, biochemical and hormonal profiles in suboptimally treated children and adolescents with beta-thalassaemia disease. *ClinEndocrinol (Oxf)* 2003;58:273-9.
11. Pietrapertosa AC, Minenna G, Colella SM, Santeramo TM, Renni R, D'Amore M. Osteoprotegerin and RANKL in the pathogenesis of osteoporosis in patients with thalassaemia major. *Panminerva Med* 2009;51:17-23.
12. Leung TF, Chu Y, Lee V, Cheng FW, Leung WK, Shing MM et al. Long-term effects of pamidronate in thalassaemic patients with severe bone mineral density deficits. *Hemoglobin* 2009;33:361-9.
13. Haidar R, Musallam KM, Taher AT. Bone disease and skeletal complications in patients with β thalassemia major. *Bone* 2011;48:425-32.
14. Guzeloglu-Kayisli O, Cetin Z, Keser I, Ozturk Z, Tuncer T, Canatan D et al. Relationship between SP1 polymorphism and osteoporosis in beta-thalassemia major patients. *PediatrInt* 2008;50:474-6.
15. Salah H, Atfy M, Fathy A, Atfy M, Mansor H, Saeed J. The clinical significance of OPG/sRANKL ratio in thalassemia patients suffering from osteopenia or osteoporosis in Egyptian patients. *Immunol Invest* 2010;39:820-32.
16. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis* 2010;21:5:11.
17. Otrick ZK, Mahfouz RA, Charafeddine KM, Rayes RF, Zahed LF, Taher AT. Vitamin D receptor genotypes and response to zoledronic acid therapy in thalassemia-induced osteoporosis. *Ann Hematol* 2008;87:947-8.
18. Morabito N, Lasco A, Gaudio A, Crisafulli A, Di Pietro C, Meo A et al. Bisphosphonates in the treatment of thalassemia-induced osteoporosis. *Osteoporos Int* 2002;13:644-9.
19. Patiroglu T, Altuner Torun Y, Kula M, Karaküküçü M. Treatment of thalassemia-induced osteoporosis with intermittent pamidronate infusions: two-year follow-up. *Türk J Hematol* 2008;25:79-82.
20. Gilfillan CP, Strauss BJ, Rodda CP, Bowden DK, Kean AM, Obaid M et al. A randomized, double-blind, placebo-controlled trial of intravenous zoledronic acid in the treatment of thalassemia-associated osteopenia. *Calcif Tissue Int* 2006;79:138-44.
21. Evran M. Beta talasemili hastalarda osteoporoz ve osteoporozteda visinde zoledronik asit kullanımı (Osteoporosis in Thalassemia Patients and Use of Zoledronic Acid in the Treatment of Osteoporosis, unpublished thesis). Adana: Çukurova Üniversitesi; 2005.
22. Yigitoglu PH, Guzel R, Evran M, Gurkan E. Use of Zoledronic Acid in Thalassemia-Induced Osteoporosis: Two Case Reports and Review of the Literature. *Türk J Phys Med Rehab* 2012;58:154-8.