THE USE OF ANABOLIC THERAPY IN PATIENTS WITH BETA-THALASSEMIA MAJOR-INDUCED OSTEOPOROSIS – REVIEW OF THE LITERATURE

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Abstract

Osteopenia/osteoporosis (OP) in young adults with beta thalassemia major (BTM) is a prominent cause of morbidity despite adequate transfusion and iron chelation therapy; the reported frequency of OP varies from 13.6% to 50%, with an additional 45% affected by osteopenia. The pathogenesis of OP in BTM is multifactorial and is related to chronic anaemia with secondary bone marrow expansion, associated endocrinopathies, nutritional deficiencies and genetic factors. These factors lead to OP/osteoporosis by increasing osteoclast activity and impairing osteoblast function. OP is a prominent cause of morbidity in BTM because of the increased risk for vertebral and long bone fractures. Although the bisphosphonates are the most used treatment for osteoporosis in BTM, in some cases there is a poor clinical response with new fractures occurring during treatment; therefore, at least in these patients, we suggest that decreased bone formation is the predominant mechanism of BTM-induced OP and anabolic treatment could be the most appropriate therapy.

Rezumat

Osteopenia/osteoporoza (OP) la pacienții tineri cu betatalasemie majoră (BTM) reprezintă o cauză importantă de morbiditate, chiar dacă se aplică tratament transfuzional și chelator adecvat; prevalența raportată a OP variază între 13,6 și 50%, în timp ce 45% prezintă osteopenie. Etiopatogenia OP la pacienții cu BTM este multifactorială și se datorează anemiei cronice cu expansiunea secundară a măduvei osoase hematogene, endocrinopatiilor, deficitelor nutriționale și factorilor genetici care acționează prin creșterea resorbției osoase, dar și afectării funcției osteoblastelor. OP contribuie la morbiditatea din BTM ca urmare a creșterii riscului de fracturi ale oselor lungi și tăsărilor vertebrale. Deși bifosfonatele sunt principalii agenți terapeutici utilizați în tratamentul OP la pacienții cu BTM, în unele cazuri răspunsul clinic este nesatisfăcător cu apariția de noi fracturi în timpul tratamentului; în aceste cazuri, afectarea formării osoase reprezintă probabil principalul mecanism al OP, justificând tratamentul anabolic.

Keywords: beta-thalassemia major, osteoporosis, anabolic therapy

Introduction

β-thalassemia (BT) is a hereditary autosomal recessive anaemia characterized by decreased/absent synthesis of β-globin chains [23, 26]. In BT, β-globin chain production ranges from near normal ((BT minor) to completely absent (BT major-BTM)). The defective synthesis of β-chains and the accumulation of α-chains lead to haemolysis and ineffective erythropoiesis with secondary anaemia and bone marrow expansion [23, 26]. Thalassemia is one of the most common genetic disorders, the worldwide prevalence of α and β-T trait is about 1.67% [26]. Bone changes are frequent in BTM and consist of diffuse bone pain, scoliosis, spinal deformities, nerve compression, spontaneous fractures, osteopenia and osteoporosis (OP) [23]. In spite of the adequate transfusion regimen and regular iron chelation therapy, the prevalence of osteoporosis varies from 13.6 to 50% with an additional 45% patients being affected by osteopenia [11, 35]. There are gender differences not only in the prevalence, but also in the severity of the osteoporosis, as males are more frequently and more severely affected than females [28]. The pathogenesis of osteoporosis in BTM is multifactorial and is related to endocrine complications, ineffective haemapoiesis with progressive bone marrow hyperplasia, iron toxicity on osteoblasts, direct toxic effect of desferrioxamine on bone growth, nutritional deficiencies [6, 23, 39], decreased physical activity and genetic factors [13]. Studies have showed that thalassaemic patients have an increased bone resorption phase and reduced bone formation resulting in low bone mineral density (BMD) despite normalisation of haemoglobin levels, adequate iron chelation and substitutive hormone replacement therapy [21]. Osteoporosis is a prominent cause of morbidity in BTM because of the increased risk for vertebral and
long bone fractures [40]. The early detection of bone disease, regular transfusions and adequate iron chelation therapy, calcium and vitamin D administration, physical activity, early identification of endocrine complications and hormone replacement therapy should be considered in every patient with BTM in order to prevent bone disease [28]. In the last decade, the use of bisphosphonates (BP) in BTM has been the mainstay of OP treatment as they are potent inhibitors of osteoclast activation and the central mechanism for bone loss in BTM patients is thought to be the enhanced bone resorption [11, 14]. Patients with BTM also exhibit a suppression of osteoblast activity with reduced bone formation markers. Therefore, some of the patients who are resistant to BP treatment could benefit from anabolic therapy with parathyroid hormone (PTH) [11, 34].

Pathogenesis of beta-thalassemia induced-osteoporosis and the risk of fracture

Osteoporosis is a frequent complication of beta-thalassemia major with an aetiology incompletely understood [3]. As a result of inappropriate haemoglobin levels and intermittent chelation therapy, patients with BTM present with several complications: chronic liver disease, cardiomyopathy from hemochromatosis and multiple endocrinopathies (delayed puberty, hypogonadotropic hypogonadism, insufficiency of the GH-IGF1 axis (growth hormone/insulin-like growth factor), hypothyroidism, parathyroid dysfunction, diabetes mellitus). All of these lead to osteopenia/osteoporosis by increasing osteoclast activity through activation of receptor activator of nuclear factor kappa B (RANK) ligand-osteoprotegerin (RANK-RANKL-OPG) pathway [11, 14] and impairing osteoblast function [3,7,13].

Hypogonadism is one of the major determinants of low bone mineral density (BMD) in BTM patients as testosterone has a direct stimulatory effect on osteoblast proliferation and differentiation [23].

IGF1 has a fundamental role in osteoblast differentiation, proliferation and function. Disturbances of the GH-IGF1 axis as a result of iron overload of different tissues (mainly anterior pituitary and liver) and infection with hepatitis C virus contributes to osteoporosis by decreasing bone formation and collagen synthesis [29].

Hypoparathyroidism is associated with low bone turnover which leads to higher bone mass compared to the age and sex-matched controls. Despite the increased bone mineral density seen on DXA (dual energy X-ray absorptiometry) scans, the skeletal microstructure is abnormal as showed by the bone histomorphometry study performed by Rubin et al. in patients with postsurgical hypoparathyroidism [9, 25]. Regarding the fracture risk in hypoparathyroid patients, there are only few studies that have addressed this issue. Mendonca et al. demonstrated that patients with postsurgical hypoparathyroidism have an increased prevalence of vertebral morpho-metric fracture [20]. On the other hand, Underbjerg et al. showed that patients with postsurgical hypoparathyroidism had a lower upper extremity fracture risk compared to controls [33]. Yet, this is insufficient data to draw a conclusion regarding the fracture risk in patients with hypoparathyroidism and other studies are needed.

Diabetes mellitus is associated with increased bone mineral density as well, but the studies performed in diabetic patients with osteoporosis demonstrated that the risk of fracture is high in this population because of the poor quality of the bone, abnormal micro- and macro-architecture and increased tendency to fall [15, 16]. Hyperglycaemia increases the production of interleukin-6, thereby stimulating osteoclast function and also stimulates calciuria leading to decreased serum calcium; the glycation of collagen impairs the bone quality in diabetic patients [15].

Chronic anaemia acting by enhancing the secretion of erythropoietin with consequent bone marrow expansion may be related to the increased bone resorption through RANK/RANKL/OPG pathway [23]. Vitamin D deficiency is also an important contributor to bone mass impairment. The recently published data regarding vitamin D status in the Romanian population revealed the fact that 97.5 % of the Romanian population has an inadequate intake with a median value of the daily intake of vitamin D of 67.31 IU, ten times less than the recommended dose [38].

The iron deposits in bone produce focal osteomalacia by incorporating iron in the crystals of hydroxyapatite and impairing mineralization [11, 23, 24]. On the other hand, desferrioxamine inhibits DNA synthesis, osteoblast proliferation and osteoblast precursor’s differentiation and increases osteoblast apoptosis [11, 23].

In conclusion, there are several factors implicated in the pathogenesis of OP in BTM patients, either by increasing bone resorption or impairing osteoblast function.

Treatment of major beta-thalassemia - induced osteoporosis

Early recognition of osteopenia and osteoporosis is very important as it may decrease the incidence of fractures, skeletal abnormalities, spinal deformsities and nerve compression. Improvement of haemoglobin levels by adequate transfusion regimen, effective iron chelation therapy, calcium and vitamin D administration during skeletal development,
encouraging physical activity and quitting smoking are the general recommendations for managing thalassemia-induced osteoporosis. Early identification and management of endocrine complications with adequate hormone replacement therapy and induction of puberty at a proper age are key points in the prevention of bone disease in patients with BTM [28, 35].

Bisphosphonates

The RANK/RANKL/OPG pathway has been recently recognised as the final mediator of osteoclast proliferation and activation [21]. Because of the proven increase of bone resorption markers in BTM, bisphosphonates have been used in the management of thalassemia-induced osteoporosis [11, 14]. Bisphosphonates are potent inhibitors of osteoclasts that act by inhibiting osteoclast recruitment and maturation, inducing osteoclast apoptosis and decreasing their attachment to the bone. Anti-resorptive therapy causes refilling of the remodelling space, an increase in secondary mineralisation and stabilisation of bone architecture, improving bone strength and thus reducing the incidence of fractures. Alendronate, neridronate and zoledronic acid seem to have the greatest efficacy in terms of increasing BMD and normalizing bone turnover markers, but there is still a lack of evidence that these agents are efficient in reducing fracture risk in BTM patients [8, 14, 18, 36, 39]. In addition, there is growing evidence that bisphosphonates could be useful for the treatment of osteoporosis in diabetic patients, increasing lumbar spine bone mineral density, even if there is no extra-suppression of resorption [22]. Further studies are needed to determine the efficacy of the therapy with bisphosphonates in diabetic BTM patients.

Other antiresorptive agents

Denosumab, a human monoclonal RANKL antibody was demonstrated to increase BMD density at both lumbar spine and femoral neck in patients with BTM [40], but long term effects of this therapy and its impact on fracture prevalence are issues that need to be clarified by further studies.

Anabolic therapy

Voskaridou et al. demonstrated that patients with BTM have increased serum levels of Dickkopf-1 (DKK1) and sclerostin [34, 37]. Dickkopf-1 is an inhibitor of the wingless-related integration site (Wnt) pathway, which is crucial for osteoblast differentiation and sclerostin is a molecule produced by osteocyte that inhibits the bone formation as well. Thus, bone formation is decreased in patients with BTM as a consequence of Wnt signalling disruption. This observation opened the possibility that anabolic therapy could have a role in alleviating osteoporosis in some patients with major beta-thalassemia.

I-CET 2013 Recommendations for Surveillance and Treatment of Osteoporosis in Thalassemia Major suggested that novel agents that stimulate bone formation, such as teriparatide, might be useful in the management of thalassemia-induced osteoporosis [11]. Teriparatide (hPTH 1-34) is a recombinant formulation of endogenous PTH, containing a 34 amino-acid sequence that is identical to the N-terminal end of the human parathyroid hormone [4]. Teriparatide has been shown to increase both the BMD and bone mass and improve bone microarchitecture of the skeleton, leading to improved bone strength and reduced incidence of vertebral and non-vertebral fractures in osteoporotic patients [10, 27]. Teriparatide treatment increases the bone turnover, in the first phase it stimulates the bone formation, and later stimulates bone turnover (both bone formation and resorption), generating the “anabolic window” [5, 27]. Parathyroid hormone therapy improves trabecular bone volume, connectivity and morphology. PTH increases cortical porosity and bone resorption in the inner endocortical surface of the bone while enhancing periosteal apposition and increasing the outer diameter of the bone, leading in the end to a better bone geometry with increased bone strength and decreased non-vertebral fracture risk, even though BMD remains unchanged or is reduced at cortical site [17, 27]. The bone formation induced by teriparatide is due to enhanced osteoblastogenesis with an increase in osteoblast differentiation rather than increased proliferation and decreased osteoblast apoptosis. It is mediated in part by a decrease in SOST/sclerostin (gene encoding sclerostin synthesis) expression in osteocyte. Also, PTH induces skeletal expression of IGF-1 that acts like a paracrine mediator for osteoblast differentiation [27]. Teriparatide is approved for treatment of osteoporosis in individuals with a high risk of fracture, including postmenopausal women, men with primary or secondary hypogonadism and osteoporosis, glucocorticoid-induced osteoporosis and in patients with contraindications/intolerance or lack of response to antiresorptive therapy. Taking into account the fact that more than 50% of patients with thalassemia major have primary or secondary hypogonadism after the age of 20 [30] leading to secondary osteoporosis and 13.5% of thalassaemic patients have hypoparathyroidism [1], some have raised the question about the efficacy of anabolic therapy in this specific population [35]. There are few data in the literature, mainly case reports [31, 32] regarding the efficacy of anabolic therapy in patients with BTM. Trotta et al. reported the efficacy of PTH 1-34 in a young thalassaemic female patient that showed
multiple vertebral fractures in spite of receiving antiresorptive therapy with alendronate. After 18 months of treatment with parathyroid hormone the patient showed a decrease in her spinal pain with an improvement of the quality of life and an increased lumbar and femoral neck T score on DXA measurements [32]. Tournis et al. reported [31] the response of a second trial of teriparatide in an adult male patient with thalassemia major and multiple vertebral fractures. After receiving the first trial of parathyroid hormone he suffered a fragility fracture while on alendronate treatment (left ischiopubic fracture) and they decided to try a second course of teriparatide that resulted in an increase in total hip and femoral neck BMD. These reports sustain the idea that long term studies are needed to address the issue of teriparatide use in osteoporotic patients with beta-thalassemia major, focusing especially on the anti-fracture risk in order to establish evidence based practice guidelines for the management of beta-thalassemia major-induced osteoporosis.

Patients with beta-thalassemia major and associated parathyroid gland dysfunction may respond better to anabolic therapy, as teriparatide has been successfully used to treat hypoparathyroidism in some clinical trials [2, 12, 25]. When teriparatide (PTH 1-34) or parathyroid hormone (PTH 1-84) were given to patients with hypoparathyroidism, the bone mineral density decreased to normal, but the bone micro-architecture improved leading to increased bone strength [25]. In spite of the reduction in bone mineral density, the risk of fracture may be decreased as an effect of the micro-architectural changes that could offer biomechanical advantages [25], but randomised clinical trials are needed to demonstrate this aspect.

Ideally, rhPTH should be given prior to BP, especially in patients with prevalent fragility fractures, because the bisphosphonates delay the response to teriparatide [2, 12]. Yet, it is difficult to perform this in every day practice as anabolic treatment is more expensive, the administration is parenteral and the anabolic therapy is reimbursed by the insurance companies under strict conditions. Observational studies suggest that BMD decreases more rapidly in patients that don't take anti-resorptive agents after the 2-year treatment with teriparatide, whereas BP therapy maintains or even increases the BMD gain [19]. Hence, sequential therapy with BP after cessation of teriparatide may be recommended in order to preserve the BMD gain, although the benefits in terms of fracture reduction have not been demonstrated yet.

**Conclusions**

Despite the improvement in the therapeutic approaches, the squeals of osteoporosis are a major cause of morbidity in BTM patients. A better understanding of the mechanisms leading to osteoporosis is of great importance for the management of these patients. Osteoporosis in BTM has a complex mechanism; both increase bone resorption and decrease its rate of formation. Although the bisphosphonates are the most used treatment for osteoporosis in BTM, in some patients, decreased bone formation is the predominant mechanism and teriparatide could be the most appropriate therapy. Patients with beta-thalassemia major-induced osteoporosis that suffer fragility fractures while on antiresorptive therapy and patients with associated hypoparathyroidism are those who will probably show most benefit from recombinant parathyroid hormone therapy.

The timing of the anabolic treatment is important as well, as therapy with teriparatide has been shown to be more efficient if it is administered before BP in patients with osteoporosis. Another key point is the fact that the anabolic therapy should be followed by antiresorptive agents in order to maintain the BMD increment.

**References**

35. Voskaridou E., Terpos E., Taher A., Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) [Internet]. 3rd edition, Chapter 10, Osteoporosis.
