**Bone Abnormalities in Β-Thalassemia Intermedia**

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**Submission**: February 20, 2017; **Published**: March 20, 2017

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**Keywords**: β-Thalassemia intermedia; Bone abnormalities; Osteoporosis

**Abbreviations**: β-TI: β-Thalassemia Intermedia; BMD: Bone Mineral Density; β-Tm: β-Thalassemia Major; IGF-1: Insulin-Like Growth Factor; NTx 1: N-Telopeptide Cross-Linked Collagen Type I; VDR: Vitamin D Receptor

**Perspective**

β-Thalassemia intermedia (β-TI) is a clinical condition of intermediate gravity between thalassemia minor, the asymptomatic carrier, and thalassemia major, the transfusion-dependent, severe anemia. These patients do not require lifelong regular transfusions, although they may need occasional transfusions in certain clinical settings and usually for defined periods of time (surgery, pregnancy, infection). It has a broad clinical spectrum, spanning from asymptomatic mild form with only a slight anaemia (Haemoglobin levels 70-100g/l) to a condition with more severe anaemia revealing itself in the early 2-6 years of life. Since these patients do not usually require routine transfusions, as mentioned above, β-TI has been classified as a non-transfusion-dependent thalassemia [1-3]. These patients require careful attention of the clinician, like thalassemia major, to improve the quality of life [4-7].

β-TI is associated with various complications including bone abnormalities. Three important factors are responsible for the clinical manifestation: ineffective erythropoiesis, chronic anaemia and iron overload. The severity of the disease primarily depends on molecular defects; considerably unstable α-chains precipitate inside erythroid progenitors leading to the deterioration of cell membrane and lysis of the cell (ineffective erythropoiesis). Medullary and extra-medullary hypertrophy of bone marrow, the result of a severe ineffective erythropoiesis, leads to the characteristic deformation of skull and facial bones, as well as cortical thinning and pathologic fractures of long bones.

Bone abnormalities in β-TI are very common, ranging from a decrease in the bone mineral density (BMD) and subsequent osteoporosis to spinal cord compression and increased frequencies of fractures. Bone abnormalities similar to those observed in β-thalassemia major (β-TM) are more severe due to enhanced ineffective erythropoiesis. The underlying causes of bone abnormalities are related to several factors including genetic factors, ineffective erythropoiesis, bone marrow expansion and iron overload [8-11]. Reduced BMD, 25-OH vitamin D deficiency and bone and joint pain complaints are common, and the prevalence of fractures in β-TI patients was reported to be 12% [12,13]. Calcium, Vitamin D and bisphosphonates are common therapeutic choices to improve BMD [14]. Most patients with β-TI have decreased levels of insulin-like growth factor 1 (IGF-1), which is a key factor in bone remodeling cycle, osteoclast stimulation, and osteoblast differentiation [15]. These patients are also observed to have an increased level of the osteoclast differentiation factor (RANKL) leading to decreased bone thickness, bone deformities, osteopenia, and fractures [16-18]. The increased levels of urinary N-telopeptide cross-linked collagen type I (NTx), as well as serum levels of Dickkopf-1 and sclerostin have been demonstrated to correlate with BMD, being good markers of bone resorption in patients with thalassemia [15,19,20]. Genetic factors have also been demonstrated to be involved in osteopenia and osteoporosis formation in these patients. A polymorphism at the recognition site for transcription factor Sp1 as well as Vitamin D receptor (VDR) polymorphisms are reportedly associated with the presence of osteoporosis [21,22].

β-TI patients have been reported to have a very high prevalence of osteoporosis (81.6%) and comparably lower incidence of osteopenia (8%) [23]. Osteoporosis is associated with a decrease in BMD and disruption of the bone architecture leading to an increased risk of fractures [24,25]. Increased bone resorption and decreased bone formation in β-TI patients have been associated with female gender, iron overload, low fetal...
hemoglobin levels and splenectomy [23,26-29]. Since these patients exhibit a higher rate of osteoporosis comparing to β-TM (22.6%), bone metabolism and abnormalities in β-TI require even closer scrutiny. More than 2/3 of the patients were observed to have a reduced BMD in the spine, femoral neck, distal radius and lumbar region [13,30]. β-TI patients receiving chelation and hydroxyurea therapy have been reported to have lower rates of osteoporosis [5]. Physical activity and daily exercise are also able to prevent bone complications by maintaining bone strength. However, despite all preventive measures, progressive bone disease and BMD loss in β-TI patients is inevitable over time [23,31-33].

The management of patients with β-TI should include a specific pharmacological agent complementary to general measures, to reduce fracture risk and prevent disability. General therapeutic measures including control of anemia, adequate chelation therapy, healthy nutrition and regular exercise are usually accompanied by vitamin D and calcium supplementation. With careful renal function monitoring, these supplements can improve BMD, although the efficacy and exact treatment regimen have not yet been defined [14,33,34].

Bisphosphonates, one of the pharmacological agents currently available for the management of osteoporosis, exhibited an improved BMD, reduced bone turnover, and decreased bone pain in patients with thalassemia-associated osteoporosis. These potent osteoclast inhibitors could achieve a safe and efficacious improve in BMD and reduction in bone complications and pain in both β-TM and β-TI [33,35-40]. Possible jaw necrosis associated with bisphosphonate therapy can be prevented by careful dental surveillance. Zoledronic, pamidronate and neridronate are the bisphosphonates with the strong evidences in thalassemia-related osteoporosis [35-40]. Despite the favorable results achieved, the long-term efficacy and outcome of bisphosphonates still need to be improved. Parathyroid hormone treatment, denosumab, teriparatide and otacacetate are alternative choices for the treatment of thalassemia-related osteoporosis needing more research and evaluation [41]. Fractures are less frequent in β-TI compared to β-TM, with the prevalence of metacarpal bones affected [42]. Approximately 12.2% of β-TI patients experience fractures increasing with age. A decreased BMD, lower lumbar bone mass, sex hormone replacement therapy, and hypogonadism are major risk factors for the development of fractures in β-TI [12].

Limited experience with pharmacological agents other than bisphosphonates and the complexity of β-TI presents diagnostic and therapeutic challenges and prevents a comprehensive and multidisciplinary approach.

References


