Asian Biomedicine Vol. 9 No. 2 April 2015; 169-174 **DOI: 10.5372/1905-7415.0902.383**

Brief communication (Original)

Risk factors for osteoporosis and the relationship between osteoporosis and hemoglobin level in adult patients with thalassemia in Rajavithi hospital

Chajchawan Nakhakes[a], Somluk Jaruluxananan[b], Yuthana Saengsuda[c], Sureerat Saengsuda[c]
[a]Department of Internal Medicine, Rajavithi Hospital, Bangkok 10400, Thailand
[b]Department of Anaesthesiology, Faculty of medicine, Chulalongkorn University, Bangkok 10330, Thailand [c]Department of Nuclear Medicine, Rajavithi Hospital, Bangkok 10400, Thailand

Background: Bone complications are common in patients with thalassemia.
Objectives: To assess risk factors for osteoporosis in patients with nonmajor thalassemia and its prevalence in randomly selected adult patients in Thailand.
Patients and methods: We included 190 adult patients (58 men and 132 women) with thalassemia intermedia or minor in this cross-sectional study. Patients with untreated hypogonadism, untreated hypothyroidism, menopause, and with a history of treatment with medications that have effects on skeletal or bone metabolism were excluded. Bone mass density (BMD) of the femoral neck was measured by calibrated dual-energy X-ray absorptiometry. Independent factors likely to be associated with osteoporosis were determined and included in the analysis to ascertain possible associations.
Results: Mean age was 35.48 ± 14.11 years (range 18–87 years). The mean Z score of femoral neck was – 0.86 ± 1.14 (range –3.7–2.40). Prevalence of osteoporosis was 22/190 (11.6%). Correlation between the pretransfusion hemoglobin level and BMD score was $r = 0.192$, $P = 0.008$. Univariate analysis found low BMI was a risk factor for osteoporosis (OR = 3.09, 95% CI 1.09–8.76, $P = 0.039$) and iron chelation therapy was a protective factor (OR = 0.24, 95% CI 0.09–0.69, $P = 0.005$). Multivariate analysis did not find these factors to be significant.
Conclusions: All patients with thalassemia at risk of osteoporosis should be screened periodically for bone disease. The uncertainty and disagreements as to the potential role of different factors indicate the necessity for further studies to recognize the pathophysiological basis of this serious complication of thalassemia.

Keywords: Bone mineral density, hemoglobin level, osteoporosis, thalassemia intermedia, thalassemia minors

Thalassemia is one of the most common genetic disorders. Thailand is an endemic area for this disease. There are approximately 12,000–13,000 newly diagnosed with thalassemia (all types) every year, while there are about 600,000 patients living with this disease [1]. In Thailand and Southeast Asia, there is a high prevalence of HbE (up to 40%–50% in some areas of Northeast Thailand), so β-thalassemia with HbE is very common, and there is a high frequency of the α-thalassemia gene (up to 20%–40% in the north of Thailand), so HbH, which is a combination of abnormalities is also common. Advances in treatment, including safer blood transfusion therapy and effective iron chelation therapy, have contributed to the longevity of patients with thalassemia. Consequently, these patients suffer from greater morbidity. Because of the heterogeneity of this disease [2], osteoporosis has a very high prevalence (up to 50%) in patients with thalassemia major (the most severe form) compared with the less severe forms (thalassemia intermedia and minor). In Thailand, there is national policy for prenatal screening of high risk women with thalassemia major, and the incidence of thalassemia major has decreased substantially since this policy was implemented. While nonmajor thalassemia (thalassemia intermedia and thalassemia minor) are more common, the exact prevalence of osteoporosis among thalassemia patients in Thailand with nonmajor forms is unknown. According to a large retrospective study of common practice in the treatment of thalassemia intermedia in Mediterranean Europe and the Middle East (OPTIMAL CARE), the

Correspondence to: Chajchawan Nakhakes, Department of Internal Medicine, Rajavithi Hospital, Bangkok 10400, Thailand. E-mail: chajchawan.n@dms.mail.go.th

prevalence of osteoporosis is 22.9% in thalassemia intermedia [3]. Because differences in geographic area, dietary calcium intake, and ethnicity, we cannot assume the same prevalence in Thailand as in Mediterranean Europe and the Middle East. The objective of this study was to measure the prevalence of osteoporosis in patients with nonmajor thalassemia in Thailand.

Osteoporosis is a prominent cause of morbidity in children and adults of both sexes with thalassemia [4-6]. Pathogenesis of thalassemia-induced osteoporosis (TIO) involves ineffective erythropoiesis and bone marrow expansion, endocrine complications, iron overload and iron chelation therapy, vitamin deficiency (especially of vitamin D), and decreased physical activity [7]. An important factor in TIO is ineffective erythropoiesis leading to increased erythropoietic activity and bone marrow cavity expansion, and then ultimately distorted bone architecture. Theoretically, suppression of erythropoietic activity by maintaining hemoglobin levels higher than baseline should decrease bone distortion that leads to cortical bone loss. It is common practice guideline for pediatric hematologists to maintain high hemoglobin levels (using a hypertransfusion regimen) at around 10–12 g/dL. Hypertransfusion regimens are proven clinically important in the maintenance of normal growth and development in children and adolescents with thalassemia. There are many observations that suboptimally transfused thalassemic patients have a lower bone mass than those with regular transfusion. However, there is no evidence-based information about maintaining a high hemoglobin level to help maintain bone mass in an adult setting. In Thailand, the most recent (2011) version of the National Practice Guidelines for diagnosis and management of thalassemia suggests the hypertransfusion regimen for thalassemic children aged <15 years. There is no recommendation for a hypertransfusion regimen or maintenance of higher hemoglobin levels in adult patients. The objective of blood transfusion in adult patients includes supportive and symptomatic treatment for anemic symptoms or special conditions, such as preoperative preparation and pregnancy. There are many concerns about the side effects from frequent blood transfusion. These side effects include iron overload, alloimmunization, and risk of infections. Because of advancement in transfusion therapy and more effective and more accessible iron chelation, the risk of all of the side effects mentioned can be minimized, and it is feasible to maintain adult thalassemic patients with a higher hemoglobin level than is the usual practice. So it is desirable to know the association between pretransfusion hemoglobin level and BMD score. To our knowledge, there are two papers reporting the prevalence of osteoporosis during childhood and adolescence in Thai patients with thalassemia major, and the prevalence is as high as 50% [8, 9]. The mechanism of pathogenesis of bone disease in thalassemia is multifactorial and complicated. Peak bone mass is reached shortly after completion of puberty and normally remains stable until the third decade of life, when age-related bone loss begins. Nontransfused patients develop bone distortion mainly because of ineffective erythropoiesis and progressive marrow expansion [10]. By contrast, in patients with severe β thalassemia with regular transfusion have greater BMD than patients with moderately severe β thalassemia without regular blood transfusion [11]. So the reduction of the rate of marrow erythropoiesis by blood transfusion, which is reflected by a high hemoglobin level would be the factor that reduces the severity of low BMD in thalassemic patients. This was confirmed in a study of different transfusion schemes in 52 patients with β thalassemia that showed a strong association between prehemoglobin transfusion and erythropoiesis ($r = –0.77$, $P < 0.001$) [12, 13]. However, a correlation of BMD with rate of marrow erythropoiesis has not yet been demonstrated in adult patient settings. Other than prevalence and risk factors for osteoporosis in adult patients with thalassemia intermedia and minor, we sought to determine whether a high hemoglobin level (which suppresses erythropoietic activity in bone marrow) correlates with high BMD.

Method

This was a cross-sectional study of 190 adult patients with thalassemia including thalassemia intermedia and thalassemia minor who were treated in Rajavithi Hospital, tertiary medical center in Bangkok, Thailand. Rajavithi Hospital Institutional Review Board approved the study protocol. Written informed consent was provided by all the patient participants.

Thalassemia intermedia and minor were confirmed by criteria used for documented hemoglobin typing (HPLC method). Data included age, sex, body mass index (BMI), type of thalassemia (intermedia or

minor), blood transfusion (dependent vs. independent), iron loading (ferritin level), type of iron chelation (desferrioxamine or other), splenectomy, hemoglobin level, physical activity (GPAQ), dietary calcium intake (mg/day), vitamin D level, and osteoporosis (as BMD T or Z score). For iron load status, data were classified by serum ferritin level as follows: no iron overload (below 1,000 ng/mL), moderate iron overload (between 1,000–2,500 ng/mL), and severe iron overload (more than 2,500 ng/mL). For transfusion status, data were categorized as follows: regular transfusion (patients on dependent transfusion protocols (once every 1–3 months for a pretransfusion hemoglobin (Hb) of 90 g/L) initiated mainly for failure to thrive in childhood, bone deformities, progressive splenic enlargement, persistent worsening anemia, or development of complications during the course of the disease), and independent transfusion (patients who required incidental transfusions for transient severe anemia secondary to infections, surgery). Iron chelation therapy was defined as therapy administered for at least one year, otherwise the patient was defined as nonchelated. Osteoporosis was clarified using the WHO definition, with BMD T score ≤ –2.5 or Z score ≤ –2.5. Sample size calculation use the formulation as shown.

$$n = (Z^2_{\alpha/2}PQ)/d^2$$

The prevalence of osteoporosis in thalassemia intermedia is 22.9% (23%) (OPTIMAL CARE study[3])

$Z_{\alpha/2} = Z_{0.05/2} = 1.96$

P = prevalence = 0.23

Q = 1–0.23

d = acceptable error = 0.06 (in general, acceptable d is at least 25% of prevalence)

n = 188.98 to about 190

Statistical analysis

Descriptive statistics are expressed as frequency (percentages) or means. For osteoporosis, a univariate analysis was performed to determine the effect of study parameters (age, sex, body mass index (BMI), serum ferritin level, Hb level, splenectomy, transfusion, iron chelation therapy, physical activity, dietary calcium intake, and vitamin D level) using a χ^2 and Fisher exact test. Multivariate logistic regression analysis was conducted for osteoporosis as a dependent variable to determine the independent effect of relevant variables; where all variables with *P* of about 0.1 (on univariate analysis) were entered into the model. In the multivariate model, age was divided into 2 groups (<35 y and ≥35 years) and transfusion status was defined as independent transfused vs. dependent transfused to preserve sample size. Differences in the mean number of patients with osteoporosis between different treatment modalities were evaluated using an independent samples *t* test. All tests were 2-sided with the level of significance set at $P < 0.05$.

Results

We included 190 adult patients (58 men and 132 women) with thalassemia intermedia or minor in this study. Their mean age was 35.48 ± 14.11 years (range 18–87 years). A total of 57 patients (30%) were splenectomized. Mean hemoglobin level, BMI and steady-state serum ferritin of this patient group were 7.35 ± 1.81 g/dl, 19.95 ± 3.04 kg/m^2 and 1,745.53 + 1981.42 ng/ml. Mean BMD T score overall patients was –0.86 + 1.18. The correlation between hemoglobin level and BMD T score was $r = 0.192$, $P = 0.008$. Prevalence of osteoporosis overall patients was 11.6% (22/190). After excluding thalassemia minor, prevalence of osteoporosis amongst those with thalassemia intermedia was 13.8% (19/138). Some 51/190 patients (26.8%) were blood transfusion independent and had mostly thalassemia intermedia (49). Ninety-four patients (49.5%) had iron chelation including desferrioxamine (10.6%), deferiprone (78.7%), and others.

The mean vitamin D level was 25.35 ± 26.51ng/mL (range 7.53–371.42 ng/mL), the prevalence of vitamin D deficiency (<20 ng/ml) was 35.3% (67/190). Most patients (156/190 or 82.1%) had inadequate daily dietary calcium intake. Finally, mean physical activity was 1684.43 ± 2493.74 METs-minutes-week. Comparison of mean BMD among patients with thalassemia intermedia who were blood transfusion dependent (49), with thalassemia intermedia who were blood transfusion independent (89), and with thalassemia minor (52) were –1.01 ± 1.17, –0.97 ± 1.16, and –0.54 ± 1.01 with $P = 0.017$.

Risk factors analysis

Results of univariate analysis are summarized in the **Table 1**.

Univariate analysis of risk factors for osteoporosis among study population revealed that only low BMI (<20 kg/m^2) was identified as a significant risk factor with a crude OR 3.09, $P = 0.039$, while age, sex,

hemoglobin level, splenectomy status, level of physical activity could not be demonstrated as risk factors. Moreover, iron chelation was a protective factor with a crude OR 0.24, $P = 0.005$. In a multivariate model, none of the parameters could be demonstrated to be a significant risk or protective factor. There was only a trend for low BMI as a risk factor (adjusted OR 2.92, 95% CI 0.92–9.34, $P = 0.070$) and a trend for iron chelation therapy as a protective factor (adjusted OR 0.32, 95% CI 0.08–1.14, $P = 0.076$) as shown in **Table 2**.

Table 1. Univariate analysis for risk factors of osteoporosis

Parameter	Osteoporosis (Yes)	Osteoporosis (No)	Crude OR	95% CI	*P*
Age					
≥35 years	11	87			
<35 years	11	81	0.93	0.38–2.26	0.875
Sex					
Female	14	118			
Male	8	50	1.30	0.08–2.53	0.53
Thalassemia type					
Intermedia	19	119			
Minor	3	49	0.38	0.11–1.36	0.2
Blood transfusion					
Dependent	9	42			
Independent	13	126	0.48	0.19–1.21	0.11
Ferritin					
≥1000 ng/ml	16	94			
<1000 ng/ml	6	73	2.07	0.83–5.93	0.14
Iron Chelation					
Yes	5	92			
No	17	76	0.24	0.09–0.69	*0.005**
Body mass index (kg/m^2)					
Low (<20)	17	88			
Normal (≥20)	5	80	3.09	1.06–7.15	*0.027**
Splenectomy					
Yes	8	49			
No	14	119	1.33	0.59–3.00	0.49
Physical activity					
Low (<600 METs-minutes/week)	12	63			
Normal (≥600)	10	105	1.84	0.84–4.04	0.12
Vitamin D level					
Low (<20ng/ml)	9	58			
Normal	13	110	1.27	0.57–2.82	0.56
Daily calcium intake					
Low (<800 mg/d)	18	138			
Sufficient	4	30	0.98	0.31–3.10	0.97

Table 2. Adjusted OR for risk factors of osteoporosis in multivariate model

Parameter	Adjusted OR	95%CI	*P*
Age: ≥35 years old	0.90	0.31–2.59	0.84
Sex: female/male	0.97	0.34–2.79	0.96
Hemoglobin level: ≤10 mg/mL	0.71	0.16–3.21	0.65
Type of Thal.: int. vs. minor	1.78	0.40–7.94	0.45
Splenectomy: yes	0.52	0.17–1.61	0.26
Blood transfusion: dependent	1.54	0.52–4.59	0.44
Ferritin: ≥1000 ng/mL	0.72	0.22–4.21	0.60
Iron chelation: yes	0.32	0.08–1.14	*0.076**
BMI: low (<20 kg/m^2)	2.92	0.9–9.34	*0.070**
Physical activity: low	2.33	0.84–6.43	0.10
Vitamin D level: low	1.26	0.46–3.36	0.66
Daily Ca intake: low	0.81	0.14–4.60	0.81

BMI = body mass index, int. = intermedia, Thal. = thalassemia.

Discussion

This study sought to determine the prevalence of complication of osteoporosis in thalassemia intermedia and minor in Southeast Asia, and highlights a prevalence different from that found in a large retrospective study of these groups of patients in Mediterranean Europe and the Middle East. We found a prevalence of osteoporosis to be about half of the previous study (11.6% vs. 22.9%) [3]. Because of differences in geography, the severity of thalassemia and difference in practice managements, osteoporosis complications among adult thalassemia patients in Thailand are less common than elsewhere. However, mean BMD score in patients with thalassemia intermedia and dependent blood transfusion is generally less than in those with independent blood transfusion and thalassemia minor. Most studies of thalassemia major demonstrated that osteoporosis is strongly associated with age, history of hypogonadism, and concurrent hypothyroidism. In this study, after excluding patients with a history of hypogonadism and hypothyroidism, the prevalence of osteoporosis is still high. In pediatric patients with thalassemia, there is already evidence that supports that a high hemoglobin level is associated with suppressing bone marrow erythropoietic activity. Consequently, maintaining high pretransfusion hemoglobin level results in improvement of bone mineralization. This study also demonstrated a significant association between pretransfusion hemoglobin level with BMD score. However, such association is low; and there should be many factors that have an impact on bone mineral density in adult patients with thalassemia intermedia and thalassemia minor. During the screening process, about 26% of these patients were found to have subclinical hypothyroidism. Determining the importance of this condition on osteoporosis requires further cohort study. The present study found that thalassemia patients with vitamin D deficiency have strong association with osteoporosis, while dietary calcium intake and physical activity do not have a significant association.

Low BMI and no iron chelation were found to be significant risk factors while age, sex, pretransfusion hemoglobin, splenectomy, dietary calcium intake, and physical activity could not be demonstrated to be risk factors. Possible explanations are that most of patients in this study with clinically suspected or preemptive diagnosis of delayed puberty or postmenopausal women were excluded. So patients with clinical hypogonadism and no estrogen effect were not included in this study. Sex was not identified as a risk factor for osteoporosis as consistent with the findings of others [14]. All patients were treated by hematologists, who tend to prescribe blood transfusion only for symptomatic patients, according to Thai National guidelines for the treatment adult patients with thalassemia. Most patients were identified as having inadequate dietary calcium intake according to the Thai recommended dietary advice for adults (more than 6 years old = 800 mg/day) [15]. So we could not demonstrate any association between low dietary calcium and bone complication. It might be that our study population has high prevalence of inadequate intake of daily calcium (82.1%, 156 patients). However, patients with thalassemia should be encouraged to have

adequate dietary calcium intake, despite the unknown long-term effect on osteoporosis. The prevalence of vitamin D deficiency in this study subjects was much higher (35.3%) compared with the normal Thai population (5.7%) [16]. This study could not demonstrate the importance of vitamin D level on osteoporotic complications of patients with thalassemia intermedia and thalassemia minor. There is a moderately strong correlation between vitamin D level and low BMD in thalassemia patients in North India (r = 0.398, *P* = 0.027) [17]. We recommend vitamin D level screening for thalassemia patients with osteoporosis. A study of vitamin D supplement intervention may determine whether osteoporosis and related skeletal events can be prevented.

Conclusion

Proper therapy with iron chelation can have protective effects in maintaining normal body weight for BMD. However, vitamin D deficiency is a risk factor for patients with osteoporosis.

The authors have no conflict of interest to report.

References

1. Sirinavin J, Vanachevanavin W, Tanpaijitra V, Limwong C. Thalassemia in medical practice. Bangkok: Mochao ban Press; 2001.
2. Voskaridou E, Terpos E. New insights into the pathophysiology and management of osteoporosis in patients with β thalassaemia. Br J Haematol. 2004; 127:127-39.
3. Taher AT, Musallam MK, Karimi M, El-Beshlawy A, Belhoul K, Daar S, et al. Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: the optimal care study. Blood. 2010; 115: 1886-92.
4. Pootrakul P, Hungsprenges S, Fucharoen S, Baylink D, Thompson E, English E, et al. Relation between erythropoiesis and bone metabolism in thalassemia. N Eng J Med. 1981; 304:1470-3.
5. Michelson J, Cohen A. Incidence and treatment of fractures in thalassemia. J Orthop Trauma. 1988; 2: 29-32.
6. Johanson NA. Musculoskeletal problems in hemoglobinopathy. Orthop Clin North Am. 1990; 21: 191-8.
7. Haidar R, Musallam KM, Taher AT. Bone disease and skeletal complications in patients with β thalassemia major. Bone. 2011; 48:425-32.
8. Kananarong K. Bone abnormality in thalassemia major. Khon Kaen Med Center J. 1987; 10:221-4. [in Thai]
9. Israngkul P. Bone age and bone changes in thalassemia (Thalassemia Conference in Memorial of Dr. Sa-nga Pootrakul at Mahidol University, Faculty of Medicine Siriraj Hospital. February 10–11, 1977). J Med Assoc Thai. 1978; 11:153.
10. Skordis N, Efstathiou E, Kyriakou A, Toumba M. Hormonal dysregulation and bones in thalassemia—an overview. Ped Endocrinol Rev. 2008; 6(suppl 1): 107-15.
11. Mahachoklertwattana P, Chuansumrit A, Sirisriro R, Choubtum L, Sripharpradang A, Rajatanavin R. Bone mineral density, biochemical and hormonal profiles in suboptimally treated children and adolescents with β thalassemia disease. Clin Endocrinol. 2003; 58:273-9.
12. Wonke B. Bone disease in β thalassemia major. Br J Haematol. 1998; 103:897-91.
13. Izadyar S, Fazeli M, Izadyar M, Salamati P, Gholamrezanezhad A. Bone mineral density in adult patients with major thalassaemia: our experience and a brief review of the literature. Endokrinol Pol. 2012; 63:264-9.
14. Ebrahimpour L, Akhlaghpoor S, Azarkayvan A, Saleh M, Morteza A, Alinaghi R. Correlation between bone mineral densitometry and liver/heart iron overload evaluated by quantitative T2* MRI. Hematol. 2012; 17:297-301.
15. Thai FDA. Thailand Recommendation Dietary Intake. [online] 1998 [cited 2015 April 21]. Available from: *http://www.fda.moph.go.th/eng/eng_food/Notification/182-41.pdf*
16. Chailurkit L, Aekplakorn W, Ongpiphadhanakul B. Regional variation and determinants of vitamin D status in sunshine-abundant Thailand. BMC Public Health. 2011; 11:853-9.
17. Singh K, Kumar R, Shukla A, Phadk SR, Agarwal S. Status of 25-hydroxyvitamin D deficiency and effect of vitamin D receptor gene polymorphisms on bone mineral density in thalassemia patients of North India. Hematol. 2012; 17:291-6.