

Bone Age Assessments by Quantitative Ultrasound (SonicBone) and Hand X-ray Based Methods are Comparable

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ABSTRACT: **Background:** Bone maturation is currently assessed by subjective and automated radiography.

Objectives: To evaluate the concordance and reproducibility of a quantitative ultrasound (QUS) based device versus X-ray based methods.

Methods: The study population comprised 150 children, 76 males, 4–17 years of age. X-ray scans were evaluated according to wrist, carpal and phalanx areas for bone age. QUS was performed by the the BAUS™ device (SonicBone, Rishon Lezion, Israel), using speed-of-sound (SOS) and distance attenuation factor (ATN) in similar areas. Data from 100 subjects were used to establish the device conversion equation, and 50 measurements were assigned to assess inter-modality agreement.

Results: BAUS showed high repeatability performance, 0.73% relative standard deviation for SOS and 3.5% for ATN. R² for the conversion equation including gender, SOS and ATN, was 0.80 for all methods ($P < 0.001$). There was no significant bias in bone age assessments.

Conclusions: Bone age assessment by SonicBone is comparable to the assessment by X-ray based methods.

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KEY WORDS: short stature, skeletal maturation, growth, SonicBone, BAUS™

Skeletal maturity assessment, so-called 'bone age', is frequently used for evaluating growth and puberty in children and adolescents. It is recommended as part of the routine clinical care workup of a child with short or tall stature, precocious and delayed puberty, and other conditions [1,2]. Repeated bone age assessments are an important clinical tool used during the follow-up of such patients, especially when treated with growth and puberty-related interventions [1,2].

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Currently, bone age is assessed by:

- Evaluating radiography of the hand, either by physician assessment or by an automated comparison of the shape and size of the wrist and hand bones to a standard series of representative radiographic films of hands according to the Radiographic Atlas of Skeletal Development by Greulich and Pyle (GP) [1,3]
- Using the scoring method designed by Tanner and Whitehouse, currently in its third edition (TW3) [1,4,5]

To address the disadvantages of repeated irradiation, the need for specialized radiation centers, and subjective readings [1,6–8], a new portable device, BAUS™, was developed by SonicBone (Rishon Lezion, Israel). BAUS utilizes a quantitative ultrasonographic (QUS) technology assessing the speed of sound (SOS) of ultrasonic waves, propagating along a measured bone distance, known as the distance attenuation factor (ATN) [9,10]. The aim of the current study is to assess the immediate side effects, reproducibility, and validity of the objective bone age by BAUS, according to individual SOS and ATN, and to compare them to radiographic bone age assessments by the GP subjective method and the automated reading by both the GP and TW3.

PATIENTS AND METHODS

STUDY DESIGN

This cross sectional study comprised 150 patients (76 males) who were recruited consecutively in a pediatric endocrine clinic. All bone age assessments performed by X-ray scans and QUS were conducted prior to data analysis. The participants were then randomized into two groups: analysis group (n=100, 40 males) and confirmation group (n=50, 27 males). Data obtained from the analysis group resulted in an objective conversion equation used for bone age measurement by the SonicBone device software. Data obtained from the confirmation group were used to assess the inter-modality agreement

of bone age between results from BAUS and those from the manual GP, automated GP, and automated TW3 methods.

The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The study protocol was approved by the institutional review board and by the Helsinki Committee of the Israeli Ministry of Health and registered at www.clinicaltrials.gov (NCT01346618). Written informed consent was obtained from each legal guardian, and the participants consented to the study.

STUDY POPULATION

Patients ranged from 4 to 17 years of age and were recruited from the Pediatric Endocrinology Clinic at Assaf Harofeh Medical Center, Zerifin, Israel. Inclusion criteria included all patients who underwent hand X-ray scans as part of their clinical care within 3 months of the clinic visit. Exclusion criteria included children with bone diseases and those who within the last year took medications that might have changed bone metabolism or mineralization, such as high dose steroids, bisphosphonates, high doses of vitamin D, or calcitriol.

BONE AGE ASSESSMENT ACCORDING TO THE RADIOGRAPHIC ATLAS OF SKELETAL DEVELOPMENT BY GREULICH AND PYLE

Hand X-ray scans were reviewed and assessed independently by four pediatric endocrinologists who were blinded to each other's findings and the clinical diagnosis. Each endocrinologist assigned a separate bone age to the radius, ulna and carpals, and phalanx. The mean of the three readings was defined as the child's bone age, as previously described [11,12].

In total, data for each participant included a mean score from four endocrinologists for wrist, carpal, and phalanx bone age by GP. This average of all parameters for each participant was defined as the bone age by GP.

AUTOMATED BONE AGE ASSESSMENT

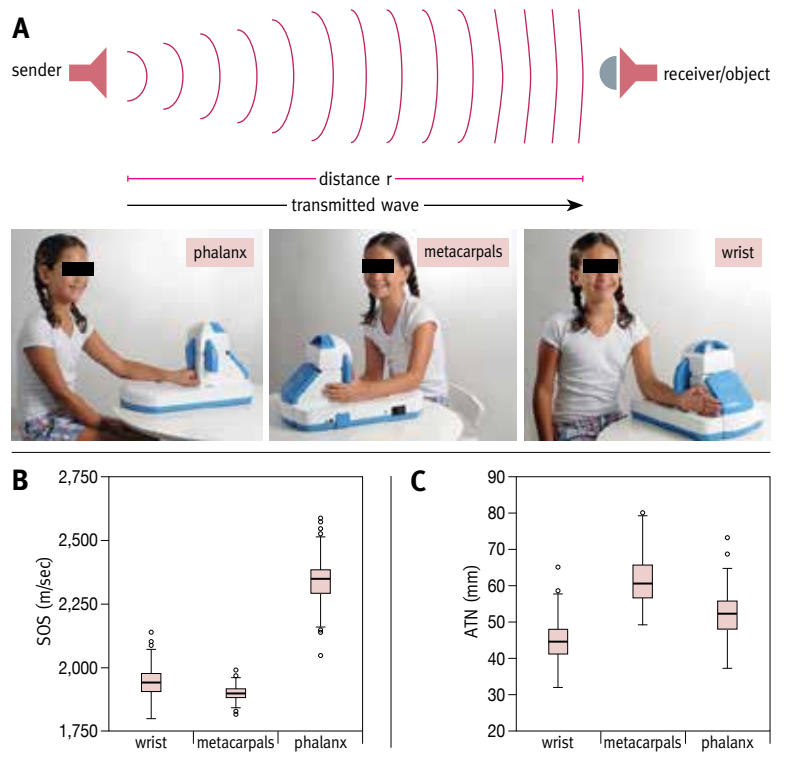
Images were analyzed using the BoneXpert version 2.1 automated method for bone age determination (Visiana, Denmark), which determines bone age by both GP and TW3 [13].

ULTRASONIC BONE AGE ASSESSMENT

BAUS™ is a small (50cm × 25cm × 25cm), portable, bone sonometer [Figure 1], which assesses three sites of the hand: wrist at the distal radius and ulna's secondary ossification centers of the epiphyses; metacarpals at the distal metacarpal epiphyses; and along the bent proximal third phalanx shaft, growth plate, and epiphysis.

The BAUS device measures two parameters: speed of propagation through bone of inaudible high frequency waves of a short ultrasound pulse (m/sec) and ATN (decay rate). Ultrasound attenuation is the decay of sound propagation, defined as the reduction in amplitude of the ultrasound beam as a function of distance through a medium. When dealing

Figure 1. BAUS Device Characteristics. 1a. illustration of device function and sites of measurement at the 3 areas: phalanx, metacarpals and wrist, and device Speed of sound in m/sec (SOS). 1b. SOS measurements, wrist (W), metacarpal (MC) and phalanx (P), in the whole study population (n=150). Lines within boxes indicate median; limits of boxes indicate 25th and 75th percentiles; circles represent outliers. 1c. Attenuation/distance in mm (ATN) assessments, according to the measured areas of the left hand, in the whole study population (n=150). Lines within boxes indicate median; limits of boxes indicate 25th and 75th percentiles; circles represent outliers



with attenuation in bone and cartilage as media, both physical processes, which are complicated modalities, have to be taken into account. In addition, the medium length and attenuation coefficient, the frequency of the ultrasound beam, and the structure and viscosity of the bone need to be considered. These parameters are called the attenuation factor [14,15].

Bone age assessment for each site, as well as the average of all three sites, was determined by the BAUS device. All ultrasonic examinations were conducted by trained personnel at the pediatric endocrinology clinic. The examiners were blinded to the clinical background and to the bone age by GP or TW3. Each subject underwent two BAUS readings by two observers. Eight additional repeated readings were performed for 10 subjects, five boys and five girls aged 6–16 years, to assess reproducibility and precision positioning assessment.

STATISTICAL ANALYSIS

Statistical analysis was performed by a professional statistician (N.K.M.) using IBM SPSS statistics software, version 21 (IBM

Corp, Armonk, New York, USA). The estimation of within subject repeatability was calculated by a one-way analysis of variance (ANOVA) model. The main analysis of the study included the correlation and hypothesis testing of equality of bone age by SonicBone's BAUS device and bone age by manual GP, automated GP, and automated TW3. The immediate side effects were monitored as the numbers of incidents, the nature of inconveniences, and other complaints. Phase 1 analysis was performed on the entire study population (n=150) using Pearson's correlation coefficient. Results demonstrated the linear relationship between bone age measurements by GP and those by BAUS SOS and ATN parameters for each area separately. Phase 2 analysis of 100 subjects (analysis group) established a conversion equation for estimating bone age by BAUS software out of the multivariate linear regression coefficients involving gender and the SonicBone parameters only. These equation provided the best R^2 result. Phase 3 analysis was performed on data from the confirmation group (n=50). Comparison of the differences between the bone age as measured by SonicBone's BAUS device and results from X-ray based methods (GP and TW3) was conducted by the paired *t*-test and further presented as 95% confidence intervals. Linear regressions were used to assess the coefficient of determination (R^2) for the mean bone age differences based on the Bland and Altman analysis. The linear correlation between bone age by X-ray and by BAUS was further demonstrated by Pearson's correlation coefficient.

RESULTS


The study population included 150 subjects (76 males), mean age 10.6 ± 3.3 years (range 4.1–17.4 years). At the time of the investigation they were diagnosed with short stature and failure to thrive (46%), growth hormone deficiency (9%), precocious or early puberty (23%), or overweight and obesity (8%). Those with normal and healthy growth who were seeking reassurance (14%) were also included. The clinical, demographic, and body composition characteristics of the analysis and confirmation groups were similar [Table 1]. The SonicBone performance analysis showed high reproducibility and repeatability according to measurements conducted independently in the same environment by two examiners. After performing 10 repeated readings on 10 subjects, the percent of relative standard deviation (%RSD) for SOS was smaller than 0.73% for all the children, with a maximum standard deviation of 13.7 mm/sec. The %RSD for ATN was less than 3.5% for all of the children with a maximum standard deviation of 1.4 mm. The %RSD is a powerful tool to statistically inspect the variation in sets of data with respect to the mean.

The distribution of SOS and ATN measurements according to skeletal area (wrist, metacarpal, phalanx) in the study population (n=150) is presented in Figure 1. The SOS measurements ranged from 1604–2647 m/sec and the ATN-surrogate distance ranged from 29.5–82.7 mm. The mean difference between the

Table 1. Demographic, clinical, and body composition parameters of the whole study population and the randomly divided analysis group and confirmation group

	All	Analysis group	Confirmation group	P value
Number	150	100	50	
Gender (female)	74	51 (51%)	23 (46%)	0.34
Pre-puberty (T1P1)	53	33 (39%)	20 (34%)	0.33
BMI SDS	0.2 ± 1.4	0.3 ± 1.3	-0.1 ± 1.5	0.09
Age (years)	10.6 ± 3.3	10.5 ± 3.2	10.9 ± 3.4	0.85
Mean BA by GP – W (years)	10.0 ± 3.4	10.1 ± 3.2	10.0 ± 3.8	0.20
Mean BA by GP – CMC (years)	10.1 ± 3.5	10.1 ± 3.3	10.0 ± 3.8	0.26
Mean BA by GP – P (years)	10.3 ± 3.4	10.3 ± 3.2	10.3 ± 3.7	0.47
Mean BA by GP (all sites)	10.1 ± 3.3	10.1 ± 3.1	9.84 ± 3.6	0.77

Puberty data are based on n=148, since 2 patients refused this part of the physical examination. T1P1 is defined as pre-pubertal by Tanner classification. Data is presented as frequency (percentage) for categorical variables and mean \pm standard deviation for continuous variables

BMI = body mass index, SDS = standard deviation score, BA = bone age, GP = Greulich and Pyle, W = wrist, CMC = , P = phalanx

manual bone age assessments by the four endocrinologists according to the GP method on a single reading was 0.59 ± 0.51 years in the wrist site, 0.60 ± 0.52 years in the metacarpal site, and 0.62 ± 0.56 years in the phalanx area. In the phase 1 analysis, we correlated between bone age by manual and automated GP and automated TW3 methods against SOS and ATN from BAUS in the entire study population (n=150). Significant correlations for both SOS ($R^2 = 0.68, 0.68, 0.69$ for manual GP, automated GP and automated TW3, respectively) and ATN ($R^2 = 0.88, 0.88, 0.89$ for the manual GP, automated GP and the automated TW3, respectively) were found, all $P < 0.001$. Statistically significant correlations were found in separate analysis of each hand area (phalanx, carpal, and wrist) between bone age by GP and SOS ($R^2 = 0.79, 0.54, 0.56, P < 0.001$) and ATN ($R^2 = 0.84, 0.81, 0.8, P < 0.001$), respectively. In phase 2, only data from the analysis group were used. Multiple linear regression analysis was used to estimate the bone age by the three methods using gender, SOS, and ATN. The linear regression coefficients are presented in Table 2. For all three methods, both SOS and ATN were significantly strong predictors for bone age. SOS was a significant predictor for bone age above the ATN. As much as 82% of the total variation in bone age is explained by ATN and SOS. Table 2 also shows the unstandardized coefficient *b* that is used for predicting future outcomes, and the standardized coefficient β that was used to evaluate the relative strength of the relationship to bone age. In the phase 3 analysis, only the data from the confirmation group were used. The assessment of bone age by BAUS was compared to the assessment of bone age by the three hand X-ray based methods [Table 3]. The differences between the bone age by BAUS and the bone age by the X-ray based methods were all non-significant ($P = 0.342, P = 0.278, \text{ and } P = 0.229$ for manual GP, automated GP, and

Table 2. The regression coefficients, used in the conversion equation from the analysis group

Technique for determining bone age	Parameter	Coefficient b	SE	Beta	t	P value	R ²
Manual GP	Constant	-28.68	4.87		-5.88	< 0.001	0.80
	Gender	0.187	0.310	0.030	0.602	0.548	
	SOS (m/sec)	1.09	0.293	0.230	3.73	< 0.001	
	ATN (mm)	0.330	0.029	0.724	11.39	< 0.001	
Automated GP	Constant	-30.77	4.88		-6.30	< 0.001	0.81
	Gender	0.345	0.31	0.053	1.11	0.268	
	SOS (m/sec)	1.160	0.293	0.236	3.96	< 0.001	
	ATN (mm)	0.341	0.029	0.722	11.75	< 0.001	
Automated TW3	Constant	-29.55	4.55		-6.49	< 0.001	0.82
	Gender	0.411	0.289	0.067	1.42	0.159	
	SOS (m/sec)	1.133	0.274	0.241	4.14	< 0.001	
	ATN (mm)	0.323	0.027	0.718	11.94	< 0.001	

SE = standard error, t = statistics value. SOS = speed of sound (measurements range from 1.604 to 2.647 m/sec), ATN = attenuation (measurements ranges from 29.5 mm to 82.7 mm), BA = bone age, GP = Greulich and Pyle, TW3 = Tanner and Whitehouse, third edition

TW3, respectively). The relatively small R² (0.186, 0.108, and 0.110 for manual GP, automated GP, and TW3, respectively), based on the Bland and Altman analysis, demonstrates almost no relationship between disagreement measurements and age. Furthermore, the results demonstrate a significant correlation between average bone age by BAUS and the average bone age by manual GP ($r = 0.89, P < 0.001$), automated GP ($r = 0.91, P < 0.001$), and automated TW3 ($r = 0.91, P < 0.001$). The data that is generated and expressed by the device is in years and months, and no further conversion is required. Since SonicBone uses only gender, SOS, and ATN for calculation, there is no subjective component in assessment. There were no adverse events reported during ultrasonic assessment.

DISCUSSION

In the dialectics of human auxology, bone age is an expression of the skeletal maturity of a child. Inferring from this tool of bone maturity, the clinician contemplates diagnostic considerations and evaluates height and pubertal prediction, and may recommend interventions [1,2]. Bone age assessment is accomplished by a variety of methods, all of which use X-ray technology and compare a given film to various standards, followed by designation of a bone age. The problematic use of repeated X-ray evaluations, including the requirement of specialized personal to interpret the radiographs and rater variability of bone age interpretation, is well-documented [6-8,16]. In this study, we presented the applicability of an objective, radiation-free bone age assessment by QUS and its concordance with all currently used bone age valuation by X-ray based methods.

Table 3. Comparison of bone age by SonicBone to the bone age by the three X-ray methods in the confirmation group of subjects

	Mean BA ± SD	Mean difference	95%CI	t	P	R ²
BAUSTM: manual GP	9.84 ± 1.68	0.228	-0.25-0.71	-0.960	0.342	0.186
BAUSTM: automated GP	9.77 ± 1.47	0.229	-0.19-0.65	01.097	0.278	0.108
BAUSTM: automated TW3	9.57 ± 1.44	0.248	-0.16-0.66	1.218	0.229	0.110

BA= bone age, SD= standard deviation, CI = confidence interval, GP = Greulich and Pyle, TW3 = Tanner and Whitehouse, third edition

BAUSTM was developed by SonicBone, Rishon Lezion, Israel

This is not the first attempt to apply QUS technology for bone age assessment. Other attempts failed to enter clinical practice. Castriota-Scanderbeg and colleagues [17,18] attempted to assess skeletal maturation by quantifying the cartilage overlying layers of the femoral head. They demonstrated a decrease in cartilage thickness with age. Yet, a comparison with the bone age by GP showed poor agreement [18]. Khan and co-authors [19] as well as Shimura and collaborators [20] assessed skeletal maturation by SOS and ATN, but only through a single site at the head of the ulna (similar to the wrist site in the current study). This skeletal site often differs from other hand bones, and in those studies other areas of the hand were not assessed [2,11,12].

The BAUS device provides three independent measurements of the radius and ulna epiphyses, metacarpals, and phalanx, similar to clinical practice assessments of hand X-ray scans. While the sites assessed by BAUS and by the X-ray methods are not identical, we demonstrated a significant inter-modality agreement between bone age by BAUS and bone age by GP and TW3 at each site separately as well as by the mean bone age.

The bone age by BAUS was generated by the conversion equation, which was integrated into the device software according to the data retrieved from the analysis of 100 subjects, including SOS, ATN, and the manual reading by the GP method. The device requirements for bone age assessment include only objective measurable data and gender. The validity of the BAUS assessment was then confirmed in 50 subjects against both manual and automated GP reading as well as the automated TW3 methods. Results showed a high performance of reliability and significant concordance. The ultrasound technique used by SonicBone is the through transmission technique, as described in Figure 1. An ultrasound wave is propagated perpendicularly through a medium containing soft tissue and bone from transmitter to receiver. Two parameters are used in this method. The primary parameter is SOS; the time of progress of the ultrasound wave over the distance from transmitter to receiver is the second. SOS correlates strongly with the structure and density of the bone. However, bone is extenuative and dispersive. The attenuation is seen in the change in amplitude of a travelling wave and in the values of the reflection coefficients. The dispersion contributes to the distortion of the wave, and we therefore included

in the equation the attenuation, the decay rate of a wave as it propagates through bone, and the distance between transmitter and receiver as an ATN. The BAUS device aims to assess bone maturity using a principle different from radiology-based devices. These devices use a set of shape criteria of the primary and secondary ossification centers and evaluate how they relate to each other. The ultrasonic device is based on the principle of a different SOS and ATN by bone and cartilage. Bone maturation is assessed by the physical properties of the two matrices, including collagen or elastin components. Those parameters directly affect the ultrasonic wave decay, which corresponds with the device reading. For all three methods, the ATN made an important contribution to the regression, yet, in all three, the SOS was an important and significant predictor for bone age above and beyond the ATN. Beyond the primary ossification centers of the carpals and secondary ossification centers of the metacarpals, bone age by BAUS includes the primary ossification centers of the phalanx. Gender is required to determine bone age by BAUS assessment because the tempo of skeletal maturation differs between females and males. The bone age by GP also relies on gender for assessment.

The measurements by SonicBone are all hand-area inclusive (wrist, metacarpal, phalanx) and objective. They are in physiological agreement to the goal of bone maturation assessment, offering a possible alternative to the present radiation based mostly on subjective GP and TW3 methods. As bone age is an essential measurement procedure for pediatric endocrinologists and is often repeated over time, BAUS offers an important advantage over the current methods. It is radiation free and involves objective readings by a device accessible at a clinician's office. The current report does not provide reference or standard for bone age by chronological age for the QUS method. This reference is currently under development using a normal population distribution for all ages according to gender and is required prior to clinical use of the device. In addition, the measurement accuracy is operator dependent. During our study, BAUS measurements were performed by trained personal. Perhaps the accuracy of measurements would be compromised if performed by a less experienced provider, and therefore, all providers should undergo training prior to implementation. It is important to add that there may still be a population requiring X-rays because of specific clinical cases, such as suspicion of skeletal dysplasia, in which an additional X-ray is required to actually look at bone structure. However, those cases are rare in children followed by pediatric endocrinologists.

CONCLUSIONS

In summary, the radiation-free assessment of bone age in the pediatric population attending endocrine clinics by the BAUS device developed by SonicBone was found to be highly reproducible and comparable to bone age assessed by X-rays based methods with no immediate side effects during usage.

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