

# Bone Status Evaluation with Calcaneal Ultrasound in Children with Chronic Rheumatic Diseases. A One Year Followup Study

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**ABSTRACT.** *Objective.* To evaluate at baseline and after one year the bone status in children with chronic rheumatic diseases (CRD) using quantitative ultrasound techniques.

*Methods.* We evaluated bone status in 67 children, 52 female, 15 male, age range 2.80 to 18.10 years; 46 juvenile idiopathic arthritis, 11 juvenile dermatomyositis, and 10 systemic lupus erythematosus. Twenty-seven of 67 patients were taking only nonsteroidal antiinflammatory drugs (NSAID), 11 were given NSAID and methotrexate (MTX), 15 were also receiving steroids (prednisone), and 14 patients were given steroids and alendronate. Broadband ultrasound attenuation (BUA) by bone was determined at the left calcaneus using two 12.5 mm diameter, 1 MHz transducers mounted in hand-held calipers linked to a pediatric contact ultrasound bone analyzer.

*Results.* At baseline in the whole patient group mean BUA values and Z scores were significantly lower than in controls:  $41.84 \pm 21.64$  vs  $61.69 \pm 17.42$  dB/MHz ( $p < 0.001$ ); Z score  $-0.91 \pm 1.07$  vs  $0.09 \pm 0.62$  in controls ( $p < 0.001$ ). At one year followup in the patient group BUA values were significantly increased compared to baseline (BUA  $46.43 \pm 21.51$  dB/MHz;  $p = 0.002$ ); no significant difference was found in Z score. The 15 children receiving steroids in addition to NSAID and MTX showed a decrease in BUA value at one year (NS), while Z scores were significantly reduced compared to baseline ( $-1.45 \pm 1.40$  vs  $-1.08 \pm 1.11$ ;  $p < 0.05$ ). The 14 patients in the group receiving NSAID and MTX who also received alendronate showed significant increases in BUA ( $56.93 \pm 19.32$  vs  $44.21 \pm 15.67$ ;  $p < 0.001$ ) and Z score ( $-0.87 \pm 1.19$  vs  $-1.56 \pm 0.82$ ;  $p < 0.002$ ).

*Conclusion.* Contact ultrasound bone analysis at the calcaneus is a useful tool in the assessment and monitoring of bone status in children with CRD. (J Rheumatol 2003;30:179–84)

## Key Indexing Terms:

CHRONIC RHEUMATIC DISEASES  
CONTACT ULTRASOUND BONE ANALYZER

BROADBAND ULTRASOUND ATTENUATION  
BONE MINERAL STATUS

Osteoporosis is common in children with chronic rheumatic diseases (CRD), particularly in those with prolonged active disease or requiring longterm treatment with high dose corticosteroids<sup>1</sup>. Bone loss may be localized at both juxtaarticular and subchondral sites, or generalized<sup>2,3</sup>. Many factors are responsible for loss of bone mass during the disease course — inflammation, reduced physical activity, imbalance of nutritional intake and malabsorption, and delayed puberty play a role in the development of bone damage<sup>4-8</sup>. As the overall inci-

dence of osteoporosis in patients treated with corticosteroids for 6 months or more is higher than 50%, the risk of vertebral and long bone fractures is significantly increased in children with CRD<sup>5,6,9</sup>. Thus, early evaluation of bone mineral content during the disease course is strongly suggested.

Dual energy x-ray absorptiometry (DEXA) is considered the gold standard technique in the estimation of bone mineral density (BMD). However, the machinery is expensive and the procedure exposes subjects to ionizing radiation and is feasible in very young patients only with sedation<sup>10,11</sup>.

In recent years, the quantitative high frequency sound (ultrasound) technique (QUS), a radiation-free tool that measures the transmission of ultrasound waves through the heel, has been proposed, in both adults and children<sup>12-16</sup>, for assessment of bone density and “bone quality” by measurements of ultrasound wave attenuation by bone; this is called broadband ultrasound attenuation (BUA)<sup>17-23</sup>. This procedure is easy to perform, accessible, relatively inexpensive, and feasible even in children<sup>24</sup>. Comparing BMD values by DEXA at the lumbar spine and BUA at the calcaneal level, we have reported that the 2 techniques are comparable in the measurement of bone density in children with CRD<sup>24</sup>.

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We undertook to prove that quantitative ultrasound techniques can be used to monitor bone status and to quantify the amount of change occurring due to disease or treatment over a one year period in a group of children with CRD.

## MATERIALS AND METHODS

**Patients.** Patients were consecutively recruited during the period 1999–2000 among those followed for CRD at the Paediatric Department, Rheumatology Unit, University of Florence (Table 1). Sixty-seven children, 52 girls and 15 boys, age range 2.80–18.10 years (mean  $10.21 \pm 4.29$ ), who agreed to take part in the study, were enrolled. Mean disease duration was  $5.17 \pm 3.02$  years (range 1.00–11.90). Forty-six patients had juvenile idiopathic arthritis (JIA) — 24 with pauciarticular and 22 with polyarticular onset, 11 had juvenile dermatomyositis (JDM), and 10 had systemic lupus erythematosus (SLE). Informed consent was obtained from the parents of patients aged less than 18 years and the study was approved by the ethical committee of A. Meyer Hospital, Florence.

Twenty-seven of 67 patients were taking only nonsteroidal antiinflammatory drugs (NSAID), 11 were taking NSAID and methotrexate (MTX), and 15 were also receiving oral corticosteroids (prednisone) at dosage of 0.5 to 1 mg/kg/day. Fourteen were also receiving alendronate (5 or 10 mg/day, according to body weight) (Table 2).

During the study period, 6 children received local steroids in the knees and/or ankles (triamcinolone hexacetonide 20 or 40 mg, according to body weight less or more than 20 kg, respectively).

Seventy healthy subjects attending the pediatric outpatient department of A. Meyer Hospital with no evidence of CRD and matched for sex, age, pubertal stage, and weight acted as controls.

**Methods.** Height, expressed as SD score (SDS), was calculated averaging 3 measurements performed with a Harpenden stadiometer. Weight was measured on a standard clinical balance. Body mass index (BMI) was calculated according to the formula weight (kg)/height (m)<sup>2</sup>. Pubertal staging was performed using the criteria of Tanner and Whitehouse<sup>25</sup>. BUA (dB/MHz), which indicates the frequency dependence of ultrasound attenuation in the frequency range 200–600 kHz, was determined at calcaneal level using two 12.5 mm diameter, 1 MHz transducers mounted in hand-held calipers linked to the pediatric contact ultrasound bone analyzer (CUBA) (McCue Ultrasonics, Winchester, UK). BUA was determined as described<sup>24</sup> on both sides in patients and in controls. The pediatric CUBA is a specific pediatric system

Table 1. Clinical data in 67 patients with chronic rheumatic diseases (CRD) and 70 controls at the start of the study.

Clinical Data	Patients with CRD	Controls
Females, n	52	56
Males, n	15	14
Age, yrs	$10.21 \pm 4.29$	$10.04 \pm 4.13$
Height, SDS	$-0.94 \pm 1.82$	$-0.29 \pm 2.06$
BMI, SDS	$0.23 \pm 1.61$	$0.28 \pm 1.49$
Mean disease duration, yrs	$5.17 \pm 3.02$	—
Pubertal stage, n		
I	31	28
II	10	14
III	15	17
IV	11	11
Disease, n		
JIA	46	—
DM	11	—
SLE	10	—

SDS: standard deviation score, BMI: body mass index, JIA: juvenile idiopathic arthritis, DM: dermatomyositis.

Table 2. Systemic and local treatments in 67 patients with chronic rheumatic diseases during the study.

Treatments	No. of Patients
Systemic treatments	
Nonsteroidal antiinflammatory drugs (NSAID)	27
NSAID and methotrexate (MTX)	11
NSAID, MTX, and corticosteroids (prednisone, 0.5–1.0 mg/kg/day)	15
NSAID, MTX, corticosteroids (prednisone, 0.5–1.0 mg/kg/day), and alendronate (5 or 10 mg/day, according to body weight)	14
Local treatment (knees and/or ankles)	5 pauciarticular with NSAID therapy 1 polyarticular with NSAID + MTX therapy
Triamcinolone hexacetonide 20 or 50 mg, according to weight less or more than 20 kg	6

containing normative data for children aged 5–15 years (Z score = 0, SD 1). We have, however, also compiled reference values for children aged 3–18 years with our personal controls (about 800 healthy subjects attending the pediatric outpatient department of A. Meyer Hospital). References values for children 5–15 years were fully comparable to CUBA normative data; we have used our references values for children younger than 5 years and older than 15 years.

In this study, we also evaluated an age, sex, and pubertal stage matched control group of 70 children.

Z scores, the difference between the patient's value and the age-specific normal value divided by the normal group's standard deviation, were calculated for each patient.

In 53 patients and in all the controls the 2 measurements did not differ significantly and the left heel only was considered. In 14 patients with JIA in whom a significant difference between the 2 sides was determined, the least compromised side was considered for statistical comparisons. On the basis of the manufacturer's instructions and of our data on healthy controls, a difference between the 2 limbs  $\geq 8\%$  was considered significant. After one year, both sides were reevaluated in these 14 patients, 6 of whom had had during followup an intraarticular corticosteroid injection in the knee or ankle of the more affected limb. These patients were evaluated by QUS every 6 months. All assessments were performed and analyzed by the same person (GB). Each value was the mean of 3 consecutive determinations. Quality control measurement of QUS equipment was performed daily. The *in vitro* coefficient of variation for BUA using phantoms was 1.8%, and the *in vivo* coefficient of variation for BUA in subjects 3–18 years old was 3.8%. *In vivo* calcaneus ultrasound measurement precision was calculated in 40 healthy volunteers over 5 consecutive determinations performed over 30 minutes.

After one year of followup, calcaneal bone ultrasound attenuation was repeated in all patients with the same equipment and by the same person (GB).

**Statistical analysis.** All results are expressed as mean  $\pm$  SD. Comparisons between patients and controls were made using the 2 tailed unpaired Student t test. The 2 tailed paired Student t test or, where the data were skewed, the Wilcoxon signed-rank test was used to compare data within groups. To compare repeated measures within the group of 6 children who received local steroids in the knees and/or ankles the Friedman test was used. The Pearson correlation test was used to determine correlation coefficients for different variables (age, pubertal stage, weight, height, disease duration), while Spearman's rank test was carried out to assess correlation coefficients in disease type. A multiple stepwise regression was performed to determine variables that may correlate independently with changes in BUA values. The pre-

dictors used in the final model were the parameters showing a significant correlation with BUA in the univariate analysis. P values < 0.05 were considered statistically significant.

## RESULTS

At baseline BUA and Z scores were significantly lower in patients than in controls: BUA  $41.84 \pm 21.64$  vs  $61.69 \pm 17.42$  dB/MHz, respectively ( $p < 0.001$ ); Z score  $-0.91 \pm 1.07$  vs  $0.09 \pm 0.62$  ( $p < 0.001$ ).

At one year followup in the whole group of patients BUA values were significantly increased compared to baseline:  $46.43 \pm 21.51$  vs  $41.84 \pm 21.64$  dB/MHz ( $p = 0.002$ ); while no significant difference was seen in Z score:  $-0.86 \pm 1.19$  vs  $-0.91 \pm 1.07$ . Patients receiving NSAID (38 subjects) showed a similar trend for both BUA values (from  $39.13 \pm 25.40$  dB/MHz to  $43.39 \pm 22.04$  dB/MHz after one year;  $p < 0.05$ ) and BUA Z scores (from  $-0.61 \pm 1.03$  to  $-0.62 \pm 1.05$  after one year).

Within this group, in the 24 patients with pauciarticular JIA and 27 children receiving NSAID alone, BUA values at one year followup were significantly increased compared to baseline [ $40.42 \pm 18.60$  vs  $35.50 \pm 22.15$  dB/MHz ( $p < 0.05$ );  $38.76 \pm 25.41$  vs  $43.45 \pm 22.74$  dB/MHz ( $p < 0.05$ ), respectively], while Z score was not significantly changed ( $-0.51 \pm 0.85$  vs  $-0.54 \pm 0.92$ ;  $-0.54 \pm 1.0$  vs  $-0.53 \pm 1.03$ ). In contrast, in the 14 patients with polyarticular JIA and the 11 children receiving MTX plus NSAID, both BUA values and Z scores remained unchanged at one year followup (BUA  $45.36 \pm 30.03$  vs  $48.50 \pm 26.95$  dB/MHz,  $40.33 \pm 26.86$  vs  $43.22 \pm 20.90$  dB/MHz, respectively; Z scores  $-0.85 \pm 1.14$  vs  $-0.81 \pm 1.31$ ,  $-0.83 \pm 1.14$  vs  $-0.82 \pm 1.10$ , respectively).

Fifteen children who received steroids in addition to NSAID and MTX showed a decrease in BUA value at one year, although not significant ( $44.33 \pm 20.26$  vs  $46.47 \pm 15.05$  dB/MHz). In contrast, Z score values were significantly reduced compared to baseline:  $-1.45 \pm 1.40$  vs  $-1.08 \pm 1.11$  ( $p < 0.05$ ).

At one year followup, all 14 patients who received alendronate in addition to steroids showed a significant increase in both BUA and Z scores. BUA was  $56.93 \pm 19.32$  vs  $44.21 \pm 15.67$  dB/MHz ( $p < 0.001$ ) and Z score  $-0.87 \pm 1.19$  vs  $-1.56 \pm 0.82$  ( $p = 0.002$ ).

Thus, in the whole group, only 43.3% of patients (29/67) showed an increase in Z score over the one year study period, and within the groups, 47.4% (18/38) of patients receiving NSAID and NSAID plus MTX, 71.4% (10/14) of patients who received steroids and alendronate, and only 6.7% (1/15) of children who received steroids in addition to NSAID and MTX showed an increase in Z score.

To detect if joint inflammation in the lower extremities might influence the evaluation of bone density, BUA was measured at both calcanea. In 14 patients, 13 with pauciarticular JIA and one with polyarticular JIA, a clear and significant asymmetry of joint involvement in the lower limbs was noted: BUA of less involved limb  $48.07 \pm 25.04$  dB/MHz vs BUA of

more involved limb  $35.50 \pm 22.48$  dB/MHz ( $p < 0.001$ ); Z score of less involved limb  $0.04 \pm 0.93$  dB/MHz vs more involved limb  $-0.81 \pm 0.71$  ( $p < 0.001$ ). After one year BUA and Z score values did not differ between the 2 sides (Figures 1 and 2).

In the 6 children who received local steroids in the knees and/or ankles, BUA was evaluated both 6 months and one year after injection. The 2 limbs showed a marked difference in variation of BUA and Z score values during followup (Figures 3 to 6). As can be seen, the limb with intraarticular corticosteroid injection showed a much greater increase of BMD detected by BUA compared to the other side, even after only 6 months. Indeed, the mean percentage of BMD variation over one year was 52.3% in the treated side (30.2% in the first 6 months, 22.1% in the last 6 months) and 17.3% in the non-treated side (5.1% in the first 6 months, 12.2% in the last 6 months).

After one year, changes in BUA values displayed the fol-

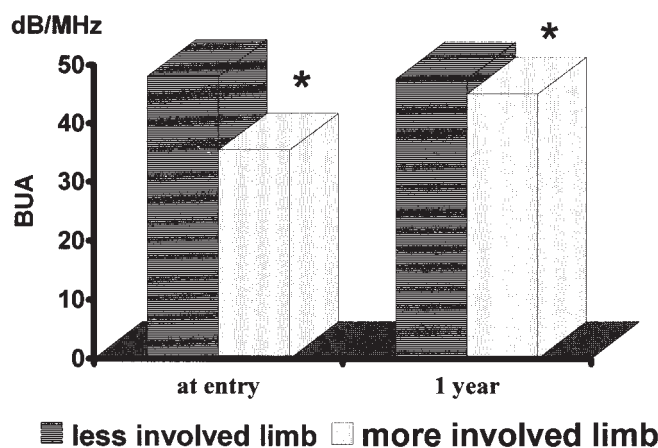


Figure 1. Mean BUA values in 14 children with asymmetry of joint involvement in the lower limbs at entry into the study and after one year of followup. \* $p < 0.001$ .

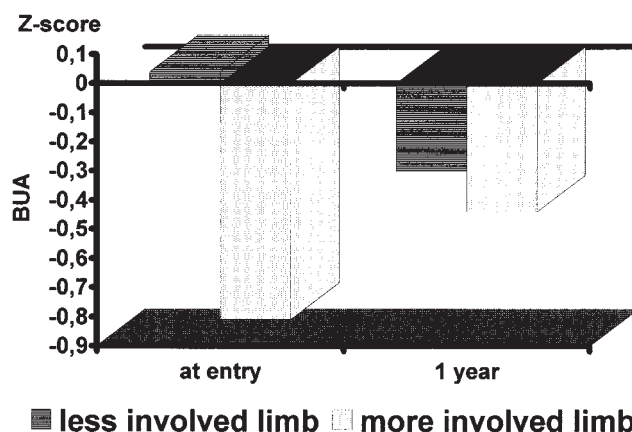


Figure 2. Mean BUA Z score values in 14 children with asymmetry of joint involvement in the lower limbs at entry into the study and after one year of followup.

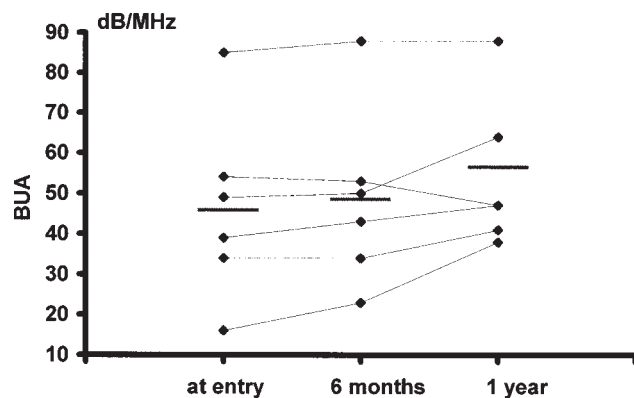


Figure 3. Change of mean BUA values in the less involved lower limb of the 6 children who received local steroids.

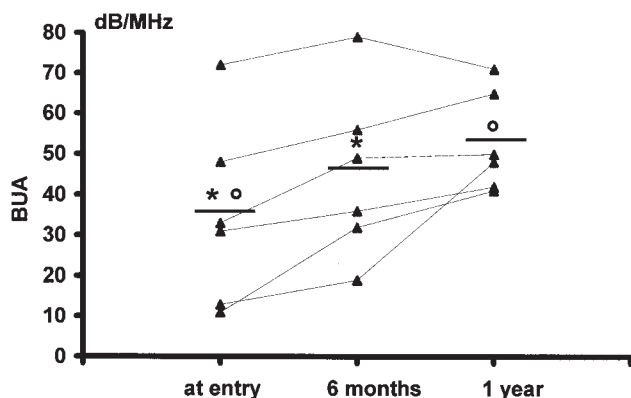


Figure 4. Change of mean BUA values in the more involved lower limb of the 6 children who received local steroids. \*, °  $p < 0.05$ .

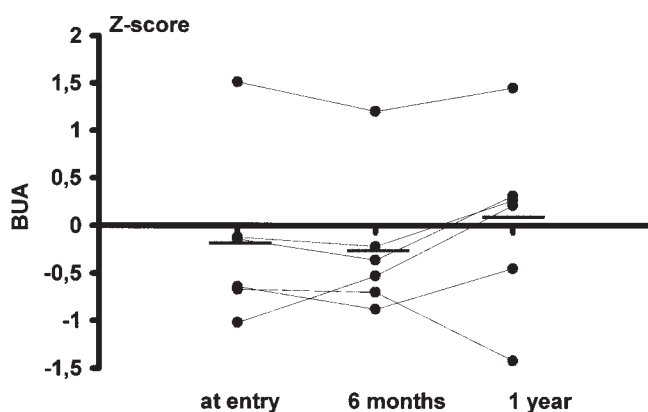


Figure 5. Change of mean BUA Z score values in children with chronic rheumatic diseases in the less involved limb.

lowing correlations: BUA increased with height ( $r = 0.33$ ,  $p < 0.001$ ), weight ( $r = 0.28$ ,  $p < 0.002$ ), age ( $r = 0.23$ ,  $p < 0.05$ ), and pubertal stage ( $r = 0.21$ ,  $p < 0.05$ ); while no significant correlation was found with disease duration ( $r = -0.10$ ,  $p = \text{nonsignificant}$ ) or disease type ( $r_s = -0.01$ ,  $p = \text{NS}$ ).

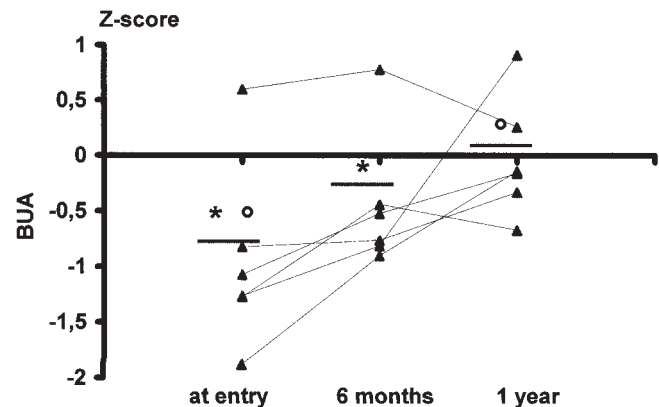


Figure 6. Change of mean BUA Z score values in children with chronic rheumatic diseases in the more involved limb. \*, °  $p < 0.05$ .

In a multiple stepwise regression analysis, the effect of weight, age, pubertal stage, and disease activity disappeared and changes in BUA values were influenced only by height ( $F = 14.56$ ,  $p < 0.001$ ), which accounted for 11% of variance in BUA values. After that, BUA values were corrected for height, and no other variables were determinants for significant difference in BUA values.

## DISCUSSION

Osteopenia and osteoporosis are common in children with chronic rheumatic diseases, mainly because of chronic inflammation and corticosteroid treatment. Vertebral and long bone fractures can occur after even a minimal trauma, impairing physical activity and further reducing bone mineralization.

To introduce the appropriate treatment for bone loss, it is important to promptly evaluate bone status at disease onset and to prospectively measure the demineralization process during the course of illness. As many factors are involved in inducing osteoporosis (e.g., genetic predisposition, nutritional intake, physical activity)<sup>4,7,8</sup>, it is difficult to predict the severity of bone damage at disease onset. Thus, it is necessary to evaluate each patient with periodic measurements of bone status, and if needed to introduce the currently available treatment(s) in order to control bone loss<sup>1,2,24,26</sup>.

Recent development of methods for measuring mineral content in children has markedly improved our ability to determine bone loss during the course of CRD. At the moment, the 3 commonly accepted techniques include DEXA, quantitative computed tomography (QCT), and quantitative ultrasound.

DEXA remains the gold standard of measurement of BMD and has been increasingly used in children; however, it exposes subjects to radiation, is expensive, and is scarcely feasible in young patients. During the early years, subjects' compliance is low and in most cases general sedation is required. In addition, DEXA is unable to account for the large changes in body and skeletal size occurring during growth.

Quantitative computed tomography could be a valid tool in



assessing both the volume and the density of bone in the axial and appendicular skeletons, without influence of body or skeletal size, with a major advantage in children over other modalities. However, the high cost, the inaccessibility of CT scanners, and the higher radiation dose limit its use in children<sup>27</sup>.

Currently, QUS seems to be an appealing alternative to measure bone status in children: low cost, portability, short duration of examination, and absence of radiation make this procedure promising<sup>28</sup>. However, studies using this technique have been performed almost exclusively in adults and few data are available in children, particularly in those with CRD<sup>23,24,29,30</sup>.

In adults, a positive significant correlation was detected between lumbar spine BMD determined by DEXA and BUA measured using QUS at the calcaneum ( $r = 0.83$ ,  $p < 0.001$ ); moreover, QUS has the potential to give more information not only on bone mineralization, as DEXA does, but also on bone structure and elasticity<sup>20</sup>. Indeed, within trabecular bone the ultrasound attenuation is accompanied by dispersion of ultrasound waves by trabeculae, which act selectively as filters for specific frequencies. Gluer, *et al*<sup>19</sup> observed that BUA values of trabecular bone *in vitro* depended on both its microstructure and trabecular orientation, and Hans, *et al*<sup>20</sup> suggested that calcaneal BUA values reflect more the microarchitecture of bone than the bone mass. Therefore, indirect evidence suggests that BUA values might be related not only to bone density but to bone architecture as well.

A study<sup>29</sup> in 22 children with juvenile chronic arthritis, comparing DEXA at lumbar spine and QUS velocity at the right mid-tibia, showed a significant correlation, albeit with wide 95% confidence intervals. Our group has also determined a significant correlation between CUBA and DEXA by a direct comparison of calcaneal BUA values with lumbar BMD measured by DXA, in a group of 53 children with rheumatic diseases<sup>24</sup>. Calcaneal BUA was significantly correlated ( $r = 0.83$ ,  $p < 0.001$ ) with lumbar spine BMD. Age and sex correction (Z score) did not change the relationship between BUA and BMD ( $r = 0.80$ ,  $p < 0.001$ ). In this study we have also assessed the mean rate of change of BMD and BUA values over time, since in 22 patients who were reevaluated with both methods after one year the mean percentage of variation ( $\Delta\%$ ) was similar for BMD (+7.4%) and BUA (+9.2%). Also, there was significant correlation between  $\Delta\%$  of BMD and BUA ( $r = 0.76$ ,  $p < 0.001$ ) and  $\Delta\%$  of bone mineral content and BUA ( $r = 0.74$ ,  $p < 0.001$ ).

In this study we have extended our previous observations showing that bone status can be monitored over time with CUBA in children with rheumatic diseases. In this regard, it is important to note that the procedure should be performed by the same investigator.

Although linear regression analysis revealed a significant correlation between BUA values and height, weight, chronological age, pubertal status, and disease type, multiple regres-

sion analysis demonstrated that only height was correlated with BUA variations over the one year study period, with a variance of 11%. After correction for height, no other determinants were significant for differences in BUA values. Not surprisingly, we have seen that patients who were taking corticosteroids decreased their bone mass, while those who were taking alendronate had an increase in Z score after one year. It is noteworthy that patients who had an intraarticular steroid injection had an increase in BUA values: even if corticosteroids should theoretically induce local osteopenia, it is likely that the decreased inflammation and increased articular motility would be responsible for the observed improvement, rather than worsening, of bone status in these joints.

Although DEXA remains the best way to measure BMD, our study indicates that CUBA is a noninvasive and feasible tool for assessment and monitoring of bone status in children with chronic rheumatic diseases. However, drug treatment and local factors such as active arthritis and previous intraarticular therapy must be taken into account.

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