Assessment of Osteoporosis by Quantitative Ultrasound versus Dual Energy X-Ray Absorptiometry in Children with Chronic Rheumatic Diseases

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ABSTRACT. ***Objective.*** To evaluate the validity of quantitative ultrasound bone sonometry (QUBS) as a screening tool for the diagnosis of osteoporosis in children with chronic rheumatic diseases (CRD), compared to the conventional dual energy x-ray absorptiometry (DEXA).

Methods. Forty children with CRD [32 with juvenile idiopathic arthritis (JIA), 6 with systemic lupus erythematosus, and 2 with dermatomyositis] aged 9.9 ± 4.3 years, were evaluated by QUBS of radius and tibia and DEXA of the lumbar spine. Twenty-five (62.5%) patients were treated with corticosteroids. Measurements of the velocity of the ultrasound wave, expressed as speed of sound (SOS) in m/s, and the results of the bone mineral density (BMD) assessed by DEXA were compared to reference data from healthy age and sex matched Israeli children.

Results. Compared to controls, patients with CRD had significantly lower values by QUBS and DEXA alike. BMD and SOS z scores < –1 SD were found in 45% and 38% of the patients, respectively. Reduced BMD and SOS values correlated with age at disease onset and corticosteroid treatment. BMD alone correlated negatively with disease duration and methotrexate therapy. BMD was significantly lower in patients with polyarticular JIA compared to patients with oligoarticular disease ($p < 0.03$). SOS values did not differ between subtypes of JIA. A significant positive correlation was found between the lumbar DEXA and radius SOS.

Conclusion. QUBS evaluation of radius and tibia yielded results comparable to DEXA and may therefore be used for screening patients with CRD for osteoporosis. QUBS might represent a promising means of evaluating bone quality in at-risk children. (J Rheumatol 2004;31:981–5)

Key Indexing Terms:
OSTEOPOROSIS
JUVENILE IDIOPATHIC ARTHRITIS
BONE MINERAL DENSITY
QUANTITATIVE ULTRASOUND BONE SONOMETRY

Disturbance of growth and of bone metabolism is a serious problem in children with chronic rheumatic diseases (CRD) including juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), and juvenile dermatomyositis (JDM). The major contributing factors appear to be chronic disease activity and corticosteroid therapy[1-3]. Children with CRD do not achieve adequate skeletal mass for their age and, if inflammation remains active through adolescence, may not attain the maximum peak of bone mass at puberty[4,5]. Early diagnosis of bone loss and timely identification of patients at risk for osteoporosis are essential for the prevention and management of this condition and its ominous consequences.

Bone densitometry using dual energy x-ray absorptiometry (DEXA) has become the standard method for assessment of total and segmental bone mineral content[6,7]. The technique's advantages are high precision and accuracy, low radiation dose, and increased scan speed. The disadvantages of DEXA are the high cost and the scarcity of centers performing the procedure. In addition, DEXA does not provide a measure of true bone density, since the increase in bone mass during the growing period is mainly caused by the increase in bone size, not density. Further, the reference absorptiometric data are usually adjusted to children's ages without taking into consideration the variability in the anthropometric data, which may lead to misinterpretation of the results[8-10]. The quantitative ultrasound bone sonometry (QUBS) technique developed recently has several advantages: it is radiation-free; it allows evaluation of bone density and may give information on skeletal fragility; it is not invasive and can be safely repeated; and it is less costly and is somewhat user-friendly, making it ideal for use in children[11-13].

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We assessed the validity of QUBS measurements in the radius and tibia bones as a screening tool for osteoporosis, in comparison to DEXA testing, in a group of patients with CRD.

MATERIALS AND METHODS

The study was approved by the Ethics Committee of Rambam Medical Center and informed consent was obtained from children's parents and guardians. Forty children diagnosed with CRD were recruited from the Pediatric Rheumatology Clinic, Rambam Medical Center, between October 2000 and October 2001. Thirty-two children had JIA diagnosed according to the revised International League of Associations for Rheumatology classification criteria[14]. Six children had SLE and 2 had JDM diagnosed according to the criteria published by the The Arthritis Foundation[15]. Thirty-one patients had chronic arthritis and 9 had systemic diseases without arthritis. All children were measured for height, weight, and body mass index (BMI) calculated by standard methods[16]. Pubertal staging was performed using the criteria of Tanner and Whitehouse[17]. Disease activity was assessed by a pediatric rheumatologist (RB) using the Pediatric Total Joint Assessment, Health Assessment Questionnaire for children, and Global Assessment of Disease Activity Scale for children with JIA[18]. Criteria for disease activity in SLE and JDM were the ones used in adults. Patients were also questioned for physical activity and nutrition habits.

Bone assessment was performed by the 2 methods on the same day, as follows.

Bone mineral density. BMD of the lumbar spine was measured by dual energy x-ray absorptiometry (DEXA) with a commercial DPX instrument (Lunar, Madison, WI, USA). The results of the second, third, and fourth lumbar vertebrae bone mineral content (BMC; g) divided by the projected area of these vertebrae (cm^2) represented BMD (g/cm^2). The results were compared to age and sex matched controls from the database at our Nuclear Medicine Institute, which has BMD measurements of more than 300 healthy Israeli children who represented the reference population for the examination. The World Health Organization has set the diagnostic criteria for osteopenia and osteoporosis in postmenopausal women only, as a T score at the spinal site between –1 SD and –2.5 SD, and more than –2.5 SD, respectively. Criteria for the diagnosis of osteoporosis in children or other populations or with other diagnosis methods have not been established.

Quantitative ultrasound bone sonometry. Measurements of the velocity of the ultrasound (US) wave, expressed as speed of sound (SOS) in m/s, were done using the Omnisense 7000S ultrasound bone sonometer device (Sunlight Ltd., Tel-Aviv, Israel) at 2 skeletal sites: distal third of radius and mid-shaft of tibia. The nondominant side was uniformly used for examinations, left usually, unless a history of fracture was present. The same operator performed all the examinations. Each value recorded was the mean of 3 consecutive determinations. Z scores (difference between the patient's value and the age-specific mean value divided by the reference group standard deviation) were calculated for each patient. The reference for the QUBS parameters was provided by the Sunlight Company, which has a large database based on more than 2000 examinations in healthy Israeli adults and children. Eighty age and sex matched children (2 for each patient) from this database were used as reference controls for our patients. Osteopenia was arbitrarily defined when the SOS Z scores were between –1 and –2.5 SD of control, and for osteoporosis when measured values were < –2.5 SD.

Statistical analysis. SPSS for Windows (SPSS, Chicago, IL, USA) was used for statistical tests. Bone SOS values of patients and controls were compared using the 2 tailed unpaired Student t test. The 2 tailed paired Student t test was used to compare within-group data. Pearson correlations were used to compare sets of paired data. The correlation of BMD/SOS with age at onset, disease duration, disease activity, and steroid or methotrexate (MTX) use was determined by linear regression analysis. Data are expressed as mean ± SD. A p value < 0.05 was considered statistically significant.

RESULTS

Patients. The study group included 27 girls and 13 boys with a mean age of 9.9 ± 4.3 years (range 4–18 yrs) and mean disease duration of 4.6 ± 3.9 years (range 0.5–15 yrs). Thirty-one children had chronic arthritis and 9 had systemic disease manifestations without chronic arthritis (5 SLE, 2 JDM, 2 systemic JIA). Of the 32 JIA patients, 21 had oligoarticular JIA (18 persistent, 3 extended), 6 polyarticular JIA, and 5 systemic JIA.

The mean weight, height, and BMI expressed as standard deviation scores were –1.5 ± 1.5 (range –4.1 to +2.8), –1.2 ± 1.9 (range –6.2 to +2.1), and –0.3 ± 1.5 (range –1.9 to +2.6), respectively. Twenty-five patients were taking corticosteroids (prednisone), with dosages that ranged from 0.5 to 1.5 mg/kg/day, for a period of at least 3 months. Fifteen patients were taking low dose MTX (10–15 mg/m^2/week).

Twenty-seven children (67.5%) had active disease at the time of the study and 33 were prepubertal (82.5%). A history of fracture was elicited in 5 (12.5%) children (all wrist fractures), all diagnosed with oligoarticular JIA.

Thirty-eight children with CRD underwent DEXA examinations and 39 had QUBS measurements. DEXA examinations were not performed in 2 children because they were too young (4 years old) and because of the absence of reference data. QUBS was technically unfeasible in one child because of overweight and thick subcutaneous tissue (BMI +2.6 SD score).

The results of QUBS and DEXA examinations in patients (as a group and by disease subtype) and in controls are shown in Table 1. DEXA examinations were performed only in patients with CRD. BMD and SOS Z scores < –1 SD were found in 45% and 38% of the patients, respectively. Overall, as a group, patients with CRD had radial/tibial SOS values and Z scores lower than controls ($p = 0.04$ and $p = 0.003$).

There were no statistically significant differences in SOS values or Z scores between children with CRD with various diagnoses.

Correlation of DEXA and US with patients' and disease characteristics. Lower scores of DEXA and radius/tibia SOS values correlated positively with age at disease onset ($r = 0.634$, $p < 0.001$, $r = 0.630$, $p < 0.001$, $r = 0.440$, $p < 0.004$, respectively) and with glucocorticoid treatment ($p < 0.005$, $p < 0.04$ only with tibia). Only DEXA correlated negatively with disease duration ($r = –0.375$, $p < 0.02$) and MTX therapy ($p < 0.04$).

When the results from children with pauciarticular JIA were compared to children with polyarticular disease, spine BMD was significantly lower in the latter group ($p = 0.03$), whereas SOS determinations did not differ between disease subtypes.

Correlation of DEXA and US with anthropometric data. Of note, in all children there was a significant correlation between DEXA and anthropometric characteristics, that is, weight ($r = 0.675$, $p < 0.0001$) and BMI ($r = 0.499$, $p =$

Table 1. US bone sonometry and DEXA results in patients and controls.

	Pauciarticular JIA, n = 21	Polyarticular JIA, 5/6 RF neg, 1/6 RF pos, n = 6	Systemic JIA, n = 5	Other CRD, n = 6	All Patients with CRD, n = 40	Controls, n = 64
US bone sonometry						
Radius: SOS, m/s	3703 ± 160	3733 ± 142	3832 ± 77	3819 ± 118	3740 ± 150	3788 ± 129*
Z score	–0.7 ± 1	–1 ± 0.7	0.4 ± 0.9	–0.4 ± 0.7	–0.6 ± 0.9	–0.05 ± 1**
Tibia: SOS, m/s	3631 ± 142	3684 ± 115	3684 ± 56	3742 ± 112	3664 ± 130	3706 ± 118*
Z score	–0.3 ± 0.8	–0.5 ± 0.7	0 ± 0.3	–0.3 ± 1.4	–0.3 ± 0.9	0.2 ± 1**
DEXA						
Spine BMD, g/cm^2	0.7 ± 0.3	0.7 ± 0.2	0.7 ± 0	0.9 ± 0.1	0.7 ± 0.2	
Z score	–0.7 ± 2	–2 ± 1.8***	–0.6 ± 1.5	–0.5 ± 0.8	–1 ± 1.8	

All data are expressed as mean ± SD. * p = 0.04; ** p = 0.003, compared to children with CRD; *** p = 0.03, compared to all other children with CRD.

0.002), with height showing the greatest correlation (r = 0.740, p < 0.0001). Radius SOS Z scores were weakly correlated with height (r = 0.47, p = 0.043) and BMI (r = 0.343, p = 0.043) but not with weight, whereas tibia SOS Z scores were not correlated with any of the anthropometric data.

Correlation of US with DEXA. A significant correlation was found between BMD at the lumbar spine and SOS at the radius (r = 0.54, p < 0.001; Figure 1), but not at tibia (r = 0.26, p < 0.12).

DISCUSSION

Children with JIA are at high risk of developing localized juxtaarticular and generalized osteoporosis. Prolonged steroid treatment and chronic disease activity appear to be the main factors responsible for the development of osteoporosis. However, many studies have described that inadequate bone mineralization is almost universal in children with JIA, even if they are not taking glucocorticosteroids[4,5,19]. The problem is aggravated by poor nutrition, medical treatments, and lack of physical activity. Early recognition of bone undermineralization would be important for prevention of the osteoporotic process. To this end, BMD should be assessed at the onset of CRD and during its course.

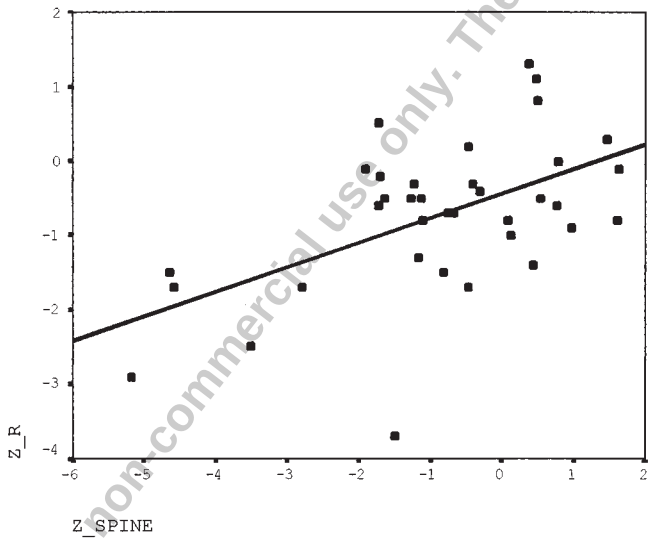

Figure 1. Correlation between lumbar spine BMD (Z Spine) and radius SOS (Z R), both expressed as Z scores in children with CRD (n = 36); r = 0.54, p < 0.001.

DEXA is presently the standard method for assessing BMD. The technique provides an apparent areal density (BMD) calculated as bone mineral content/bone area and expresses density as g/cm^2, therefore the standard DEXA technique measures not true bone mineral density (g/cm^3), but rather areal density (g/cm^2). This disadvantage is especially significant for growing children with chronic disorders associated with growth retardation; when comparing 2 bones of different size but with the same mineral content, the larger will show artificially higher BMD than the smaller one. To overcome this problem anthropometric-based prediction models for whole-body BMC have been proposed and are being validated in children[8-10]. Although DEXA has been used extensively for bone measurements in adults, there are only a limited number of studies in children. In most of these studies, including ours, the results of the patient groups are compared to controls of the same age, but not necessarily to children of the same size, which may lead to overdiagnosis of osteopenia, especially in children with chronic diseases, who tend to be smaller than their healthy counterparts[20,21]. While variations in size constitute a major drawback in the use and interpretation of DEXA in the pediatric age group, in this study, QUBS appeared to be less dependent on anthropometric parameters. These findings are in accord with those of other investigators[22].

Recently, QUBS technique has evolved as a surrogate measure of bone fragility that reflects structural properties of bone[11-13]. This technique uses the capacity of the US wave to provide information about the medium through which it is being propagated. Bone tissue can induce 2 types of alterations in the US waves, that is, change the velocity of the wave (speed of sound) or reduce the amount of energy transmitted and attenuate the wave (ultrasound attenuation). The

most investigated US parameters are speed of sound (SOS) (or ultrasound velocity) and broadband US attenuation (BUA) as alternatives to BMD. Statements concerning the correlation between US and BMD measurements at different skeletal sites are disputable because of the differences in the ratio of trabecular to cortical bone at different sites[23]. Using devices similar to the Omnisense bone sonometer, several studies have compared tibial and multisite SOS to lumbar, hip, or total body BMD as assessed by DEXA in healthy and disease affected adult populations[24,25]. In addition, other studies showed a significant correlation between DEXA and tibial SOS in both healthy control children and those with arthritis[25-30].

JIA is a complex disorder; osteopenia in JIA is multifactorial and each factor involved in its etiology affects differently axial/appendicular skeleton, trabecular or cortical bone, and bone formation or resorption in different disease stages. Appendicular skeleton is affected earlier and more severely in JIA, related to the periarticular bone loss. In addition, metabolic studies have shown that in JIA bone formation is more affected than bone resorption and this affects the appendicular skeleton more than the axial[5]. In contrast, glucocorticoid use is associated with significant bone loss, especially at axial sites; therefore comparing appendicular (radius, tibia) to the axial skeleton (lumbar spine) does not look so wrong, at least in patients treated with steroids. In any case, we examined the role of radius and tibia QUBS as a screening tool and did not intend to extrapolate any of our findings to the spinal site.

The results we obtained with both techniques were consistent with data from the literature showing a reduced BMD in patients with CRD[27]. On both techniques our patients showed a positive correlation of the reduced bone parameters, i.e., BMD and SOS, with early age at onset and with corticosteroid treatment. In addition, children with polyarticular course of JIA had significantly lower measurements of spine BMD than children with oligoarticular JIA, similar to findings in other studies[3,18,28]. In contrast to others, we were unable to determine a correlation between disease activity and osteoporosis, probably because of the study design. Cross-sectional studies are not a suitable design to assess the effect of disease activity on bone mass. Bone status evaluated in cross-sectional studies reflects the "outcome" of genetic and environmental factors including years of disease activity, medication effects, functional capacity, diet, and more. Active disease in the past may leave permanent marks on children's skeletons even after the disease has become quiescent. Longitudinal studies of BMD or assessment of biochemical indices are more sensitive in detection of the influence of disease activity on bone[5,29,30].

On the other hand, we detected a negative effect of low dose MTX treatment on bone density only with DEXA studies. The question whether low dose MTX affects bone metabolism remains open. A recent study on psoriatic/rheumatoid arthritis in adult patients failed to show a deleterious effect of MTX treatment on axial bone mass[31]. However, many of their subjects were postmenopausal women, while our group consisted of young children. The number of patients in our group who were treated with MTX was too small to draw conclusions, and further studies are needed to resolve this question.

There are several limitations to our study. We had a limited number of heterogeneous patients, and few had abnormalities of bone quality assessed as BMD by DEXA or SOS by ultrasound; larger studies are needed to strengthen our findings and conclusions. Additionally, we use arbitrarily defined set-points for the definition of osteoporosis and osteopenia by QUBS, although the validity of these criteria is not yet established.

We conclude that the quantitative ultrasound bone sonometry technique for detecting osteoporosis in peripheral bones is less dependent on body size of children, and gives results that are in great part comparable to those of lumbar DEXA. QUBS seems to be a valid and inexpensive method for screening of patients with pediatric CRD. Because ultrasound is noninvasive, is safely repeated, and does not expose patients to radiation, QUBS is a promising means of evaluating bone quality in at-risk children.

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REFERENCES

1. Woo PM. Growth retardation and osteoporosis in juvenile chronic arthritis. Clin Exp Rheumatol 1994;12 Suppl 10:S87-90.
2. Bardare M, Bianchi ML, Furia M, Gandolini GG, Cohen E, Montesano A. Bone mineral metabolism in juvenile chronic arthritis: the influence of steroids. Clin Exp Rheumatol 1991;9 Suppl 6:29-31.
3. Laan RF, Buijs WC, Verbeek AL, et al. Bone mineral density in patients with recent onset rheumatoid arthritis: influence of disease activity and functional capacity. Ann Rheum Dis 1993;52:21-6.
4. Cassidy JT, Hillman LS. Abnormalities in skeletal growth in children with juvenile rheumatoid arthritis. Rheum Dis Clin North Am 1997;23:499-522.
5. Pepmueller PH, Cassidy JT, Allen SH, Hillman LS. Bone mineralization and bone mineral metabolism in children with juvenile rheumatoid arthritis. Arthritis Rheum 1996;39:746-57.
6. Front D, Israel O, Jerushalmi J, et al. Quantitative bone scintigraphy using SPECT. J Nucl Med 1989;30:240-5.
7. Kotaniemi A, Savolainen A, Kautiainen H, Kroger H. Estimation of central osteopenia in children with chronic polyarthritis treated with glucocorticosteroids. Pediatrics 1993;91:1127-30.
8. Prentice A, Parsons TJ, Cole TJ. Uncritical use of bone mineral density in absorptiometry may lead to size-related artifacts in the identification of bone mineral determinants. Am J Clin Nutr 1994;60:837-42.
9. Compston JE. Bone density: BMC, BMD, or corrected BMD? Bone 1995;16:5-7.
10. Nelson DA, Koo WW. Interpretation of absorptiometric bone mass

measurements in the growing skeleton: issues and limitation. Calcif Tissue Int 1999;65:1-3.
11. Prins SH, Jørgensen HL, Jørgensen LV, Hassager C. The role of quantitative ultrasound in the assessment of bone: a review. Clin Physiol 1998;18:3-17.
12. Mughal MZ, Ward K, Qayyum N, Langton CM. Assessment of bone status using the contact ultrasound bone analyser. Arch Dis Child 1997;76:535-6.
13. Hausler KD, Rich PA, Barry EB. Water bath and contact methods in ultrasonic evaluation of bone. Calcif Tissue Int 1997;61:26-9.
14. Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban 1997. J Rheumatol 1998;25:1991-4.
15. Klippel JH. Primer on the rheumatic diseases. Atlanta: The Arthritis Foundation; 1997.
16. Cole TJ, Freeman JV, Preece MA. Body mass index references curves for the UK, 1990. Arch Dis Child 1995;73:25-9.
17. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity and stages of puberty. Arch Dis Child 1976;51:170-9.
18. Duffy CM, Lovell DJ. Assessment of health status function and outcome. In: Zorab R, Carrol C, editors. Textbook of pediatric rheumatology. Philadelphia: W.B. Saunders; 2001:178-87.
19. Brik R, Keidar Z, Schapira D, Israel O. Bone mineral density and turnover in children with systemic juvenile chronic arthritis. J Rheumatol 1998;25:990-2.
20. Ellis KJ, Shypailo RJ, Pratt JA, Pond WG. Accuracy of dual-energy x-ray absorptiometry for body-composition measurements in children. Am J Clin Nutr 1994;60:660-5.
21. Schonau E. Problems of bone analysis in childhood and adolescence. Pediatr Nephrol 1998;12:420-9.
22. van den Bergh JP, Noordam C, Ozyilmaz A, Hermus AR, Smals AG, Otten BJ. Calcaneal ultrasound imaging in healthy children and adolescents: relation of the ultrasound parameters BUA and SOS to age, body weight, height, foot dimensions and pubertal stage. Osteoporos Int 2000;11:967-76.
23. Baron R. Anatomy and ultrastructure of bone. In: Coe FL, Favus MJ, editors. Primer on the metabolic bone diseases and disorders of mineral metabolism. New York: Raven; 1993:3.
24. Prevrhal S, Fuerst T, Fan B, et al. Quantitative ultrasound of the tibia depends on both cortical density and thickness. Osteoporos Int 2001;12:28-34.
25. Van Rijn RR, van der Sluis IM, Lequin MH, et al. Tibial quantitative ultrasound versus whole body and lumbar spine DXA in a Dutch pediatric and adolescent population. Invest Radiol 2000;35:548-52.
26. Njeh CF, Shaw N, Gardner-Medwin JM, Boivin CM, Southwood TR. Use of quantitative ultrasound to assess bone status in children with juvenile idiopathic arthritis: a pilot study. J Clin Densitom 2000;3:251-60.
27. Falcini F, Bindi G, Ermini M, et al. Comparison of quantitative calcaneal ultrasound and dual energy X-ray absorptiometry in the evaluation of osteoporotic risk in children with chronic rheumatic diseases. Calcif Tissue Int 2000;67:19-23.
28. Polito C, Strano CG, Rea L, et al. Reduced bone mineral content and normal serum osteocalcin in non-steroid-treated patients with juvenile rheumatoid arthritis. Ann Rheum Dis 1995;54:193-6.
29. Gough AK, Peel NF, Eastell R, Holder RL, Lilley J, Emery P. Excretion of pyridinium crosslinks correlates with disease activity and appendicular bone loss in early rheumatoid arthritis. Ann Rheum Dis 1994;53:14-7.
30. Shenstone BD, Mahmoud A, Woodward R, et al. Longitudinal bone mineral density changes in early rheumatoid arthritis. Br J Rheumatol 1994;33:541-5.
31. Cranney AB, McKendry RJ, Wells GA, et al. The effect of low dose methotrexate on bone density. J Rheumatol 2001;28:2395-9.