The Ability of Lumbar Spine DXA and Phalanx QUS to Detect Previous Fractures in Young Thalassemic Patients With Hypogonadism, Hypothyroidism, Diabetes, and Hepatitis-B: A 2-Year Subgroup Analysis From the Taranto Area of Apulia Region

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Background: Osteoporosis is a leading cause of morbidity in patients affected by β-thalassemia major or intermediate; we aimed to assess the association between demineralization observed in young thalassemic patients.

Methods: A total of 88 patients with β-thalassemia were recruited at Microcitemia Center of Taranto Hospital under the Prevention Osteoporosis and Fractures research project from 2008 to 2010. All the patients were screened with both dual energy x-ray absorptiometry (DXA) and quantitative ultrasound (QUS). *T* score and *Z* score values were obtained for each subject.

Results: The overall prevalence of demineralization was 84% with DXA and 70% with QUS, whereas normality was found in 16% of patients screened with DXA and in 30% of cases with QUS. Hypogonadism, hypothyroidism, diabetes mellitus, hepatitis-B, and the presence of previous fragility fractures were significantly associated with the demineralization status (lower *T* scores values) both with DXA and QUS.

Conclusion: Our data confirm that DXA and QUS examinations are both useful for detecting bone demineralization in thalassemic patients.

Key Words: osteoporosis, thalassemia, hypogonadism, fractures, ultrasound (QUS)

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β-Thalassemia is a heterogenous family of inherited disorders affecting hemoglobin synthesis. It is characterized by the complete absence or reduced synthesis of the β chain of hemoglobin, resulting in increased, but ineffective, erythropoiesis. The β-thalassemia phenotypes are variable, ranging from severe conditions requiring blood transfusions (thalassemia major [TM]) to milder forms (intermediate thalassemia [TI]). Patients affected by TM always present a severe microcytic and hypochromic anemia, associated with hepatosplenomegaly, and usually come to medical attention within the first 2 years of life. Treatment with regular blood transfusions and chelation therapy, which is aimed at reducing transfusion-induced iron overload, allows normal growth and development of these children. This therapeutic approach has extended patients' life expectancy up to the age of 30 or 40 years, with a substantially improved survival and quality of life.[1]

Subjects presenting TI show a later onset of the disease, characterized by milder anemia rarely requiring blood transfusion. These patients also present liver and spleen enlargement, typical bone modifications, and mild to moderate jaundice.[2] Current epidemiological data show that approximately 7% of the global population present genes associated with hemoglobin disorders (healthy carrier of the disease). It is estimated that 300,000 to 500,000 children suffering from TM are delivered annually, 80% of who are living in developing countries.[3] As the longevity of patients with TM increases, osteoporosis has emerged as an important cause of morbidity and disability in adult patients.[4] The etiology of bone diseases in patients with thalassemia is more complex than in individuals without thalassemia. Factors such as anemia, massive ineffective erythropoiesis, bone marrow expansion with thinning of cortical bone, endocrine dysfunction, iron overload, desferrioxamine toxicity, metabolic factors (ie, deficiencies in calcium, vitamin D, and zinc), inadequate physical activity, and genetic factors may all play a role in the reduction of bone mass in these patients. In the last decade, the presence of osteopenia and osteoporosis in thalassemic patients receiving all the current gold standard treatments for this disease has been described in different studies, showing a high prevalence of up to 50%.[5,6] Two main techniques are commonly used for evaluation of bone mineral density and fragility fracture risk: dual energy x-ray absorptiometry (DXA) bone densitometry is the "gold standard" method for diagnosis of osteoporosis, with this condition being defined by a reduction of bone mineral density (BMD) > 2.5 SD below the values observed in healthy young

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subjects (T score < -2.5 SD). DXA has been widely accepted as a reference method for BMD measurement in adults and in pediatric subjects.[7] However, it seems that other factors, in addition to BMD reduction, such as elasticity and bone microarchitectural bone characteristics are also important in determining bone fragility. Therefore, different quantitative ultrasound (QUS) methods have been developed for the assessment of fracture risk.[8,9] QUS measured at the phalanx is a novel kind of noninvasive, radiation-free, and portable method that can be used extensively to get both qualitative and quantitative information.[10–12] As comorbidities (ie, hypogonadism, hypothyroidism, and other illnesses) might play a relevant role in inducing bone demineralization, the aim of this study was to assess the ability of DXA and QUS to evaluate fracture risk in thalassemic patients, with particular focus on the effect of age and concurrent diseases on T score values.

MATERIALS AND METHODS

Within the Prevention Osteoporosis and Fractures Project, which is an innovative disease management program aimed at preventing osteoporotic fractures in the Salento region, we have enrolled 88 young thalassemic patients being followed up at SS Annunziata Hospital in Taranto.

Of the 88 enrolled patients, 42 (48%) were male patients (aged 22 to 69 y; mean age: 34.1 y; SD ± 7.9), and 46 (52%) were female patients (aged 13 to 48 y; mean age: 34.5 y; SD ± 6.7). The majority of patients was affected by TM (n = 58; 66% of the sample), whereas the remaining 30 patients (34% of the sample) were affected by TI. These 2 groups were following different kinds of treatments based on the severity of the disease: patients with TM assumed iron-chelating therapy (desferrioxamine, deferasirox, or deferiprone) every day and underwent blood transfusion 2 times per month. TI patients followed a variable therapeutic regimen based on daily iron-chelating therapy, with blood transfusion being infrequently necessary.

For all patients, QUS measurements at the phalanx were performed using ultrasound densitometer DBM Sonic 1200 Bone Profiler (IGEA S.r.l.; Carpi, MO, Italy). DXA measurements at the lumbar spine (L1-L4) were also obtained for all patients by using Hologic QDR 4000 machine (Bedford, MA). All measurements were performed between 2008 and 2010, and informed consent was obtained from all the patients. T score and Z score values were obtained for all patients. For the DXA method, osteoporosis and osteopenia were defined according to the World Health Organization definitions (osteoporosis: T score < -2.5; osteopenia: T score between > -2.5 and < -1; normal: T score > -1).[13] For QUS of the phalanx, different cutoff values have been directly provided by the manufacturer (osteoporosis: T score < -3.2; osteopenia: T score between > -3.2 and < -1; normal: T score > -1).[14] Calibration of QUS densitometer was carried out daily using manufacturer's verification phantom for quality control and assurance. T score values obtained with both methods (DXA and QUS) were correlated to age, sex, body mass index, type of thalassemia (TM or TI), previous fragility fractures, and presence of the following concurrent diseases: diabetes, hypothyroidism, hypogonadotrophic hypogonadism, and hepatitis (HBV). Fragility fractures were defined as resulting from low-energy trauma at different skeletal sites (ie, hip, humerus, vertebrae, wrist, leg, and ankle). Fractures that occurred at workplace or as a consequence of car accidents, as well as fractures of fingers and big toe, were excluded from statistical analyses because they were likely to be related to high-energy trauma. Statistical analyses were performed using STATA 11.0 (StataCorp LP, College Station, TX). Paired and unpaired Student t test was used to compare the comparisons. Ratios were compared by the χ^2 or Fischer exact test. Linear regressions were performed to evaluate the effect of age, height, and weight on T scores obtained with both methods.

RESULTS

Nine of 88 patients (10% of the sample) presented a previous diagnosis of diabetes mellitus, whereas 10 patients had hypothyroidism (11%), 43 were affected by HBV (49%), and 52 (59%) presented hypogonadotrophic hypogonadism. There were 23 (26%) patients with a previous fragility fracture.

Table 1 shows the characteristics of the study population. Patients' height and weight were higher in the male than in the female patients, with this difference reaching statistical significance ($P < 0.05$). T score values did not show any statistically difference when adjusted by height and weight ($P = 0.487$ and 0.283, respectively). All the other examined parameters showed no correlation with sex. In Table 2, we report T score and Z score values obtained

TABLE 1. Characteristics of Study Population (n = 88)

	Males (n = 42)				Females (n = 46)				
	Mean	SD	Min	Max	Mean	SD	Min	Max	*P*
Height (cm)	168	7	153	187	158	7	141	177	< 0.05
Weight (kg)	65	9.0	47	84	56	9.6	40	85	< 0.05
BMI (body mass index)	23.3	2.7	17.7	29.1	22.7	3.4	17.8	33.2	> 0.05
Age_QUS (y)	34.0	7.9	22	69	34.5	6.7	13	48	> 0.05
T score QUS	−1.9	1.6	−6.4	0.49	−1.5	0.89	−3.91	0.29	> 0.05
Z score QUS	−1.7	1.6	−6.36	−1.99	−1.44	0.95	−3.91	0.34	> 0.05
Age_DXA (y)	33.0	8.0	19	67	32.9	6.7	2	47	> 0.05
T score DXA	−2.7	1.3	−5.9	−0.1	−2.3	1.3	−4.4	1	> 0.05
Z score DXA	−2.8	1.2	−5.7	−0.1	−2.2	1.3	−4.4	1.1	< 0.05
Age at start of iron-chelating therapy (y)	4.6	3.4	1	20	5.5	4.8	1	28	> 0.05
Age at start of transfusion (mo)	2.2	3.8	0.2	24	2.1	2.9	0.3	13	> 0.05

DXA indicates dual energy x-ray absorptiometry; QUS, quantitative ultrasound.

TABLE 2. *T* Scores Obtained With Both Methods According to Different Clinical Variables

	T Score QUS		*Z* Score QUS		*T* Score DXA		*Z* Score QUS		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	n
Type of thalassemia									
Major	−1.76	1.38	−1.62	1.39	−2.64	1.35	−2.61	1.38	58
Intermediate	−1.56	1.08	−1.42	1.10	−2.27	1.07	−2.20	1.11	30
Hypothyroidism									
Yes	−2.24	1.23	−1.86	0.78	−2.60	0.84	−2.77	1.11	10
No	−1.62	1.29	−1.51	1.35	−2.51	1.32	−2.43	1.33	78
Hypogonadotrophic hypogonadism									
Yes	−2.03	1.26	−1.92	1.18	−2.83	1.22	−2.80	1.26	52
No	−1.21	1.17	−1.01	1.29	−2.06	1.22	−2.01	1.24	36
Diabetes									
Yes	−2.70	1.45	−2.65	1.45	−2.80	0.93	−2.71	0.94	9
No	−1.58	1.23	−1.42	1.23	−2.48	1.30	−2.45	1.34	79
Hepatitis-B									
Yes	−1.95	1.28	−1.85	1.19	−2.98	1.02	−2.96	1.09	43
No	−1.45	1.26	−1.26	1.35	−2.07	1.33	−2.00	1.33	45
Previous fractures									
Yes	−1.72	1.30	−1.67	1.29	−2.97	1.28	−2.93	1.10	23
No	−1.68	1.29	−1.51	1.31	−2.35	1.13	−2.31	1.33	65

DXA indicates dual energy x-ray absorptiometry; QUS, quantitative ultrasound.

by using both DXA and QUS according to the type of thalassemia, presence of hypothyroidism, hypogonadotrophic hypogonadism, diabetes, HBV, and previous fragility fractures. The comparison of *T* score and *Z* score values between TM and TI patients did not show statistically significant differences for both techniques.

The 52 subjects suffering from hypogonadotrophic hypogonadism showed lower *T* score values compared with the 36 patients not affected by hypogonadism. Lower values were observed also in case of hypothyroidism, although the number of patients (n = 10) is too little to extend this observation. Patients with HBV (almost 50% of the sample) showed lower *T* score values compared with patients not affected by HBV.

Similarly, also diabetes was associated with low *T* score values, although no statistical significance was reached due to the small number of subjects affected (n = 9). As reported in Table 3, both DXA and QUS were equally able to detect the demineralization status in almost all patients with previous fragility fractures (91% for DXA and 83% for QUS).

The overall prevalence of osteopenia and osteoporosis defined by DXA and QUS are presented in Tables 4 and 5, respectively. Using DXA, 60% of the male patients (25/42) and 45% of the female patients (21/46) were found to be osteoporotic, whereas osteopenia was reported in 28% of male patients (12/42) and in 35% of female patients (16/46). Overall, osteoporosis showed a global prevalence of 52% (46/88) by DXA and only 10% by QUS (9/88), whereas osteopenia was found in 32% (28/88) and in 60% (53/88) of cases using DXA or QUS, respectively. Up to 12% of male and 20% of female patients presented DXA *T* score values higher than −1 SD (normality). Normal findings were more frequent when QUS was used (28% of male patients: 12/42; 31% of female patients: 14/46). When performing the Fisher exact test, there were no differences in the ratios between the male and female patients both for DXA ($P = 0.420$) and QUS ($P = 0.184$).

DISCUSSION

This is the first study addressing the issue of DXA and QUS ability to detect fragility fractures and concurrent pathologies in thalassemic patients. In a previous study aimed at comparing DXA and quantitative computed tomography (QCT), Mylona and colleagues observed a strong difference in the prevalence of osteopenia and osteoporosis in patients with β-thalassemia according to the technique used. In this study we observed a different prevalence of osteoporosis for DXA and QUS.[15] The classification of our patient into normal, osteopenic, and osteoporotic categories is exclusively based on *T* score

TABLE 3. Ability of DXA and QUS to Detect Patients With Previous Fragility Fracture

	DXA, n (%)		QUS, n (%)	
Previous Fractures	Normal (%)	Demineralization (%)	Normal (%)	Demineralization (%)
Yes	2 (9)	21 (91)	4 (17)	19 (83)
No	12 (18)	53 (82)	22 (34)	43 (66)
Total	14 (16)	74 (84)	26 (30)	62 (70)

DXA indicates dual energy x-ray absorptiometry; QUS, quantitative ultrasound.

TABLE 4. Prevalence of Osteopenia and Osteoporosis Derived by the DXA Method

	Normal *T* Scores > -1 (%)	Osteopenia *T* Scores -1 to -3.2 (%)	Osteoporosis *T* Scores < -3.2 (%)
Males	5 (12)	12 (28)	25 (60)
Females	9 (20)	16 (35)	21 (45)
Total	14 (16)	28 (32)	46 (52)

$P = 0.420$ (Fisher exact test).
DXA indicates dual energy x-ray absorptiometry.

values. Osteoporosis and osteopenia are nowadays highly prevalent in patients affected by TM or TI, with increased patient survival and multifactorial pathogenesis being responsible for that (iron inclusions in the bones, desferrioxamine-induced bone dysplasia, ineffective erythropoiesis, and multiple endocrine dysfunctions).

Hormonal deficiency is an important cause of demineralization in TM and TI, as lower testosterone levels in men are associated with low BMD and an increased incidence of spine and hip fractures.[16] It is known that adolescents with hypogonadism do not achieve optimal bone mass.[17] In addition, delayed puberty, hypoparathyroidism, and hypothyroidism have been proposed as causes of reduction in BMD.[18,19] Another metabolic/endocrine disorder such as diabetes mellitus has been reported to negatively influence bone density in thalassemic subjects,[20] although a different study has not confirmed this observation.[15] The crucial role of hormonal regulation is confirmed by the high number of thalassemic patients with hypogonadotrophic hypogonadism (52/88) showing low *T* scores by both DXA and QUS. The prevalence of osteoporosis and osteopenia with DXA was 52% and 32%, respectively. These results are consistent with those of previous studies.[20,21] In contrast with other reports,[15,22,23] we found a relevant difference between sexes. However, this finding was reported by several authors.[24] Although DXA sensitivity for the detection of osteoporosis was higher, both DXA and QUS were able to detect the demineralization status (osteopenia or osteoporosis) in the vast majority of subjects with previous fragility fractures.

With both techniques, osteoporosis was found to be more frequent in the male than in the female patients (60% vs. 45% by DXA, and 17% vs. 4% by QUS), whereas osteopenia was more prevalent among the female compared with the male patients (35% vs. 28% by DXA and 65% vs. 55% by QUS). Normal *T* score values (> -1 SD) were more frequently obtained by QUS (26 patients of 88; 30% of the sample) than with the DXA method (14 patients of 88; 10% of the sample). Data obtained with the QUS technique were particularly interesting, showing only a 10% prevalence rate for osteoporosis, and a higher number of osteopenic patients (60%) compared with DXA. This result places the QUS method in an intermediate position between DXA and QCT, which identify the majority of patients as osteoporotic and normal,[15,25,26] respectively. In their direct comparison study, Mylona et al[15] have reported 44% and 6% of patients as osteoporotic with DXA (normal findings only in 4% of the subjects) and QCT (54% of normal findings), respectively. DXA and QCT methods provide a measure of BMD, which is currently considered the best predictor of osteoporotic fractures.[27] However, these techniques are able to explain only 60% to 80% of the variability in bone strength, and it has been demonstrated that other mechanical aspects of the bone are important in determining fracture risk. These factors include microarchitectural parameters and geometric and elastic properties of bone tissue, which cannot be assessed using DXA.[28] QUS techniques have been developed over the past 10 years to determine bone quality and the state of the skeleton on the basis of various studies suggesting how sonographic parameters are able to provide information on bone density and structure, including elastic properties.[29]

TABLE 5. Prevalence of Osteopenia and Osteoporosis Derived by the QUS Method

	Normal *T* Score > -1 (%)	Osteopenia *T* Score -1 to -3.2 (%)	Osteoporosis *T* Score < -3.2 (%)
Males	12 (28)	23 (55)	7 (17)
Females	14 (31)	30 (65)	2 (4)
Total	26 (30)	53 (60)	9 (10)

$P = 0.184$ (Fisher exact test).
QUS indicates quantitative ultrasound.

Many authors report that low DXA values do not reflect the behavior of vertebrae under stress conditions,[30] thus suggesting that BMD represents only 1 factor involved in determining bone strength, and that bone quality is independent from mineral density. Despite the lack of specific correlation studies between DXA and QUS findings, large prospective studies, carried out both in the elderly and early postmenopausal women, indicate that these 2 techniques are equally able to predict patients at risk for future fragility fractures.[31–33] The discriminatory power in classifying individuals with or without vertebral fractures was tested in cross-sectional studies using different QUS methods, including QUS of the phalanx, and DXA in a sample of older postmenopausal women.[34] In addition, a multicentric study assessed the performance of 5 different ultrasound devices and their association with prevalent vertebral fractures compared with DXA in a group of European women.[35] In addition, this study showed that QUS findings are similar to DXA femoral BMD in identifying subjects with prevalent vertebral fractures.

According to our study, the classification of β-thalassemic subjects as osteoporotic or osteopenic yields variable results, and this depends on the technique used. If we consider DXA to be more specific, most of the patients should be classified as osteopenic and/or osteoporotic, a finding not in accordance with the low incidence of previous fragility fractures observed in our sample. Our study demonstrates a "profitable" correlation between QUS and DXA measurements in thalassemic patients. In summary, our study showed that the ability of the QUS method to detect patients with previous fracture outside the range of normal *T* scores is high, as much as that of DXA. High prevalence of osteoporosis and osteopenia among patients with thalassemia requires more attention to therapeutic approaches for the prevention and treatment of these skeletal disorders. Osteoporosis is a progressive disease that can start in early childhood in this kind of patients. Therefore, prevention and early diagnosis become particularly important, as well as treatment of the established disease. Annual screening of adolescent thalassemic

patients and correction of endocrine factors by replacement therapy might be a promising approach to prevent osteoporosis in subjects with thalassemia. Further studies should be performed to clarify the optimal approach to these patients, who are already undergoing a large number of invasive clinical procedures. Our study showed that the ability of QUS to detect thalassemic patients with prevalent fragility fractures is comparable to that of DXA. In fact hypogonadism, hypothyroidism, HBV, and the presence of previous fragility fractures (but not diabetes) were significantly associated with the demineralization status (lower *T* scores values) both with DXA and QUS.

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