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Can ultrasound be used to estimate bone mineral density in children with growth problems?

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Abstract

Aim—To assess predictability of bone mineral density (BMD) of the lumbar spine (LS) determined by dual energy x-ray absorptiometry (DXA) using by ultrasound- speed of sound of the right and left radii (SOS-R and SOS-L) in patients with growth problems.

Methods—Ultrasound and DXA were compared in patients with advanced, normal and delayed bone ages assessed by Greulich and Pyle (GP) and Tanner and Whitehouse (TW3) methods.

Results—There was a strong correlation (r), of raw scores, between SOS-R and SOS-L, $r=0.81$, $P=0.000$, and their respective Z-scores, $r=0.78$, $P=0.000$. Z-score correlations were poor between SOS-R or SOS-L and LS-BMD. Sensitivity, specificity, positive- and negative predictive value of SOS-R, Z-scores for predicting normal (>-1 to <1) and low (<-1) LS-BMD, Z scores were poor. For high (>1) LS-BMD, Z scores were 22%, 93%, 29%, and 90% respectively for SOS-R and for SOS-L, 25%, 89%, 20%, and 91%. For very low (<-2) LS-BMD, SOS-R and SOS-L were the same, respectively 29%, 91%, 40%, and 86%.

Conclusion—Ultrasound of the radius is a poor predictor of radiologically assessed BMD at the lumbar spine, especially with delayed bone age.

Keywords

delayed bone age; growth; radial ultrasound; DXA

Introduction

Dual energy x-ray absorptiometry (DXA) is the recommended method for assessing bone mineral density (BMD). The lumbar spine (LS) and femoral neck are the sites that provide critical information for patient management in adults [1]. In children the LS has been the primary site for assessment of BMD although total body (TB) BMD is also used in current

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pediatric clinical practice [2]. A BMD of -2 standard deviations (SD) is considered abnormal; in adults it is expressed as a T-score (compared to young healthy age matched controls) whereas for children this is expressed as a Z-score (compared with age and gender matched controls). The validity of the DXA methodology as an accurate assessment of bone mineralization in children has been debated. Specifically, BMD is a two-dimensional measure that does not fully reflect the 3-dimensional structure of bone, and in particular the volumetric change of bone mineralization in growing children [2, 3]. This is further complicated in deriving a score for TB-BMD where a single density value is assigned to the whole skeleton. Despite these limitations DXA remains the only valid methodology to assess bone mineral status in children that can be applied to routine clinical practice.

Ultrasound has been proposed as an alternative method for assessment of bone density [4]. It is especially attractive in growing children in that there is no exposure to ionizing radiation. Additional advantages include portability, ease of use and low cost. Methodologies that employ ultrasound are based on the principle that the intensity and speed of sound waves are measurably altered when passing through a substance. Indeed, the change in the speed of sound (SOS) through bone has been shown to correlate to BMD measurements by DXA in adults [4]. Further, measurement of SOS along the axis of cortical bone may be less affected by bone size and has been shown to correlate with DXA measurements in children [5]. A correlation between two methods however does not necessarily imply that one can be substituted for the other [6, 7]. In addition, reports demonstrate a difference between ultrasound and DXA when assessing bone mineral status in certain pediatric populations [3]. In children with poor growth, reduced BMD may be a consequence of poor bone mineralization and/or reflective of underlying skeletal immaturity. The aim of the present study was to determine the efficacy of BMD measured by ultrasound compared to DXA in children with potential growth problems and how this may be affected by delayed or advanced bone age. Low BMD is a major concern in clinical practice and our aim was to examine whether ultrasound would be able to predict low or normal BMD as defined by the current standard LS-BMD Z-score.

Methods

This was a single-center, cross-sectional study approved by the University of Minnesota Institutional Review Board. Written informed consent was obtained from the patients, parents or guardians. Pediatric patients being evaluated in the endocrinology clinic and scheduled to undergo a hand radiograph for bone age were recruited to have ultrasound-SOS assessment of the left radius and DXA of the LS.

Bone Age

As part of routine standard care, posterior-anterior radiographs were taken of the left hand and wrist for evaluation of bone age by a trained technologist on a single cassette (Agfa CR system, Agfa, Ridgefield Park, New Jersey) using the following parameters: filter 1.0 mm aluminum, film focus distance 40 inches, focal spot 0.6/1.0 mm, tube voltage 60kVp, exposure 1.6–3.2 mAs. The digital images were then uploaded to a picture archiving and communication system (PACS; IDX Imagecast, Burlington, Vermont) for analysis. The

images were assessed by a pediatric radiologist using the Greulich and Pyle (GP) atlas and used as part of this study (see method section on statistics below).

Ultrasound- Speed of Sound

Subjects underwent SOS at both distal radii using the Sunlight Omnisense 7000S device (Sunlight Technologies, Rehovot, Israel) that employs a hand-held ultrasound probe that emits and receives sound. In brief, the technology involves an ultrasound pulse of a specific frequency that is refracted through a specific angle from soft tissue to bone, with a proportion of the emitted sound returning from the bone at the same angle [8, 9]. The device calculates the SOS- meters/second (m/sec) by the time from emission of the signal and its detection at the transducer. The manufacturer's standard measurement techniques were used to define the site of measurement; the radial site is halfway between the edge of the olecranon and the end of the middle finger. Ultrasound gel was applied and the probe moved to the lateral and medial sides in a smooth motion over the area of interest. The manufacturer's internal algorithm determined 3 cycles that generated consistent SOS values and then combined the data from these cycles to generate a single SOS value for the measurement that it produces as a report. Alternatively if a consistent SOS value cannot be arrived at the algorithm fails to produce a report. All measurements were carried out by the same trained operator blinded to both bone age and DXA data though age and gender and whether right or left arms are used are provided for the algorithm. The measurements were converted by the same algorithm to Z-scores using the manufacturer's data bank for age-matched SOS values for the right (SOS-R) and left (SOS-L) radii. Prior to each use, the device was standardized against a phantom control supplied by the company.

Bone Density

Bone mineral content (BMC, g), bone area (cm²), and the resulting bone mineral density (BMD, g/cm²) for the whole body and lumbar spine (L2–L4) were generated with a DXA instrument (Lunar Prodigy DXA scanner, GE Medical Systems, Madison, Wisconsin, USA). The instrument was operated by trained personnel from the clinical research center. Our coefficient of variation for DXA was 3.9% during the study period.

Statistical Analysis

Ultrasound and DXA data were collected throughout the duration of the study. At the completion of recruitment all the hand radiographs were evaluated for bone age by a pediatric endocrinologist (author BM) blinded to the previous reports and chronological age, using a GP atlas (BM-GP) and the latest Tanner-Whitehouse (TW3) standards (BM-TW). Data analysis was performed using (MINITAB software, Minitab Inc. State College, PA). The results were considered significant at $P = 0.05$. Descriptive statistics were computed for patient characteristics mean $\pm$ SD, and the student t-test (paired) was used for comparison of means. Linear regression was performed to examine the correlation between bone age readings. Linear regression was also used to compare DXA and SOS Z-scores. *In order to examine the accuracy of ultrasound-SOS for approximating DXA derived BMD for different bone ages, correlation between methods was repeated after categorizing the patients into convenient samples by bone age using the GP atlas and TW standards (BM-GP and BM-TW) as follows: normal ($< \pm 1$ year from the chronological age), delayed (-1 year) and*

advanced ($+1$ year). The degree to which the methods agreed with each other was examined by the Bland–Altman analysis i.e., calculating the mean $\pm$ SD of the difference between measurements taken in pairs [6, 7]. This has better discrimination than correlation for comparison of measurements [3, 6, 7]. The means were compared using analysis of variance. In order to examine the value of SOS in predicting LS-BMD the patients were divided using the LS-BMD measurements in to those with Z-scores and -1 , -1 to $+1$ and -1 for convenience and -2 for *clinical relevance*, i.e., *osteopenia*. The sensitivity, specificity, the positive and negative predictive values were calculated for SOS-R and SOS-L [7, 10]. Sensitivity is defined as the percentage of true positives, and specificity as the percentage of true negatives. The predictive value of a positive test is the percentage of individuals with a positive test who have the disease. The predictive value of a negative test is the percentage of individuals with a negative test who do not have the disease.

Results

Patients

A total of 100 subjects (50 males, 50 females) were recruited for the study. The mean age was 10.3 ± 3.8 years, median 10.2 (range 2.3 – 19.4). The majority were Caucasian ($n=86$). Other groups included 4 African Americans, 4 Asians and 6 Hispanics. The mean body mass index (BMI) was 17.97 ± 4.33 , median 16.7 (range 3.62–30.55). The major diagnoses under investigation at the time of recruitment were: short stature, $n = 25$, precocious puberty, $n = 17$, poor prepubertal growth without neurological deficit, $n = 11$, hypothyroidism, $n = 6$, congenital adrenal hyperplasia, $n = 5$, delayed puberty, $n = 5$, growth hormone deficiency, $n = 5$, metabolic disease, $n = 5$, chronic renal disease, $n = 5$. Skeletal abnormalities identified by radiographs include fused epiphyses (1), fifth finger clinodactyly (2), short fourth or fifth metacarpals (7), and epiphyseal arrest lines (1). Only 5% of patients were left-handed. Five patients failed to attend for radiographs after consent. Z-scores for BMD were not generated for 10 patients primarily because of age < 3 years or > 18 years and in 11 individual assessments radial ultrasound failed to produce a Z-score.

Bone age

The GP and TW bone age readings by the author BM showed a strong correlation with each other, $P=0.000$. The bone age was advanced in 20/95 (21%), normal in 36/95 (38%), and delayed in 39/95 (41%) by the GP readings (Table 1). The TW readings showed the bone age to be advanced in 19/95 (20%), normal in 36/95 (38%), and delayed in 40/95 (42%).

Speed of Sound and Bone Densitometry

The mean SOS-R and SOS-L arms were dissimilar, respectively, 3683.3 ± 168.3 m/sec, and 3702.6 ± 168.5 m/sec, though the difference was not statistically significant, $P=0.068$. The corresponding mean Z-scores were also dissimilar, -1.01 ± 1.53 and -0.82 ± 1.57 , $P=0.086$. Of note, non-dominant arms had higher mean SOS and Z-scores. The mean LS-BMD was, 0.74 ± 0.16 g/cm², the Z-score was, mean -0.78 ± 1.35 . Comparing Z-scores for LS-BMD to SOS-R showed no statistically significant difference, $P=0.702$, similarly SOS-L, $P=0.210$.

Bone Age, Speed of Sound and Bone Densitometry

Table 1 also shows the linear regression analysis between SOS and BMD for patients divided in to the different bone age groups for both the GP and TW readings. There was a correlation between SOS-R and -L raw scores ($r = 0.81$, $P=0.000$). When divided in to advanced, normal and delayed bone age groups by the GP method there remained strong correlation in each group, respectively $r=0.85$, $r=0.77$, $r=0.81$, $P=0.000$. When patients were divided using the TW method the correlations were similarly strong, respectively $r=0.86$, $r=0.87$, $r=0.1$, $P=0.000$.

The strongest Z-score correlation was between SOS-R and -L ($r= 0.78$, $P=0.000$) but extremely poor were noted between either SOS-R or -L and LS-BMD (Table 1). Figures 1 and 2 show the relationship between LS BMD Z scores SOS-R and SOS-L Z scores respectively. Comparison of the difference between Z-score measurements taken in pairs for GP and TW bone age readings, divided in to normal, delayed and advanced bone age categories showed equal variability apart from for the delayed bone age group (Table 2): the mean of the differences between SOS-R and SOS-L was smaller than the difference between either and LS-BMD, for GP ($P= 0.03$) and TW ($P= 0.001$).

The sensitivity, specificity and the positive and negative predictive values for prediction of LS-BMD by SOS were similar between right and left radii (Table 3). The sensitivity, specificity and the positive and negative predictive values of SOS-R and SOS-L, Z-scores for predicting LS-BMD Z-scores were generally very poor for high, normal, low or very low BMD except for the specificity and negative predictive value for those with high or very low BMD (Table 3).

Discussion

Data from adult studies and the small number of published pediatric series show a correlation between ultrasound-SOS and BMD determined with DXA [4, 5, 8, 9, 11]. Pediatric studies employing a similar technique to ours have also found a similar low though statistically significant correlation in children [12, 13, 14, 15] and adults [16]. In a study on pediatric patients with leukemia by Ahuja, et al. strong correlations with TB, LS and femoral neck were reported using calcaneal ultrasound [17]. Beyond deriving simple linear regression there are almost no data that scrutinize further the relationship between these two techniques. In the study by Williams et al. a Bland-Altman analysis was also used to look at the difference between methods in three pediatric populations [3]. The authors noted that while there was a correlation the difference between the techniques was significant and ultrasound could not be used as an alternative to DXA. Despite our patient population being different to theirs our conclusions are the same (Table 2). We went further in our analysis in attempting to predict low BMD by SOS and predicting osteopenia and found that the sensitivity of ultrasound is very poor though the specificity is high (Table 3). Similarly in the study by Brukx and Waelkens, low BMD as determined by DXA could not be predicted by ultrasound measurements at the heel [11]. And in a study by El-Desouki et al. osteoporosis in adults was not predictable with ultrasound analysis at more than one site when compared to DXA [16].

The focus of this study was on how bone age affects the correlation between these two techniques, a likely prospect in pediatric patients at risk for osteopenia. Our findings indicate that the correlation between ultrasound and DXA is clearly less robust in individuals with a reduced bone age (Figure 1 and 2). The relationship between ultrasound-SOS and bone age needs further analysis. In a study by Lequin et al. the relationship between bone age and tibial derived SOS gave rise to a non-linear relationship [12]. And in a previous study we determined that the bone age derived with ultrasound did not predict GP and TW derived bone age [7].

A secondary aim of this study was to examine the reliability of the methodology by studying both radii and it was also important to know whether there would be differences if the dominant versus non-dominant arm were to be used. In that regard it is not clear why the non-dominant arm had a slightly higher mean value for SOS (see results).

Our study was limited in that the patient group was a cross-section and did not constitute a uniform patient group. Additionally, we did not derive multiple SOS readings at multiple sites. In that regard, our aim was to reproduce what would be reasonable in a clinic setting and with the aim of allowing the instruments internal algorithms to produce a consistent reading. We did not have Z-scores for the TB-BMD at the time of the study however the SOS Z-score data was so poorly correlated to LS-BMD in this study that the results are unlikely to be changed.

In conclusion our results indicate that while ultrasound and DXA show a correlation in pediatric patients' ultrasound measurements are significantly different and not a replacement for DXA measurement of bone mineralization. The sensitivity for predicting low BMD is poor with SOS measurement at the radii especially, in patients with delayed bone age.

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Abbreviations

BMD	Bone mineral density
BMI	Body mass index
DXA	Dual energy x-ray absorptiometry
GP	Greulich and Pyle
L	Left radius
LS	Lumbar spine
PA	Posterior Anterior
PACS	Picture Archiving and Communication Systems
R	Right radius

SD	Standard deviation
SOS	Speed of sound
TB	Total body
TW	Tanner and Whitehouse

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Key Notes

- The speed of sound as determined by ultrasound is affected by changes in bone mineralization at the radius.
- Ultrasound readings of the radius do not correlate well with radiologically determined bone mineral density at the lumbar spine.
- Ultrasound of the radius cannot accurately predict osteopenia as determined by radiologically determined bone mineral density at the lumbar spine.

Figure 1.
Lumbar spine bone mineral Density (LS-BMD) Z scores and ultrasound- speed of sound (SOS) Z scores of the right (R) radius

Figure 2.
Lumbar spine bone mineral Density (LS-BMD) Z scores and ultrasound- speed of sound (SOS) Z scores of the left (L) radius

Table 1

Correlation of Ultrasound-SOS to LS-BMD

		r						
		Bone Age-GP			Bone Age-TW			
Measurement pairs	Total n= 95^a	Advanced n= 20	Normal n= 36	Delayed n= 39	Advanced n= 18	Normal n= 36	Delayed n= 40	
SOS-R(Z) SOS-L(Z)	0.78	0.86	0.71	0.81	0.91	0.83	0.72	
SOS-R(Z) LS-BMD(Z)	0.08*	0.24*	0.16*	0.1*	0.65	0.34* ⁺	0.14*	
SOS-L(Z) LS-BMD(Z)	0.3*	0.39*	0.11*	0.06*	0.43*	0.03*	0.12*	

Ultrasound-speed of sound (SOS)-m/sec, of the right (R) and left (L) radii, bone mineral density-g/cm² (BMD) of the lumbar spine (LS, L2-4). Age and gender matched standard deviations scores (Z)

Bone age interpreted from the left hand and wrist radiographs with the Greulich and Pyle (GP) and Tanner and Whitehouse (TW) methods. Normal, delayed and advanced bone ages were based on the blinded measurements by author BM: normal bone age ($\leq \pm 1$ year from the chronological age), delayed bone age (-1 year) and advanced bone age ($+1$ year)

Correlation coefficient (r)

^a (n) number of individuals who had undergone a bone age measurement.

All the correlations were statistically significant to $P=0.00$, apart from those indicated by*

⁺ Inverse relationship

Table 2

Differences in Z-scores between SOS and BMD, taken in pairs

	n=95	SOS-R SOS-L	SOS-R LS-BMD	SOS-L LS-BMD	P
GP	Advanced n= 20	0.03 ± 0.74 -1.6 to 1.0	0.99 ± 1.37 -0.3 to 4.7	0.95 ± 1.39 -0.6 to 3.8	NS
	Normal n= 36	0.18 ± 1.07 ^a -2.3 to 2.9 ^b	0.22 ± 1.4 -2.5 to 3.6	-0.05 ± 1.26 -2.1 to 3.0	NS
	Delayed n= 39	0.19 ± 1.09 -1.7 to 2.5	-0.82 ± 1.7 -5.2 to 2.4	-1.02 ± 1.89 -4.0 to 2.7	0.03
	P	NS	0.001	0.001	
TW	Advanced n= 19	-0.09 ± 0.68 -1.6 to 0.8	0.35 ± 0.8 -1.0 to 2.0	0.45 ± 1.33 -1.8 to 2.9	NS
	Normal n= 36	0.07 ± 0.91 -2.3 to 1.7	0.23 ± 1.95 -4.6 to 4.7	0.28 ± 1.64 -3.7 to 3.8	NS
	Delayed n= 40	0.32 ± 1.18 -1.7 to 2.9	-0.59 ± 1.55 -5.2 to 1.9	-0.95 ± 1.75 -4.0 to 2.7	0.001
	P	NS	NS	0.004	
	Total	0.19 ± 1.02 -2.3 to 2.9	-0.07 ± 1.67 -5.2 to 4.7	0.25 ± 1.73 -4.0 to 3.8	NS

Age and gender matched standard deviations scores, (Z), of ultrasound-speed of sound (SOS)- m/sec, of the right (R) and left (L) radii, and bone mineral density (BMD)-g/cm², of the lumbar spine (LS, L2-4).

Bone age interpreted from the left hand and wrist radiographs with the Greulich and Pyle (GP) and Tanner and Whitehouse (TW) methods. Normal, delayed and advanced bone ages were based on the measurements by author BM: normal bone age (< ± 1 year from the chronological age), delayed bone age (-1 year) and advanced bone age (+1 year)

^aMean of difference between measurements ± standard deviation/years

^bRange of differences/years

P value (one way analysis of variance)

Table 3

Accuracy of interpreting LS-BMD Z-scores with ultrasound-SOS Z-scores

	LS-BMD Z-scores	%			
		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
SOS-R	1	22	93	29	90
	>-1 to <1	53	60	50	63
	-1	53	61	56	58
	-2	29	91	40	86
SOS-L	1	25	89	20	91
	>-1 to <1	50	49	43	56
	-1	35	62	45	52
	-2	29	91	40	86

Lumbar spine (L2-4) bone mineral density (LS-BMD) age and gender matched standard deviations scores (Z) and ultrasound-speed of sound (SOS)- m/sec, of the right (R) and left (L) radii