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Guideline

Guideline for Diagnosis and Treatment of Osteoporosis in Transfusion-Dependent Thalassemia Patients

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Abstract

The health-related quality of life and management of patients with thalassemia has significantly improved in recent years due to standard treatments and safe blood transfusions with effective chelation therapy to reduce iron overload. Transfusion-dependent thalassemia is associated with numerous skeletal abnormalities, including osteoporosis, which is a significant cause of morbidity in these patients. Osteoporosis is characterized by low bone mass and an increased risk of fractures, particularly in the lumbar spine and in patients with extramedullary hematopoiesis. It remains a significant problem in adult transfusion-dependent thalassemia, particularly in patients under chelation therapy. A fracture history is significantly associated with lower Dual-Energy X-ray Absorptiometry (DEXA) T/Z scores, which decrease with age. Improved management and modern treatments for transfusion-dependent thalassemia patients with osteoporosis should be prioritized to prevent bone fractures and improve quality of life in older age.

1. INTRODUCTION

Beta-thalassemia major, or Cooley's anemia, is the most severe form of this syndrome (1). It is characterized by a severe lack of beta protein in hemoglobin, which can be life-threatening and requires frequent blood transfusions and extensive treatment of complications (2). This condition is also associated with several complications, including bone deformities, iron overload, enlarged spleens, growth retardation, immune system disorders, liver disease, and heart failure due to iron accumulation in the body that leads to an increase in reactive oxygen species (ROS) production, which can cause cell death, fibrosis, and cause various endocrine complications (3-6).

Patients with blood transfusion-dependent thalassemia are prone to different skeletal complications such as spinal

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deformities, fractures, osteopenia, and osteoporosis (7, 8). In osteoporosis, bone mineral density decreases, the bone structure becomes fragile, and the amount of non-collagenous bone proteins changes. These changes increase bone fragility and the risk of fractures even without significant trauma (9-12). Various factors such as anemia, ineffective erythropoiesis, iron overload, iron chelator toxicity, bone marrow expansion, vitamin D deficiency, liver dysfunction and cirrhosis, hypogonadism, defective growth hormone -insulin like growth factor-1 axis, hypothyroidism, hypoparathyroidism, diabetes, and growth hormone deficiency play a role in thalassemia-related osteoporosis pathogenesis (13-16). Osteoporosis in thalassemia arises from an imbalance in bone turnover, where there is an excessive bone resorption compared to bone formation (17). In recent decades, the life expectancy of thalassemia patients has increased due to advances in treatment (18). This has caused osteopenia and osteoporosis to manifest more as a significant cause of morbidity in these patients (17). The prevalence of osteoporosis in various studies has been reported to be between 13.6-50%. A study conducted in Iran in 2014 revealed that the prevalence of osteoporosis in a population of blood transfusion-dependent thalassemia with a mean age of 29±8 years is 65.6% (19).

Given the high prevalence of thalassemia-related osteoporosis in Iran and the burden resulting from the complications of this disease on the individual and the health system, developing a national protocol to prevent the advancement of this disease, early diagnosis, and timely treatment is necessary.

2. METHODS AND MATERIALS

Designing a guideline for osteoporosis in transfusion-dependent thalassemia involves a systematic process consisting of several steps. Firstly, a committee was formed, comprising experienced individuals in the field of treating thalassemia and osteoporosis in these patients, to develop the guideline. This committee, consisting of clinicians, researchers, and patient advocates, brought diverse expertise and perspectives to ensure the guideline's development was evidence-based, relevant, and practical. They followed a clear charter and terms of reference, outlining their roles, responsibilities, and scope of work. Regular meetings were held to review available evidence, discuss recommendations, and incorporate feedback from stakeholders, including patients and their families, to create a comprehensive and relevant guideline.

A literature review was conducted to gather information on osteoporosis in transfusion-dependent thalassemia, encompassing epidemiology, risk factors, diagnosis, treatment, and outcomes. This comprehensive review served as a foundation for the guideline development process. Analyzing the available evidence was crucial for the committee to identify areas of consensus and controversy, taking into account the local context such as country-specific epidemiology, healthcare system, and patient population.

Based on the evidence, the committee developed evidence-based recommendations for diagnosing, treating, and managing osteoporosis in transfusion-dependent thalassemia. To ensure the guideline's relevance and currency, it underwent periodic review and revision, incorporating new evidence and best practices.

Finally, the guideline was widely disseminated to healthcare professionals, patients, and other stakeholders to facilitate its effective implementation

3. DIAGNOSTIC CRITERIA FOR OSTEOPOROSIS BASED ON AGE

3.1. In patients over 50 years old

Figure 1 illustrate the criteria for diagnosis of osteoporosis in patients over 50 years with TDT (20).

World Health Organization Criteria for Classification of Osteopenia and Osteoporosis	
Category	T- score
Normal	–1.0 or above
Low bone mass (osteopenia)	Between –1.0 and –2.5
Osteoporosis	• –2.5 or below Or Low-trauma spine Hip fracture (regardless of BMD) • Osteopenia or Low bone mass (T-score between –1 and –2.5) with a fragility fracture of proximal humerus, pelvis, or possibly distal forearm • Low bone mass or osteopenia and high fracture risk assessment tool

Figure 1. Criteria for diagnosis of osteoporosis in patients over 50 years with TDT.

3.2. Patients under 50 years old

The criteria for diagnosis of osteoporosis in patients less than 50 years old is low bone mass (bone density Z- score ≥ 2 SD below the expected range for age (21).

4. PRIMARY SCREENING, DIAGNOSIS, AND PREVENTION PRINCIPLES

1. It is recommended to start screening blood transfusion-dependent thalassemia patients for decreased bone density from age ten (22, 23).

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2. Screening includes conducting bone mineral density (BMD) for every two years, and vertebral fracture assessment (VFA) for every two years (24, 25).

3. If the examinations yield normal results during the screening program, it is important to continue the program and recommend principles of osteoporosis prevention to the patient. These principles include regular exercise, quitting smoking, following standard iron chelation therapy, maintaining hemoglobin (Hb) levels above 9g/dl, consuming vitamin D and calcium supplements as directed in **Figure 2**, and undergoing routine screening for conditions such as hypogonadism, hypothyroidism, hypoparathyroidism, and diabetes. Proper control measures should be implemented if abnormal results are observed (26-28).

Recommended doses of calcium and vitamin D intake by age

Age (years)	Ca (mg/day)	Vit D (IU/day)
9-18	1300	200
19-50	1000	200
51-70	• 1ooo (male) • 1200(female)	400
≥71	1200	600

Figure 2. *Daily Recommended dose of calcium and vitamin D according to age*

4. If the patient meets the diagnostic criteria for osteoporosis based on the definitions, the following tests should be performed: calcium, phosphorus, and ferritin levels; vitamin D assessment; measurement of parathyroid hormone (PTH) levels; complete blood count with differential (CBC-diff), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR); thyroid-stimulating hormone (TSH) test; fasting blood sugar (FBS) measurement; evaluation of creatinine, serum glutamic-oxaloacetic transaminase (SGOT), and serum glutamic-pyruvic transaminase (SGPT) levels; testing for Anti-Endomesial Antibodies (EMA); and referral to an endocrinologist if secondary sexual characteristics do not appear in boys over 14 years old and girls over 13 years old (29-31).

5. Patients who are candidates for treatment initiation should be referred to a pediatric/adult endocrinologist.

6. It is crucial to evaluate patients for bone mineral density using a consistent measurement method and device to ensure comparable results (32, 33). This is important for accurate diagnosis and treatment planning. Using a consistent density measurement method and device is essential to ensure comparable results when evaluating patients for bone mineral density (34). This helps to provide accurate and reliable information for diagnosis and treatment. However, it is also essential to consider the limitations and potential sources of error associated with each measurement method and device. For example, different devices may use different algorithms to calculate bone mineral density, affecting the results. Therefore, choosing the appropriate measurement method and device based on the specific clinical context and patient population is essential, and using standardized protocols and guidelines ensures accurate and reliable results.

5. PRINCIPLES OF TREATMENT AND FOLLOW-UP

1. Appropriate treatment for underlying disorders.

2. All patients should consume adequate iron chelation (35).

3. In patients with hypogonadism, treatment with testosterone (for men) and estrogen (for women) should be started with the opinion of a pediatric/adult endocrinologist (16, 36-38).

4. All patients should receive 500-1000 mg of elemental calcium and 400-800 IU of vitamin D daily (39).

5. Patients diagnosed with osteoporosis should be treated with one of the following medications. Alendronate 70 mg weekly is a recommended option. If oral alendronate is prescribed, patients should be advised to take the medication on an empty stomach and maintain an upright position (standing or sitting) for 30 minutes after intake (40, 41). In cases where patients are intolerant to oral medications or have a history of fractures or low bone mineral density (Z-score <-3 SD), injectable treatments may be considered. Injectable options include zoledronic acid 4mg intravenous (IV) administered every 3-6 months, pamidronate 30 mg per month, or denosumab 60 mg every 6 months (42-44).

6. Bisphosphonate treatment should continue for 2-3 years (45). Moreover, the use of bisphosphonates is not recommended in women planning pregnancy (46).

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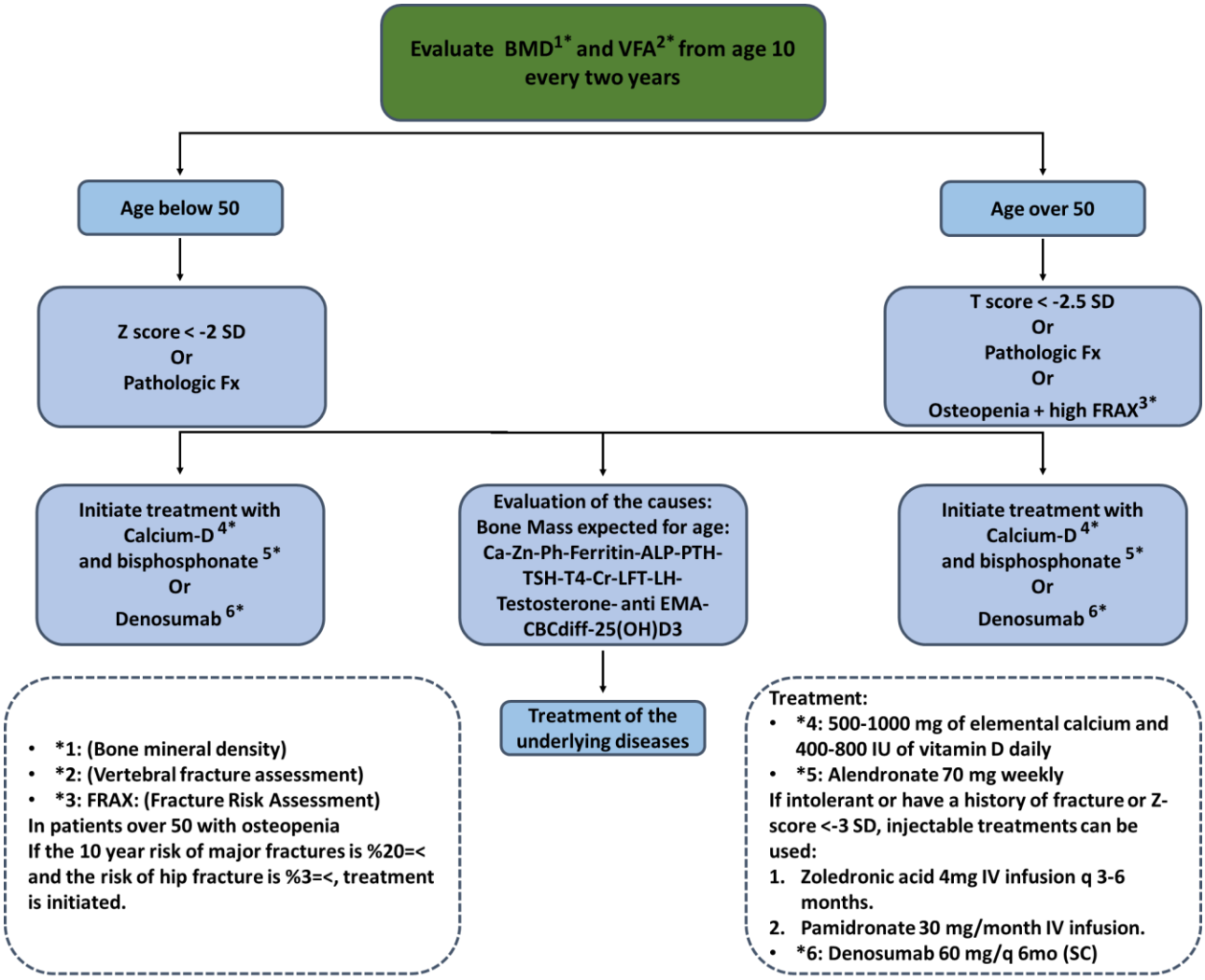

Figure 3. Approach to osteoporosis in TDT.

7. After completion of treatment, screening with BMD should continue annually (47).

8. The daily recommended calcium and vitamin D dose varies depending on age. It is essential to consult with a healthcare professional to determine the appropriate dose for your individual needs (48, 49).

Even with consistent adherence to transfusion, appropriate sex hormone replacement, and chelation therapy, individuals diagnosed with thalassemia major (TM) display an imbalance in bone turnover. This imbalance is characterized by an elevated resorptive phase that is not effectively balanced by a corresponding neoformation rate. As a result, there is a reduction in bone mineral density (BMD), particularly noticeable at the vertebral level, where trabecular bone is predominantly located (50, 51).

6. CHARACTERISTICS OF COMPETENT PHYSICIANS APPROVED FOR THALASSEMIA TREATMENT AND INTRODUCED BY MEDICAL UNIVERSITIES TO PRESCRIBE AND PROVIDE SERVICES

- Pediatric/adult hematology and oncology subspecialists
- Pediatric/adult endocrinology subspecialist
- Pediatric specialist
- Internal medicine specialist
- General practitioner

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7. CONCLUSION

Patients with thalassemia are at increased risk of developing osteoporosis due to a combination of factors, including chronic anemia, excessive iron overload, chronic transfusions, and poor nutrition. These factors can lead to decreased bone density and increased risk of fractures, particularly in the spine, hips, and legs. Osteoporosis in thalassemia patients can significantly impact their quality of life, including decreased mobility, pain, and reduced independence. Poor nutrition can also contribute to osteoporosis in thalassemia patients as a calcium and vitamin D measurement deficiency, which is essential in diagnosing and treating osteoporosis in thalassemia patients. Therefore, early detection and management of osteoporosis is critical in this patient population. Treatment of osteoporosis in thalassemia patients may include lifestyle modifications, such as dietary changes and exercise, as well as medications, such as bisphosphonates or denosumab. It is essential to consult with a healthcare professional to determine the appropriate treatment plan for each patient.

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Conflict of interest

The Authors declare no conflict of interest for any financial or personal relationships that could potentially bias work or influence the recommendations provided in the guidelines.

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