

Evaluation of alendronate efficacy on bone mineral density in thalassemic patients

Fatemeh Shirani¹, Mahin lashkari¹, Ali Shahriari Ahmadi¹, Mohsen Arabi², Nastaran Asefi³

¹Rheumatology Department of Rasoul-e Akram Hospital, Tehran University Of medical sciences, Tehran, Iran

²Hematology-Oncology department, Rasoul-e Akram Hospital, Tehran University Of medical sciences, Tehran, Iran

³Radiology Department of sina Hospital Tehran University Of medical sciences, Tehran, Iran

Corresponding author: Mohsen Arabi, MD, Hematology-Oncology department, Rasoul-e Akram Hospital, Tehran University Of medical sciences, Tehran, Iran

Email: Arabimohsen@yahoo.com

Tel: 021 66903653

Abstract

Introduction: Thalassemia is the most common genetic disorder, affecting around 200 million people worldwide. The etiology of this bone disease is multifactorial. Seemingly, in the setting of increased bone turnover which manifests by increased bone resorption and remodeling; bone density decreases. In this research, thalassaemia patients with osteoporosis were placed on oral alendronate therapy for one year and their pre-and post-study bone mineral densitometry were compared.

Method: Thalassaemia patients, comprising the major and intermedia types, in the range of 20 to 50 years old were included in the study. They were admitted to three different centers: Tehran Center of Thalassaemia, Iranian Blood Transfusion Organization and the Rheumatology Clinic of Rasool Akram(s) Hospital. First of all, osteoporotic patients diagnosed on the basis of densitometry were placed on oral regimen of 10mg of alendronate daily. After a year, their densitometries were repeated and compared for the changes in BMD(g/cm²) and T-score. Also, patient's serum calcium, phosphorus and alkaline phosphatase levels were measured at the beginning and the end of the year and the results were compared.

Results: Ninety-six of 120 patients who underwent first and second bone density measurements showed an increase in BMD and T-score at the end of the study. BMD increased in patients who used their drugs regularly, while no increased BMD was found in patients who used drugs irregularly or essentially did not use any drug.

Conclusion: we concluded that bisphosphonates like alendronate are highly effective at improving bone density of neck of femur and vertebral bones without having dangerous side effects. So, early diagnosis, treatment and prophylaxis of osteoporosis in this group of patients are highly recommended

Key word: Thalassaemia, Osteoporosis, BMD, Alendronate

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Introduction

Thalassemia is an inherited anemia in which production of polypeptide chains is disturbed, leading to decline in hemoglobin (Hg) synthesis and make anemia that in α and β thalassemia there is disorder in α and β chains.

Since Hg is responsible for carrying oxygen to the tissues, various symptoms of this disease are subsequently created the anemia. This disease observed in immigrants to the United States like Italians was first introduced in 1925 by a physician called Thomas Koly. Thalssa means the sea and hemia is the synonym of anemia [1, 2].

Prevalence of genetic disorder of thalassemia is more in American and Asian regions and in Northern Province of Iran. About 4% of the populations in Iran are carriers of a thalassemia gene.

Thalassemia shows various symptoms in different organs; bone lesions, hormonal disorders like hypogonadism, hypothyroidism, hypothyroidism, hepatomegaly, splenomegaly and changes in the personal appearance are some of these symptoms [3, 4].

One of the symptoms of this disease is osteoporosis which is preventable and curable with proper diagnosis by bone mineral

densitometry (BMD). Treatment of osteoporosis in these patients includes exercise, consumption of calcium (Ca 1200 mg daily, vitamin D 400 U daily), sexual hormone replacement, adequate treatment with desferal since childhood and using bisphosphonates like alendronate [5, 6]. In one study about osteoporosis on 25 patients with major thalassemia in Italy, alendronate 10 mg/d showed acceptable outcome after two years [7]. In another study on 26 thalassemic patients in Greece, pamidronate IV showed considerable changes in BMD after one year and bone markers also changed [8].

Materials and methods

This study was performed on patients with major and intermediate thalassemia (age range of 20-50 years). Patients who were referred to the Thalassemia Outpatient Clinic of Tehran Center of Thalassemia, Iranian Blood Transfusion Organization and the Rheumatology Clinic of Rasool Akram Hospital were enrolled into the study.

At the beginning, bone density of lumbar vertebrae L2-L4 and neck of femur were measured using densitometry system (DXA), Norland type in all the participants were repeated after one year treatment with alendronate, then T-Score of Ap spine and neck of femur was evaluated. Serum levels of ferritin, calcium, phosphor, alkaline phosphatase were also measured at the beginning and one year after use of alendronate 10 mg.

Patients received alendronate 10 mg/d (Modava Co., Iran), calcium 100 mg/d (Darupakhsh Co., Iran) and vitamin D 400 U (two Ca-D tablets daily). All the patients were visited at 1, 3, 6, 9 and 12 months. Accurate consumption of drugs and their side effects were asked from the participants and were registered in the questionnaire.

Consumption of the drug was recorded in three ways:

- 1- Non- use: alendronate was discontinued in weeks 1-4 and then was never used.
- 2- Irregular use: less than 70 mg (7 tablets) in a week
- 3- Regular use: at least 70 mg in a week.

In cases of incorrect use of the drug or considerable gastrointestinal complications like

gastric ulcer or gastritis, patients were taken apart. BMD was performed at the beginning and one year after treatment. Changes more than 3% in the spine and 6% in the neck of femur were considered as significant.

Statistical analysis

Results were reported as mean \pm standard deviation (SD) for quantitative variables and percentages for categorical variables. Initial and final values of each variable were compared using paired T test. Statistical significance was based on two-sided design-based tests evaluated at the 0.05 level of significance. All the statistical analyses were performed using SPSS version 16 (SPSS Inc, Chicago, IL, USA) for Windows.

Results

A total number of 120 thalassemic patients, consisted of 59 (49.2%), males and 61(50.8%) females, with a mean age of 33 (range, 20-50 years) were enrolled into the study. Twenty-seven (64.2%) patients had major thalassemia, while 43 (35.8%) had intermediate type.

Among all the participants, 96 patients completed both initial and final BMD, 14 cases were excluded because of incorrect drug use or drug side effects and one patient died due to complications of the disease.

The mean initial T-score of the femur was -2.87 ± 0.94 and its secondary average (after one year) was -2.23 ± 1.01 . A Paired-T test showed a significant difference between pre-and post-T scores ($p < 0.001$).

The mean T-score of the spine was -2.91 ± 0.73 at the initial of the study, but in the second measurement it changed significantly to the average of -2.32 ± 0.66 ($P < 0.01$).

The mean value of BMD (gr/cm^2) in the lumbar spine was 0.682 ± 0.108 in the first session and then increased to the 0.773 ± 0.11 . This increase was associated with the regular drug consumption, showing more than 3 % increase in 79 (95.2%) out of 83 patients and 4.85% decrease in 4 other patients.

In the group with irregular drug use, 3 patients (60%) had considerable increase, while 2 others (40%) had a decrease in the bone density (Table 1).

A considerable increase was not seen in 13 (13.5%) patients; among them 7 consumed drug

irregularly. In the group with noticeable increase in BMD, 72 (95.2%) patients used drug regularly and 3 ones consumed it irregularly which implies the significant association between regular drug use and increase in the BMD ($P<0.01$).

Table 1. Association between use of alendronate and BMD changes in the spine.

BMD changes	Irregular use	Non-use	Regular use	Total
Decrease <3%	2 (40%)	7 (100%)	4 (4.8%)	13 (13.5%)
Increase >3%	3 (60%)	0 (0%)	79 (95.2%)	83 (86.5%)
Total	5 (100%)	7 (100%)	83 (100%)	96 (100%)

The mean values of BMD (gr/cm²) in femur were 0.099 ± 0.682 and 0.11 ± 0.750 in the first and second sessions, respectively. This increase was associated with regular drug use in these patients. In 83 cases with regular drug use, 57 (68.7%) showed a considerable increase more than 6% and in 26 (31.3%) a decrease in this value was found. In 5 patients with irregular drug consumption, only one case (20%) showed a considerable increase, while 4 other patients (80%) had a decrease in bone densitometry (Table 2).

Table 2. Association between use of alendronate and BMD changes in the femur.

BMD changes	Irregular use	Non-use	Regular use	Total
Decrease <6%	4 (80%)	7 (100%)	26 (31.3%)	38 (39.6%)
Increase >6%	1 (20%)	0 (0%)	57 (68.7%)	58 (60.4%)
Total	5 (100%)	7 (100%)	83 (100%)	96 (100%)

Regarding calcium serum level, 95.8% (92) of the patients had normal level (8-10 mg/dl), 1-2% (2) had less than 8 mg/dl and in 2 others it was more than 10 mg/dl, showing no significant association between consumption of alendronate and calcium serum level ($P=0.229$). Sixty-three (65.6%) of the patients had normal phosphor serum level (3.5-5 mg/dl), while 33 (34.4%) had an increase in this value. No significant relationship between increase in phosphor serum level and drug consumption was found.

Regarding ALP serum levels with the normal range of 150- 300, 89.6% (86) of patients were normal, 1% (1) was less than normal and 9.4%

(9) were upper than its normal range, showing no statistically significant association with drug use ($P=0.986$)

Discussion

Considering the fact that thalassemic patients are prone to osteoporosis and several factors like bone marrow extension, iron concentration, genetic factors and decline in sexual hormones are effective on it [3, 4]; screening of these patients, as well as finding their osteoporosis with various diagnostic techniques are necessary, so the best method is using DXA system for evaluating bone density [1, 2]. In patients less than 30 years of age, Z-scores of spine and femoral neck should be used. In this study, T-score of spine and femur was measured. However, other methods like sonography are also used for bone density measurement. In one study a comparison of DXA system and ultrasound for measuring of bone density showed that ultrasound is weaker than DXA system for bone densitometry [9].

Adequate treatment of the thalassemia since early childhood can decrease the incidence of osteoporosis. A study on 35 young thalassemic patients (5-20 years) with appropriate treatment showed that they had normal Z-score compared to the control group [6]. A 2007 study in Iran conducted by pediatric hematology group on 203 thalassemic patients (10-20 years old), the prevalence of osteoporosis was found 7.5% in spine, 10.8% in femur and 7.9% in both. Factors affecting osteoporosis risk in patients involved in the study were height, weight, delay in puberty or hypogonadism, age at the beginning of desferal use as well as its duration and serum level of zinc [10]. The results of the study conducted in 2008 revealed that patients treated with zoledronic acid for 2 years had significantly better bone density [11].

In a study conducted in Athens (2006) and Lykone general Hospital, 66 thalassemic patients with osteoporosis were divided into three groups; 23 patients in group A that received zoledronic acid 4 mg/IV each 6 months, 21 patients in group B that received zoledronic acid 4 mg/IV each 3 months and 22 patients in group G that received placebo each 3 months. This study last for one year in which bone density of lumbar spine, neck of femur and waist of hand, pain and markers of bone resorption (Telopeptide collagen type I),

markers of bone formation (alkaline phosphatase) TRAP isoform b as well as osteocalcin and osteoclast stimulators (Osteopontin, osteoprotegrine) were evaluated before and after treatment protocol. All markers of bone formation and resorption and osteoclast stimulators were considerably high before the study. After treatment, bone density of group A remained constant, but bone pain, bone formation markers and osteoclast stimulators were decreased. In group B, there was a considerable increase in bone density of lumbar vertebra with decrease in bone pain and markers for bone formation, resorption and osteoclast stimulators. Patients in group G had no difference in bone density or bone pain, and showed an increase in bone resorption.

In a study conducted at University of Messina (2002), 25 patients with major thalassemia were randomly divided into groups which received placebo, clodronate 100 mg/IM each 10 days or alendronate 10 mg/d. All patients received calcium 500 mg and colecalciferolo 400 U with their night food. After 2 years of follow-up, bone resorption markers in the group with placebo did not change, but in those groups who were under treatment with clodronate and alendronate these markers were considerably decreased. Osteocalcin and bone formation markers did not show any difference in the placebo group before and after the treatment, while in other two groups they decreased a little but not significantly. At the end of the study, BMD of lumbar spine in the placebo group decreased, in clodronate group did not show a noticeable change, while in the alendronate group increased but not significantly. BMD of femoral neck decreased in the placebo group did not change in the clodronate group, but increased significantly in the alendronate group. During this study, no drug side effect was reported and finally it was concluded that in thalassemic patients alendronate can effectively increase BMD [7].

In a study conducted in Greece (2004), 26 thalassemic patients with osteoporosis received pamidronate/IV 30-60 mg for 12 months. BMD, osteoclast function markers including soluble receptor activator of nuclear factors Kappa-B ligands (SRANKL), osteoprotegrine (OPG), bone remodeling, N terminal telopeptide collagen type I (NTx), tartrate-

resistant acid phosphatase-sb (TRACP-sb), bone alkaline phosphatase (ALP-b) and osteocalcin (OC) were then measured. Thirty healthy people were selected as a control group in this study. NTX, TRACP-sb, ALP-b and OC were considerably higher in thalassemic patients compared to the control group, but OPG was lower and SRANKL was in the normal range. After completion of the study, NTX, TRACP-sb, OPG and OC decreased in thalassemic patients and BMD of lumbar spine significantly increased [8].

In our study, thalassemic patients with osteoporosis diagnosed by BMD underwent oral alendronate 70 mg/week. At the beginning and after one year of treatment with alendronate, BMD was performed (neck of femur, L2-L4). At the end of the study, BMD of femur and spine increased significantly in the group with regular drug use. There was a significant association between regular drug use and increase in T-score and BMD ($P < 0.001$).

Patients who did not have an increase in BMD were among those who had a history of irregular drug use, discontinuing of drug because of gastrointestinal complications and low compliance. In this study, we used oral bisphosphonates approved by FDA for the treatment of osteoporosis for they are produced in the country and affordable to patients. Evaluation of bone resorption and formation markers (except ALP) are used as treatment monitoring in some studies which were not easily accessible in our country, so in this study we used the BMD to monitor markers of bone resorption and formation.

One-hundred and twenty thalassemic patients were recruited in the present study, but only 96 completed the second BMD.

In this study, the rate of fractures was not evaluated. Further studies with attention to risk of fractures in thalassemia patients are needed.

There is a limitation in the diagnosis of osteoporosis because all densitometry systems are not able to measure BMD in patients less than 20 years, so diagnosis of osteoporosis in thalassemic patients whose problem begins at childhood is hard, but in these patients diagnosis, prevention and treatment should always be borne.

Conclusion

Regarding the BMD increase in patients who used their drugs regularly and no increase in patients who used drugs irregularly or essentially did not use any drugs, we concluded that the role of bisphosphonates in increasing bone density and decreasing risk of fractures in neck of femur, vertebral and non-vertebral bones were remarkable without having dangerous side effects. So, early diagnosis, treatment and prophylaxis of osteoporosis in this group of patients are highly recommended.

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