Bone Density Changes in Thalassaemic Patients with Age and Time Period

F MOHSENI, MR MOHJERI-TEHRANI, B LARIJANI, Z HAMIDI

Abstract

Purpose: Chronological and longitudinal changes of bone density in patients with secondary osteoporosis, have been shown helpful in providing a model of calcium and bone metabolism. This model can be used in the understanding and management of bone disorders in primary osteoporosis. Objective: The aim of our study was to investigate bone density changes in thalassemic patients. Method: Thalassaemic patients from 7-33 y/o were included in this study. Sixty-five bone mineral density (BMD) scans were collected (21 scan related to paediatric patients (<20 y/o) and others related to adults). BMDs were repeated one year later in all patients. A Norland XR-46 device was used for BMD measurement. Results: There was no case of "low bone density for chronologic age (Z-score ≤-2)" in children. "Z-score ≤-2" was found in 53.4% (23 cases) of adult patients, respectively. The odds of Z-score ≤-2 in patients at age 21 y/o and older, in femoral region were 13.12 times greater than for younger patients (CI=1.596-107.962, P-value=0.017). The odds of Z-score ≤-2 in patients at age 22 y/o and older, in femoral region were 8 times greater than for younger patients (CI=1.626-39.354, P-value=0.011). BMD changes in spinal and femoral regions, were not different significantly in various age groups of patients. Conclusion: As thalassaemic patients got older, though their absolute BMD increases, but in comparison to their age and sex matched controls, it decreases and their delay in acquiring peak bone mass is clear.

Key words Bone mineral density; Osteoporosis; Thalassaemia

Introduction

Monitoring longitudinal alterations in bone density of secondary osteoporosis patients provides a good model of bone changes and metabolism that can be used in understanding and management of bone disorders in primary osteoporosis. Thalassaemia diseases are a group of hereditary disorders of haemoglobin synthesis that bone disorders and secondary osteoporosis are one of the most common findings in them. Different methods of bone densitometry, though not generally in good agreement, consistently showed high prevalence of this complication in thalassaemic patients.

Delay in bone formation due to bone marrow expansion causes cortical thinning, increased instability and bone fragility. Also, Baldini et al explained the chronic requirement to produce blood cells as an important contributor in osteoporosis. Overstimulation of hematopoietic system increases the number of osteoclasts and osteoblasts that increases bone turn-over and bone loss. Iron overload or haemochromatosis is a major complication of hyper-transfusion treatment of thalassaemia and as it continues, iron interferes with osteoid maturation and mineralisation. Binding of iron to calcium hydroxyapatite crystals affects hydroxyapatite crystals growth and increases osteoid tissue in bone. On the other
hand, iron overload leads to major complications include hypogonadism, diabetes, hypothyroidism and other endocrine disorders, that by themselves are risk factors for osteoporosis. However, thalassaemia-induced osteoporosis (TIO) is found also in patients with adequate transfusion and iron chelation therapy. Gender, in some studies was suggested to be an effective factor not only on prevalence, but also on the severity of osteoporosis syndrome, but not all studies agree on these finding. Achieving normal complete peak bone mass occurs at the end of the second decade of life and delay in achieving peak bone mass (PBM) is another problem in thalassaemic patients. In normal population, this occurs first in axial skeleton (predominantly trabecular bone), and later in appendicular skeleton (predominantly cortical bone). By the age of 18 years old (y/o), about 90% of peak bone mass is completed and 5-12% will be achieved during the third decade. But in thalassaemic patients, achieving PBM may be delayed to ages 22.4 and 29.8 in men and women, respectively.

There is little and conflicting data about the prevalence of low bone mass and its longitudinal changes in children and adults with thalassaemia. As BMD studies have an ethical background in all age groups of thalassaemic patients and monitoring thalassaemic patients from childhood to pubertal stage and finally adulthood is recommended in valid guidelines like I-CET (The international network on endocrine complications in thalassaemia) guideline, in our prospective study we assessed the bone status and also the bone changes that occur over one year period in thalassaemic patients in order to find the effect of disease on bone growth and development.

Material and Methods

Subjects

This prospective study was performed between years 2006 and 2010, in endocrine and metabolism research centre of Tehran University of Medical Sciences (EMRI of TUMS). The study received approval by the local institutional review board. Their transfusion regimen and chelating protocol for patients are the same in almost all Iran regions. Almost all patients received blood transfusion every 3-4 weeks. The mean deferoxamine use of patients was 19±5.4 per week (10-40 vials per week).

Patients with age ranged from 7-33 y/o (mean age 20.5±6.1) entered this study. Sixty-five BMD scans were collected, of which 21 scans were related to paediatric patients (<20 y/o) and 44 were obtained from adult patients. Female to male ratio was 37/28. Inclusion criteria included: being beta-thalassaemia major patient and having more that one BMD scan (after 1 year). Exclusion criteria included: finding other osteoporosis risk factors in medical records of patients. This risk factors included history of drugs (corticosteroids, Levothyroxine, Phenobarbital, Heparin, Phenytoin and Carbamazepine) and disorders (hyperthyroidism, hyperparathyroidism, hypogonadism, type I diabetes, rheumatoid arthritis, cirrhosis and chronic renal failure) that affect bone density in a negative manner. As skeletal health assessment in children and adolescents (males and females ages 5-19) has different software (paediatric software), we classified patient to children and adults at age 20 years. For better understanding of bone mineral density (BMD) changes in different age groups, each group further divided into two groups, group 1, 7-12 y/o and group 2, 13-19 y/o. This age grouping is recommended since the cut-off point for monitoring endocrine disorders in thalassaemic patients is 12 y/o and endocrine disorders are major risk factors for low bone mass. As mentioned before, thalassaemic patients achieved PBM in ages 22.4 and 29.8 in men and women, respectively.10

BMD Measurement

Dual-energy X-ray absorptiometry (DXA) method, the gold standard for bone densitometry, was used for the measurement of the BMD at the lumbar spines (L2-L4 anteroposterior view) and femoral neck of patients. All BMDs were done by one machine (Norland, XR-46) in endocrine and metabolism research centre of Tehran University of Medical Sciences (EMRI of TUMS) and all densitometries were supervised and analysed by the chief operator of BMD centre. BMDs were repeated one year later in all patients.

The results of children scans were analysed by paediatric specific software. The WHO based the diagnosis of postmenopausal osteoporosis on the presence of a BMD T-score of 2.5 or greater below the mean for young women. As children have smaller bones, other criteria for paediatric low BMD is introduced. That is a Z-score equal or below -2.0 and is named as “low bone mineral density for age”. No diagnosis entity as osteoporosis is used in children. Also, as ISCD recommended, in BMD reporting in females prior
to menopause and in males younger than 50 y/o, Z-scores are preferred and a Z-score of -2.0 or lower is defined as "below the expected range for age".12,14,15

**Statistical Analysis**

SPSS16 was used for statistical analysis. Continuous variables were summarised as means, SDs, and ranges. Categorical variables were summarised as simple percentages. For testing the normality of variable distribution, we used normality plots with tests. The independent-samples T-test procedure was used for comparison of means for two groups of cases. We used Mann-Whitney tests to compare independent samples of non-parametric variables and binary logistic regression for multinomial logistic regression procedure. Odd ratio was calculated using binary logistic regression. The odds ratio is a measure of effect size, describing the strength of association or non-independence between two binary data values. Bivariate correlations procedure was used to measure the correlations (how variables or rank orders are related). Pearson's correlation coefficient was used for normal distributed variables and Spearman's rho for not normal distributed variables. Difference of absolute BMD changes in four groups was tested by one way ANOVA. All comparisons were made two-tailed, and statistical significance was set at 5%.

**Results**

Mean age of patients was 10, 16, 22.2 and 29.6 years , in groups 1, 2, 3, 4, respectively (they were significantly different, P-value <0.001). BMD characteristics of participants are shown in Table 1. There was no case of "low bone density for chronologic age (Z-score ≤ -2)" in children. Z-score ≤-2 were found in 53.4% (n=23) of adult patients, respectively. Prevalence of low bone density among adult thalassaemic patients is shown in Table 2. We found that femoral BMD had a significant relation with gender (P-value <0.001) with males having more dense femoral bones. We found no significant relation between spinal BMD and sex. BMD of spine increases as patients got older (P-value <0.001) but Z-scores decrease significantly with age in spinal and femoral regions (P-value <0.001). No significant relation was found between age and femoral BMD, while a negative significant relation presents between age and Z-score ≤-2 in spine (p=0.045) and femur (P=0.026) in adult patients.

Being 21 y/o and older increased the risk of Z-score ≤-2 in femoral region, by 13.12 times compared to younger patients (CI=1.596-107.962, p-value=0.017). Being 22 y/o and older increased the risk of Z-score ≤-2 in femoral region, by 8 times compared to younger patients (CI=1.626-39.354, P-value=0.011). Being 21 y/o and 22 y/o can be considered as the cut-off point of age for Z-score ≤-2. We didn't find significant relation in spinal region, between Z-score ≤-2 and age groups. BMD changes in spinal and femoral regions was not significantly different in different age group of patients (P-values=0.170 and 0.360, respectively). BMD changes during study are shown in Table 3. It means BMDs were changing (positively) even in the group of 27-33 y/o, so even patient with mean age of 29.6 years, did not reach peak bone mass. Spinal and femoral Z-scores changes also were not significantly different in different age groups of patients (P-values=0.069 and 0.261, respectively). Tables 2 and 3 show the results of study respective to age groups.

No significant differences were found between BMD of different age groups when males and females' results were analysed separately.

Table 1  Bone mineral density characteristics of participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD of femur (1)</td>
<td>0.705±0.119</td>
<td>0.853±0.172</td>
<td>0.830±0.130</td>
<td>0.777±0.09</td>
<td>0.044*</td>
</tr>
<tr>
<td>Z-score of femur (1)</td>
<td>-0.23±0.63</td>
<td>-0.45±0.73</td>
<td>-1.62±1.06</td>
<td>-1.78±0.59</td>
<td>0.000*</td>
</tr>
<tr>
<td>BMD of spine (1)</td>
<td>0.540±0.059</td>
<td>0.748±0.099</td>
<td>0.761±0.124</td>
<td>0.813±0.158</td>
<td>0.000*</td>
</tr>
<tr>
<td>Z-score of spine (1)</td>
<td>-0.34±0.60</td>
<td>-0.73±0.47</td>
<td>-2.03±0.72</td>
<td>-1.75±0.88</td>
<td>0.000*</td>
</tr>
<tr>
<td>BMD of femur (2)</td>
<td>0.735±0.139</td>
<td>0.876±0.167</td>
<td>0.82±0.129</td>
<td>0.803±0.102</td>
<td>0.124</td>
</tr>
<tr>
<td>Z-score of femur (2)</td>
<td>-0.17±0.71</td>
<td>-0.47±0.81</td>
<td>-1.62±1.04</td>
<td>-1.53±0.60</td>
<td>0.000*</td>
</tr>
<tr>
<td>BMD of spine (2)</td>
<td>0.564±0.037</td>
<td>0.790±0.087</td>
<td>0.777±0.104</td>
<td>0.864±0.123</td>
<td>0.000*</td>
</tr>
<tr>
<td>Z-score of spine (2)</td>
<td>-0.46±0.55</td>
<td>-0.699±0.64</td>
<td>-1.95±0.610</td>
<td>-1.44±0.68</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

*Significant differences
Discussion

In this study, we could not detect any thalassaemic child with Z-score lower than -2, while prevalence of Z-score ≤-2 among our adult participants (with mean age 24.1 y/o) was high. Male subjects had higher femoral BMD. BMD changes in spinal and femoral regions, is not significantly different in different age group of patients so we concluded that our adult patients are far from peak bone mass. Many studies have reported a high prevalence of low BMD in their paediatric patients. However, in our study we found no case of "low bone mineral density for age" among our children subjects. Though it is in agreement with our previous studies, one possible reason might be our small sample size compared to other studies. However, lower age of our paediatric subjects might be another reason for not seeing any case of low BMD. Vogiatzi et al found adolescence as a critical period for onset and progression of low bone mass in thalassaemia. It is possible that since our paediatric subjects were young and just at the beginning of starting adolescence period (with mean age of 13.2 y/o), the deteriorative effects of puberty on bone gain has not been clear in them, yet. Unlike children, our adult patients (≥20 y/o) showed a high incidence of low BMD in comparison to reference control group. Though one of the most common endocrine disorder in patients with thalassaemia is hypogonadotrophic hypogonadism, we didn’t find it in our patients.

Analysis of our data showed the odds of Z-score ≤-2 in patients at 21 y/o and 22 y/o and older, in femoral region were 13 and 8 times greater than younger patients, respectively. Though we found such cut-off point in our study, we could not find a scientific reason behind these observations.

In our study, sex had a significant effect on absolute BMD of patients. Male patients had higher BMD, but this significant effect was undermined by its ineffectiveness on Z-core.

BMD changes during our study period in spinal and femoral regions were not significantly different in different age groups of patients. On the other hand, BMDs were increasing even in adult subjects who were in the age group of 27-33 y/o. BMD of our adult patients was changing as much as BMD of our paediatric patients. Although some delay in gaining PBM in thalassaemic patients was reported before, our finding showed that even patients with mean age of 29.6 y/o have not reached their PBM yet. One might interpret this data as more bone fragility in adult thalassaemic patients. Moreover, since thalassaemic patients do not reach their PBM even in adult age - in contrary to normal adults - measures of boosting bone density in thalassaemic patients, even in older ages, may be useful.

However, the small sample size of our study and lack of of careful longitudinal monitoring (from childhood to adulthood) of thalassemic patients, for tracking endocrine disorders that may explain the high prevalence of low BMD in older patients, are limitations of our study.

Lack of serum vitamin D concentration measurements, lack of determination of whole body BMD, bone mineral apparent density, height-adjusted Z-scores and iron overload parameters in our patients are some other limitations of this study. However, as we are checking the difference of mean BMD of our patients in paediatric and adult age groups, this limitation should not affect the generalisation of our finding seriously.

Table 2 Prevalence of low bone density among adult thalassaemic patients

<table>
<thead>
<tr>
<th>Age groups</th>
<th>20-26 years old</th>
<th>27-33 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z ≤-2 (femur)</td>
<td>38%</td>
<td>33%</td>
</tr>
<tr>
<td>Z ≤-2 (spine)</td>
<td>55%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Table 3 Bone mineral density changes during study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD changes of femur</td>
<td>0.030±0.097</td>
<td>0.017±0.056</td>
<td>0.0006±0.049</td>
<td>0.025±0.029</td>
<td>0.360</td>
</tr>
<tr>
<td>BMD changes of spine</td>
<td>0.024±0.055</td>
<td>0.016±0.057</td>
<td>0.016±0.057</td>
<td>0.051±0.068</td>
<td>0.170</td>
</tr>
<tr>
<td>Z-score changes of femur</td>
<td>0.12±0.55</td>
<td>-0.11±0.39</td>
<td>0.04±0.40</td>
<td>0.25±0.23</td>
<td>0.261</td>
</tr>
<tr>
<td>Z-score changes of spine</td>
<td>-0.18±0.65</td>
<td>-0.05±0.28</td>
<td>0.07±0.34</td>
<td>0.31±0.41</td>
<td>0.069</td>
</tr>
</tbody>
</table>
Conclusion

In conclusion, our findings suggest that low BMD in paediatric thalassaemic patients are less common compared to adult. However they are at high risk of being osteoporotic as young adults. Medical workers involved in management of young thalassaemic patients should have a high awareness of the potential bone disorders, and must carefully monitor them for early diagnosis and treatment of low bone mass.

Acknowledgement

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Declaration of Interest

The authors have no conflict of interest regarding this study to declare.

References