Prevalence of Osteoporosis among Thalassemia Patients from Zafar Adult Thalassemia Clinic, Iran

Hashemieh M¹, Azarkeivan A²*, Radfar M³, Saneifard H⁴, Hosseini-Zijoud SM⁵, Noghabaei G⁶, Yaseri M⁷

1. Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Research Center of Iranian blood Transfusion Organization, Thalassemia Clinic, Tehran, Iran.
3. Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
4. Mofid Childrens’ Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
5. Hamadan University of Medical Sciences, Hamadan, Iran.
6. Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
7. Department of Epidemiology and Biostatistics, Tehran University of Medical Sciences, Tehran, Iran.

*Corresponding Author: Azarkeivan A, Email: azazarkeivan@yahoo.com

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Abstract

Background: The advances in treatment regimes for thalassemic patients have increased the survival among them; therefore osteoporosis has emerged as an important cause of morbidity. The aim of this study was to determine the prevalence of osteoporosis and osteopenia in patients with thalassemia from Zafar Adult Thalassemia Clinic, Tehran, Iran.

Patients and Methods: In this cross sectional investigation, we studied 239 patients with β thalassemia major and 87 patients with thalassemia intermedia with a mean age of 29±8 years. All demographic data including age, weight, height, sex, age at diagnosis, age at blood transfusion initiation, chelating agent therapy and serum ferritin level were obtained from patients’ history. Bone mineral density of the lumbar spine (L1-L4) and femoral neck was determined using dual-energy X-ray absorptiometry (DEXA).

Results: The prevalence of osteoporosis was 65.6% (214 out of 326 patients). Osteoporosis was present in 10.7%, 11% and 43.9% of patients in the lumbar spine alone (L1-L4), femoral neck alone and both places, respectively. In the rest of patients 18.7% showed osteopenia and only 15.7% were normal. Osteoporosis was more prevalent in patients with thalassemia intermedia compared to thalassemia major (p<0.001). Also higher age of patients, longer duration of transfusion and longer intervals between transfusions had a positive correlation with osteoporosis.

Conclusion: The prevalence of osteoporosis among Iranian thalassemia patients is similar to prevalence reported elsewhere. Bone Mineral density is a good index of bone status in patients with thalassemia and recommended to be done for thalassemic patients annually.

Key words: Thalassemia, bone mineral density, osteoporosis, DEXA.

Introduction

Thalassemia is a group of inherited disorders of hemoglobin synthesis, and is the most common monogenetic disease worldwide ¹. In β thalassemia, mutations of the β globin gene lead to an imbalance in globin chain synthesis and ineffective erythropoiesis. The low number of mature red blood cells leads to anemia and other associated health problems ¹. Patients with beta-thalassemia major are susceptible to osteopenia and osteoporosis due to several factors which interfere with bone remodeling. Delay in sexual maturation, presence of diabetes and hypothyroidism, accelerated hemopoiesis with progressive marrow expansion and direct iron toxicity have been identified as major causes of osteoporosis in thalassemic patients ². Reduced bone mass, skeletal pain and fractures are common causes of morbidity and disability among patients with homozygous β thalassemia. Bone abnormalities, such as spinal deformities, scoliosis, nerve compression, spontaneous fractures, osteopenia and osteoporosis have also been described in patients with thalassemia ³.

Over the past three decades, management of patients with thalassemia has improved
dramatically with hypertransfusion therapy, which
has nearly normalized pre-transfusion hemoglobin
levels, reduced the ineffective erythropoietic
process and prevented bone deformities. Iron
chelation using prolonged subcutaneous infusions
of desferrioxamine, has also improved the survival
and diminished the endocrine complications of
transfusional hemochromatosis. As treatment
with transfusion programs and chelation therapy
has significantly prolonged the survival in
thalassemia patients, osteopenia and osteoporosis
represent prominent causes of morbidity in young
adults of both genders with thalassemia major or
thalassemia intermedia.

During the last decade, many studies have
shown low bone mass in adult patients with
thalassemia. Bone mass is the result of a
balance between bone formations gained during
growth and the subsequent bone loss. According
to the World Health Organization, osteoporosis
is a disease characterized by low bone mass
and microarchitectural deterioration of bone
tissue, leading to enhanced bone fragility and a
consequential increase in fracture risk. Thalassemic patients show a variety of bone
disorders including bone pain, bone deformity,
growth failure, rickets, scoliosis, spinal deformities,
pathologic fracture, osteopenia and osteoporosis.
In a large study, adult thalassemia major patients
presented a 51% prevalence of osteoporosis and
45% prevalence of osteopenia.

Several sensitive techniques are available for
the quantitative assessment of the degree of
total bone mass. Bone mineral density (BMD)
measurement by dual X-ray absorptiometry (DEXA)
of the lumbar spine, femoral neck and forearm is
recommended as one of the most reliable and
non-invasive techniques for the assessment of
bone mass. DEXA is an excellent non-invasive
choice for repeated measurements of any temporal
changes of BMD because of its 1% precision rate
and low radiation exposure. As shown in previous
works by other authors in thalassemic population,
the lumbar spine and femoral neck BMD is below
the normal reference.

Earlier studies of bone mineral metabolism in
thalassemic patients have mainly concentrated on
the pediatric and adolescence age groups. As
mentioned, osteoporosis and osteopenia is common
even in well-treated thalassemic patients. There
were more than 13,000 thalassemic patients in Iran
at 2007, but the current frequency of osteopenia
and osteoporosis in various thalassemia syndromes
has not been well assessed in Iran.

In the present study Data from the Zafar Adult
Thalassemia Clinic, Tehran, Iran, were analyzed to
determine the current prevalence of osteopenia
and osteoporosis among thalassemic patients.

Materials and Methods

Patients
A total of 326 patients with beta-thalassemia
attending the Zafar Adult Thalassemia Clinic in
Tehran (239 thalassemia major, 87 thalassemia
intermedia) from June 2012 to April 2013 were
enrolled in this study. They had a mean age of
29 ± 8 years (range 12–52 years) with an average
body mass index (BMI) of 20.18±2.96 (Table 1). All
patients were examined by one hematologist and
one endocrinologist.

For this study, beta-thalassemia major (TM)
was defined as homozygous or compound
heterozygous beta-thalassemia requiring eight
or more transfusions in the 12 months prior to
enrolling in the registry. Thalassemia intermedia
(TI) was defined as beta-thalassemia receiving less
than 8 units per year. All TM patients were receiving
regular transfusions from the age of 2 years. History
of chelation and transfusion therapy, initiation and
duration of blood transfusion, pre-transfusion
hemoglobin, ferritin values and desferrioxamine
(DFO) dosage in the last year were obtained from
the patients’ medical records. None of the patients
or controls was treated with vitamin D or calcium
supplements. Characteristics of study group are
shown in table 1.

The study was performed according to the
principles of the Declaration of Helsinki and was
approved by the ethic committee of the Shahid
Beheshti University of Medical Sciences, Tehran,
Iran. Each subject above 18 years old or the
patient’s parent or guardian for patients under 18
years old gave written consent before patient being
included in this study.

Bone mineral density (BMD)
In all patients, BMD was determined using dual
X-ray absorptiometry (DEXA, Lunar DPX-Plus), both
at the lumbar spine (L1–L4) in A-P projection and at
the femoral neck.
The instrument was calibrated on a daily basis according to the manufacturer’s instructions. Reproducibility was calculated as a CV obtained by weekly measurements of a standard phantom on the instrument and by repeated measurements obtained in three patients of different ages. The CV of our instrument was 0.5% with the standard phantom; and in vivo, we calculated a CV of 1.1% for

| Table 1: Demographic findings of patients with thalassemia major and thalassemia intermediate. |
|-----------------|-----------------|-----------------|
| Age (Mean ± SD) | 29 ± 8           | 27 ± 6          | 35 ± 8          |
| Age (Median)    | 28 (12 to 52)   | 27 (12 to 49)  | 34 (14 to 52)  |
| Sex             | Male 163 (50.0%)| Female 163 (50.0%) |
| Age at Diagnosis (Mean ± SD) | 3.2 ± 5.3 | 1.8 ± 2.6 | 7.3 ± 8.1 |
| Age at the start of Transfusion (Mean ± SD) | 3.5 ± 5.6 | 2.2 ± 3.6 | 7.9 ± 8.2 |
| Transfusion Interval (days) (Mean ± SD) | 29 ± 28 | 24 ± 14 | 45 ± 48 |
| Duration of Transfusion (years) (Mean ± SD) | 25 ± 7 | 25 ± 6 | 36 ± 9 |
| Splenectomy     | Yes 195 (59.8%) | No 131 (40.2%) |
| Use of Desferal | Yes 281 (86.2%) | No 34 (10.4%) |
| Desferal Dose (mg/Kg) (Mean ± SD) | 26.7 ± 12 | 28.2 ± 12.1 | 20.6 ± 9.5 |
| Dose of Desferal (vial/week) (Mean ± SD) | 18 ± 7 | 19 ± 7 | 16 ± 7 |
| Height (Mean ± SD) | 159 ± 12 | 158 ± 13 | 162 ± 9 |
| Weight (Mean ± SD) | 52 ± 10 | 51 ± 11 | 54 ± 8 |
| BMI (Mean ± SD) | 20.2 ± 3 | 20 ± 3 | 20.7 ± 2.7 |
| Ferritin (ng/ml) (Mean ± SD) | 1876 ± 1790 | 2072 ± 1905 | 1337 ± 1290 |

*TM = Thalassemia Major  
**TI = Thalassemia Intermedia
the lumbar spine and 1.5% for the neck. BMD data were expressed as grams per square centimeter and compared with BMD values of normal subjects of the same age and sex. Osteopenia or osteoporosis was calculated according to WHO criteria, based on BMD expressed as Z-score indicating osteopenic (Z-score between –1 to −2.5 SD) and osteoporotic patients (Z-score below –2.5 SD). We considered the patients osteoporotic if they showed osteoporosis in at least one site and osteopenic if they showed osteopenia in at least one site.

**Ferritin Assay**

In all patients, after an overnight fasting, blood samples were obtained and serum level of ferritin was determined by ELISA method using materials provided by RAMCO (TX, USA). In all assays, the intra-assay coefficient of variation was 6% or less, and the inter-assay coefficient of variation was 15% or less.

**Statistical analysis**

Data were analyzed using SPSS software, version 19 (SPSS Inc., Chicago, IL, USA). Students’ t-test was applied to compare the means. Association between variables was compared using Pearson’s Chi-Square test. Results are expressed as mean±SD. P values <0.05 were considered significant.

**Result**

This study included 239 patients with thalassemia major (116 women and 123 men; mean age: 13.2±5.8 years) and 87 cases with thalassemia intermedia (47 women and 40 men; mean age: 14.2±6.9 years). Basic demographics and therapeutic characteristics are presented in table 1. The prevalence of osteopenia and osteoporosis and its relation to different variables is presented in table 2. According to our data, the prevalence rate of osteoporosis, based on the WHO criteria was 65.6% (214 out of 326). In 35 patients (10.7%) only lumbar spine was osteoporotic, in 36 patients (11%) only femur was osteoporotic and in 143 (43.3%) patients both femur and lumbar spine were osteoporotic. The prevalence of osteopenia was estimated as 18.7% (61 out of 326).

<table>
<thead>
<tr>
<th>Subject</th>
<th>Osteoporosis Number (%)</th>
<th>Osteopenia Number (%)</th>
<th>Normal Number (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>214 (65.6)</td>
<td>61 (18.7)</td>
<td>51 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>31 ± 8</td>
<td>27 ± 6</td>
<td>25 ± 8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>29 (13 to 52)</td>
<td>27 (17 to 45)</td>
<td>24 (12 to 49)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>103 (63.2)</td>
<td>33 (20.2)</td>
<td>27 (16.6)</td>
<td>.376</td>
</tr>
<tr>
<td>female</td>
<td>111 (68.1)</td>
<td>28 (17.2)</td>
<td>24 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>3.7 ± 6</td>
<td>2.1 ± 2.9</td>
<td>2.7 ± 4.1</td>
<td>.124</td>
</tr>
<tr>
<td></td>
<td>1 (0.1 to 37)</td>
<td>1 (0.1 to 20)</td>
<td>1 (0.1 to 20)</td>
<td></td>
</tr>
<tr>
<td>Type of thalasemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TM</td>
<td>143 (59.8)</td>
<td>54 (22.6)</td>
<td>42 (17.6)</td>
<td>.001</td>
</tr>
<tr>
<td>TI</td>
<td>71 (81.6)</td>
<td>7 (8)</td>
<td>9 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Transfusion interval</td>
<td>32 ± 34</td>
<td>22 ± 8</td>
<td>24 ± 10</td>
<td>.011</td>
</tr>
<tr>
<td></td>
<td>23 (10 to 365)</td>
<td>20 (10 to 60)</td>
<td>20 (12 to 60)</td>
<td></td>
</tr>
<tr>
<td>Duration of Transfusion</td>
<td>26 ± 7</td>
<td>25 ± 5</td>
<td>23 ± 7</td>
<td>.007</td>
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<tr>
<td></td>
<td>26 (9 to 48)</td>
<td>25 (14 to 38)</td>
<td>23 (6 to 45)</td>
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</tr>
</tbody>
</table>
In men, the prevalence rate of osteoporosis was 63.2% and of osteopenia was 20.2%. In women, the rate of osteoporosis was 68.1%, whereas osteopenic rate were 17.2%. There was no correlation between the sex and the prevalence of osteoporosis (p = 0.378).

In this survey there was a significantly higher rate of osteoporosis in TI patients than TM cases (p<0.001). Also higher age of patients, longer duration of transfusion and longer intervals between transfusions had a positive correlation with osteoporosis.

Discussion

Since osteoporosis is a progressive disease, prevention and early diagnosis are equally important as well as treatment of the established disease. Despite normalization of hemoglobin levels, adequate hormone replacement, and effective iron chelation therapy patients show an unbalanced bone turnover with an increased resorptive phase resulting in diminished bone mineral density.

Various studies have demonstrated that multiple acquired factors are involved in the pathogenesis of osteopenia/osteoporosis in thalassemia. They include the primary disease, itself causing bone marrow expansion, and several secondary factors, such as hormonal deficiency, iron overload, desferrioxamine toxicity, calcium, zinc and vitamin D deficiencies, hypothyroidism, hypoparathyroidism, diabetes mellitus, hypogonadism and inadequate physical activity. These factors mainly act by inhibiting the osteoblast activation and/or increasing the osteoclastic function, leading to bone loss and osteoporosis.

This study presents the current osteoporosis and osteopenia prevalence in a large series of thalassemia patients from Iran. The results of the current study indicate a high prevalence of osteoporosis among thalassemic Iranian patients (65.6%). This data is in agreement with other cross-sectional studies indicating the prevalence of osteoporosis to be 52-96% among thalassemic patients.

According to this study patients with TM and TI had low bone mineral density. In this study, reduced BMD of the spine and femoral neck was present in about two-thirds of adult patients with beta-thalassemia major and intermedia which is in agreement with previous works by other authors. Our longitudinal data suggest that, despite long-term transfusions, iron chelation and hormone replacement therapy, thalassemic patients continue to lose BMD over time. It seems that underlying genetic factors play a significant role in the imbalance of bone remodeling.

In the current study there was no significant gender difference regarding bone mineral values. This finding is in agreement with a previous report, but was in contrast to the findings of Jensen et al. who reported that the bone lesions in thalassemic are more frequent and more prominent in males.

Conclusion

The prevalence of osteoporosis among Iranian thalassemia patients is similar to prevalence reported elsewhere. Bone Mineral density is a good index of bone status in patients with thalassemia and recommended to be done for thalassemic patients annually.

References

8. Orvieto R, Leichter I, Rachmilewitz EA, Margulies JY. Bone density, mineral content, and cortical index in patients with thalassemia major and the correlation to their bone fractures, blood transfusions, and treatment with desferrioxamine. Calcified tissue...