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# Bone mineral density in adult patients with major thalassaemia: our experience and a brief review of the literature

## Gęstość mineralna kości u dorosłych chorych na talasemię *major*: własne doświadczenia i krótki przegląd piśmiennictwa

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### Abstract

**Introduction:** Metabolic bone disease represents a major cause of morbidity in patients with thalassaemia major. The aim of our study was to assess the prevalence and underlying contributory factors of osteopenia/osteoporosis in a randomly selected population of adult patients with thalassaemia major.

**Patients and methods:** The study population was selected using the random sampling method from the patients' database of our thalassaemia clinic. Only transfusion-dependent beta-thalassaemia patients aged over 17 and with no history of treatment with bisphosphonates were included. BMD of lumbar spine and right femoral neck were measured by means of the calibrated dual energy X-ray absorption method. Independent factors likely to be associated with low bone mass were determined and included in the analysis to ascertain possible associations.

**Results:** Our study included 40 patients (19 female and 21 male; mean age: 23.0 ± 4.1). The mean Z score of the right femoral neck was –1.2 (95% CI: –0.9 to –1.5) and for lumbar spine was –2.1 (95% CI: –1.7 to –2.5). The prevalences of osteopenia and osteoporosis involving the right femoral neck were 37.5%, and 12.5%, respectively. The respective prevalence rates for lumbar spine were 47.5% and 37.5%. Our study showed patient's weight, age, duration of the disease and history of hypogonadism or concurrent hypothyroidism are significant contributory factors or predictors of bone mineral loss.

**Conclusions:** Regarding the high prevalence of osteopenia/osteoporosis in patients with thalassaemia major, all patients should be screened periodically for bone disease. The uncertainty and disagreements as to the possible role of different factors indicate the necessity for further studies in order to recognise the pathophysiologic fundamentals of this serious complication of thalassaemia major. **(Endokrynol Pol 2012; 63 (4): 264–269)**

***Key words:*** *thalassaemia, bone mineral density, osteoporosis, osteopenia*

### Streszczenie

**Wstęp:** Zaburzenia metabolizmu tkanki kostnej są główna przyczyną chorobowości u pacjentów z talasemią *major*. Celem niniejszego badania była ocena częstości osteopenii/osteoporozy i określenie czynników przyczyniających się do ich rozwoju w losowo wybranej grupie chorych na talasemię *major*.

**Pacjenci i metody:** Uczestników badania wybrano losowo z bazy danych pacjentów poradni leczenia talasemii. Do analizy włączono jedynie chorych w wieku powyżej 17 lat z transfuzjozależną talasemią beta, nieleczonych wcześniej bisfosfonianami. Metodą absorpcjometrii podwójnej wiązki promieniowania rentgenowskiego zmierzono BMD odcinka lędźwiowego kręgosłupa i szyjki prawej kości biodrowej. Określono niezależne czynniki, które mogły wpływać na niską masę kostną i uwzględniono je w analizie, aby wykryć wszelkie możliwe związki.

**Wyniki:** Do badania włączono 40 chorych (19 kobiet i 21 mężczyzn, średnia wieku 23,0 ± 4,1 roku). Średnie wartości *Z score* wynosiły –1,2 (95% CI: od –0,9 do –1,5) dla szyjki prawej kości biodrowej i –2,1 (95% CI: od –1,7 do –2,5) dla kręgosłupa lędźwiowego. Częstość osteopenii i osteoporozy, oceniana na podstawie gęstości mineralnej szyjki prawej kości udowej, wynosiła odpowiednio 37,5%, i 12,5%. W badaniu wykazano, że masa ciała, wiek, czas trwania choroby i hipogonadyzm w wywiadzie lub współistniejąca niedoczynność tarczycy są istotnymi czynnikami ryzyka lub predyktorami utraty minerału kostnego.

**Wnioski:** W związku z częstym występowaniem osteopenii/osteoporozy u wszystkich chorych na talasemię *major* należy okresowo przeprowadzać badania w kierunku chorób kości. Wątpliwości i rozbieżne opinie na temat potencjalnej roli różnych czynników w rozwoju tych poważnych powikłań talasemii *major* wskazują na konieczność prowadzenia dalszych badań w celu poznania ich patofizjologii. **(Endokrynol Pol 2012; 63 (4): 264–269)**

***Słowa kluczowe:*** *talasemia, gęstość mineralna kości, osteoporoza, osteopenia*

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## Introduction

Thalassaemia major, as a chronic haematologic disorder, leads to altered bone metabolism, which is due to imbalanced osteoclastic bone resorption versus constructive osteoblastic activities [1]. Furthermore, the disease causes chronic anaemia and tissue hypoxia that disturb normal growth and puberty, also resulting in gonadal dysfunction. These underlying problems also lead to smaller bone size [1] and abnormal bone formation [2], both of which may partly contribute to decreased bone mineral density (BMD) in patients with thalassaemia. The presence of diabetes mellitus and hypothyroidism, the parathyroid gland dysfunction, the accelerated haematopoiesis with progressive bone marrow expansion, the direct iron toxicity on osteoblasts, the effects of iron chelating agents, the deficiency of growth hormone or insulin like growth factors, and genetic factors all have been proposed as other causes of osteopenia and osteoporosis in thalassaemic patients [3–9]. Hence, numerous explanations have been suggested for the unpleasant process of bone mineral loss in thalassaemia major.

Metabolic bone disease represents a major cause of morbidity in patients with thalassaemia major [5, 10––13]. Elucidating the underlying pathogenic mechanisms of bone mineral loss in thalassaemia (which are not yet fully understood) is urgently needed, as it will allow the design of optimal therapeutic and preventive measures for these patients [10, 14]. However, significant discrepancies among published reports concerning the underlying pathophysiologic contributors of bone mineral loss have resulted in inconsistencies of preventive and therapeutic measures among children, adolescents and adults with thalassaemia major.

The aim of our study was to assess the prevalence and underlying contributory factors of osteopenia/osteoporosis in a randomly selected population of adult patients with thalassaemia major.

## Patients and methods

The study population was selected using the random sampling method from the patients' database of the thalassaemia clinic at our hospital. Only transfusion-dependent beta-thalassaemia patients older than 17 were included in the study. All patients were on the standard treatment protocol for thalassaemia at the thalassaemia clinic of the hospital. None of the patients had a history of treatment with bisphosphonates. Informed consent was obtained from all participants prior to inclusion in the investigation. The study was conducted following the approval of the ethical committee at Tehran University of Medical Sciences in keeping with the guidelines of Helsinki.

Medical history by interview and review of medical records and physical examinations were performed. Demographic and anthropometric data and history of all treatments, as well as menstrual and pubertal histories, were collected. Independent factors likely to be associated with low bone mass (i.e. age, gender, history of gonadal or pubertal dysfunction, history of bone fracture in first degree relatives, history of iron chelating therapy, history of treatment with calcium and vitamin D, pre-transfusion haemoglobin level, serum levels of calcium, phosphorus, alkaline phosphatase, and thyroid function indices (T3, T4 and TSH)) were determined and included in the analysis to ascertain possible associations.

The assessment of BMD was carried out by means of the calibrated dual energy X-ray absorption (*LEXX-OS*-DMS, France) method. BMD of lumbar spine (L1–L4) and right femoral neck were measured. The BMD values are expressed as mean values (g/cm$^2$) ± SD. Z-score, which is the number of SD above or below the average of age- and sex-matched control subjects' BMD, was calculated. Based on the World Health Organisation definition, a Z-score of less than –2.5 SDs below the mean in relation to the patient's age was defined as osteoporosis, and between –1.0 and –2.5 SDs as osteopenia.

The student T test and ANOVA were used to analyse the significance of the differences between the quantitative and the qualitative variables. Also, Chi square (X2) statistic and Fischer exact test were used to compare distributions of categorical variables. A p value of $< 0.05$ was considered statistically significant. All statistical analyses were conducted using SPSS version 13 (SPSS Inc., Chicago, IL, USA).

## Results

Our study population included 40 patients (19 female and 21 male; mean age: 23.0 ± 4.1, range 17–30 years) with major beta-thalassaemia. Patients' characteristics are summarised in Table I.

**Table I.** *Patients' clinical characteristics*
**Tabela I.** *Charakterystyka kliniczna badanych*

| Clinical characteristic | Mean ± SD (range) |
|---|---|
| Age | 23.0 ± 4.1 (17–30) |
| Height | 156.5 ± 8.6 (137.0–170.0) |
| Weight | 50.9 ± 7.0 (38.0–66.0) |
| Haemoglobin | 9.4 ± 1.6 (6.5–12.0) |
| Serum calcium | 7.8 ± 0.6 (6.8–8.9) |
| Serum phosphorus | 4.6 ± 0.7 (3.3–5.7) |
| Serum alkaline phosphatase | 119.0 ± 48.4 (58.0–210.0) |

The mean Z score of the right femoral neck was –1.2 (95%CI: –0.9 to –1.5) and the same figure for lumbar spine was –2.1 (95% CI: –1.7 to –2.5). The prevalences of osteopenia and osteoporosis involving the right femoral neck were 37.5%, and 12.5%, respectively. The respective prevalence rates for lumbar spine were 47.5% and 37.5%. All patients with abnormal right femoral neck BMD showed abnormally low spinal BMD.

Regarding the prevalence of abnormal BMD, there was no significant difference between males and females (p value = 0.8). The patients' weight and height showed significant associations with BMD values of both hip and lumbar spine (all p values < 0.01). There was a significant decrease in the BMD with increasing patient age (Fig. 1, p value < 0.001). All patients older than 25 years suffered from osteoporosis. Based on the regression analysis, BMD of the right femoral neck could be calculated using the following formula: **BMD of the right femoral neck = 1.40 – 0.023 × patient,s age.** Similar formulas can be generated using height: **BMD of the right femoral neck = –0.84 + 0.01 × patient's age height [cm]** and weight **BMD of the right femoral neck = 0.40 + 0.01 × patient's age weight [kg],** as the independent variables.

We found a significant relationship between pre-transfusion haemoglobin level and lumbar spine BMD Z score (p < 0.01), while there was not such an association between pre-transfusion haemoglobin level and right femoral neck BMD Z score (p = 0.1). There was no significant correlation between serum concentrations of calcium, phosphorus, and alkaline phosphatase and BMD of hips and spines (all p values more than 0.1). Although there was no significant correlation between recent serum concentrations of Thyroxin (T4), Thyronine (T3), and Thyroid Stimulating Hormone (TSH), a history of hypothyroidism (as depicted by current treatment with thyroid hormones) showed significant association with bone mineral loss in both hip and spine (both p values < 0.01): BMD Z score at the right femoral head in patients with a history of hypothyroidism was –1.6 compared to –1.1 in patients with no history of hypothyroidism. Although there was no significant correlation between recent serum concentrations of testosterone, oestradiol, luteinising hormone (LH), and follicle stimulating hormone (FSH), as illustrated by Figure 2, there was a significant relationship between bone mineral loss and history of gonadal dysfunction (as depicted by current or past treatment with related hormones) or impaired puberty (p = 0.01).

Eleven patients were treated using desferrioxamine regularly, 18 patients received desferrioxamine irregularly/intermittently, and 11 patients stated that they had discontinued receiving desferrioxamine for more than six months. There was no association between the frequency and regularity of treatment with iron chelating agent and BMD (p values > 0.2). Similarly, there was no relationship between a family history of bone fracture in first degree relatives and BMD (p values > 0.2). In our population, 42.5% of the patients were receiving calcium and vitamin D supplementations. However, calcium and vitamin D

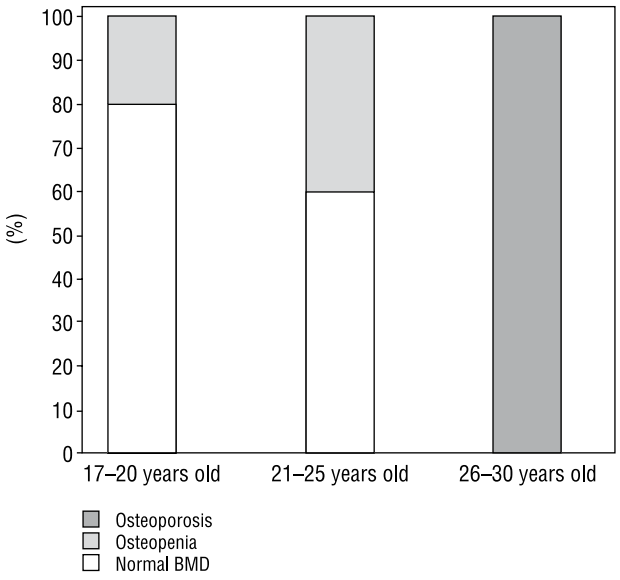


**Figure 1.** *Association between patients' age and bone mineral density (BMD)*

**Rycina 1.** *Zależności między wiekiem chorych a gęstością mineralną kości (BMD)*

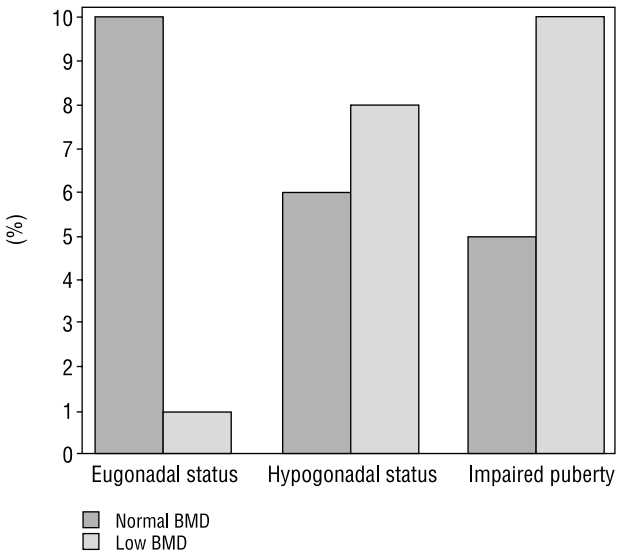


**Figure 2.** *Significant association between bone mineral loss and history of gonadal dysfunction or impaired puberty; BMD — bone mineral density*

**Rycina 2.** *Istotne zależności między utratą minerału kostnego a dysfunkcją gonad i zaburzeniami dojrzewania płciowego; BMD — gęstość mineralna kości*

supplementations showed no significant association with BMD values (p values > 0.2).

## Discussion

Osteopenia and osteoporosis are the commonest bone complications of beta-thalassaemia, despite regular transfusions and iron chelation therapy [6, 11, 12, 15, 16]. At least half of our thalassaemics suffered from some degree of bone mineral loss. Hence, impairment of bone mineral density in Iranian thalassaemics even on proper treatment is severe and prevalent, as was expected. Similar or more severe figures have been reported by others [6, 11, 13, 14, 17]. Therefore, bone densitometry should be included in the periodical evaluation of patients with thalassaemia in order to help guide proper treatment in appropriate time [18].

The aetiology of thalassaemia major-induced bone mineral loss is multi-factorial and complicated [14, 19], and, as our study showed, a patient's weight, age, duration of the disease and history of hypogonadism or concurrent hypothyroidism are significant contributory factors or predictors. These findings are confirmed by similar previous reports [15].

### *Site of bone mineral loss*

In our study, Z-score of BMD at the lumbar spine was significantly lower than at the femoral neck. All previous reports agree that bone mineral loss is more severe in the spinal column compared to the femoral neck [6, 11, 14, 17, 28–30]. The explanation of this differential bone mineral loss can be the accelerated haematopoiesis with progressive bone marrow expansion, a process which involves the spine more severely than the proximal femurs.

### *Patient's age*

Normally, peak bone mass is attained shortly after completion of puberty and is stable until the third decade of life [13, 10]. It is just after the age of 30 that age-related bone mineral loss initiates [10]. However, in thalassaemic patients, this process starts much sooner and progresses more swiftly.

Based on our study findings and those of others [13, 20–23], BMD Z score significantly deteriorates with age. It is known that in those patients whose lifespan is getting longer, osteopenia and osteoporosis are among the major causes of morbidity, with a strong negative impact on the quality of life [11, 24].

### *Gender*

In accordance with Chapelon et al. [2] and Shamshirsaz et al. [17], we found no significant association between BMD and gender in our post-pubertal group of patients. However, significant gender differences have been found by other groups [14, 25, 26].

### *Patient's weight and height*

In our study, a patient's weight was a significant predictor of BMD. The same finding has been reported by numerous groups of investigators [11, 13, 17, 27], who have shown that body fat and lean mass were positive predictors for BMD Z-scores following adjustment for possible confounding factors such as transfusion status, age, sex, ethnicity, calcium intake, and baseline physical activity. It seems that there is a general consensus regarding the protective effects of maintaining normal body weight for BMD.

In accordance with our study findings, most previous reports found that a patient's weight is also a significant predictor of BMD [13, 17, 21, 23].

### *Pre-transfusion haemoglobin level*

In our study, femoral BMD Z score showed no relationship with pre-transfusion haemoglobin level. The same conclusion has been made by other groups: the normalisation of haemoglobin levels does not affect the unbalanced bone turnover in thalassaemic patients [5, 13, 21, 25, 26]. However, this hypothesis has been rejected by others [7, 18, 31], who found that BMD is positively correlated with the haemoglobin level and frequency of blood transfusions. These discrepancies emphasise the need for future studies on a larger number of patients.

### *Calcium and vitamin D*

As found by previous investigators, regular intake of calcium and vitamin D [2, 12, 16, 29] do not affect the process of bone mineral loss. However, some authors do not agree with such a conclusion and advise that to optimise BMD in thalassaemic patients, it is essential to ensure sufficient intake of calcium and vitamin D [13, 28, 32].

### *Iron chelating therapy*

We found no association between the frequency and regularity of treatment with iron chelating agents and BMD. Similar statements have been made by others, emphasising that despite effective iron chelation, patients continue to show increased bone resorptive phase, resulting in seriously diminished BMD [5, 12, 13, 21, 26]. However, numerous reports have come to a contrary conclusion [17, 18, 29, 33].

### *Endocrinopathy*

Although we could not find a significant relationship between serum levels of steroid or thyroid hormones and BMD Z scores, other groups [3, 4, 9] have found such a relationship. The small size of our patient group may limit the power of the study to unveil all possible relationships.

In our study, those patients with a history of hypothyroidism, gonadal dysfunction or impaired puberty showed lower BMD values. In this line, other investigators [3, 8, 11, 14, 20, 22, 26, 29, 32, 34–37] have also stated that low BMD values are found more commonly in the background of endocrinopathies. These authors believe that gonadal dysfunction probably has the most dominant role in the pathogenesis of bone disease in thalassaemia major. Christoforidis et al. [33] also stated that management of possible endocrine complications is crucial in order to protect normal bone health during adulthood.

The anabolic effects of sex steroids in bone are essential, not only for the acquisition of bone mass during adolescence and puberty, but also for the maintenance of peak bone mass during adulthood [4, 10, 38]. It has been emphasised that "thalassaemic patients are often hypogonadal and therefore the lack of sexual hormones in critical periods, such as puberty, contributes to the failure to achieve optimal peak bone mass and to maintain bone mineral density later in life" [3, 10, 30, 39, 40]. On the other hand, it has been emphasised that adequate hormone replacement therapy does not necessarily correct the underlying pathologic mechanisms leading to bone mineral loss in thalassaemic patients [5, 12, 13, 38].

### *Limitations of the study*

The main limitation was the small number of patients studied, which reduced the power of the study to elucidate some possible associations.

## Conclusions

Regarding the high prevalence of osteopenia/osteoporosis in patients with thalassaemia major, all patients should be screened periodically for bone disease. The uncertainty and disagreements on the possible role of different factors indicate the necessity of further studies in order to recognise the pathophysiologic fundamentals of this serious complication of thalassaemia major.

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