Bone age assessment by a novel quantitative ultrasound based device (SonicBone), is comparable to the conventional Greulich and Pyle method.

Rachmiel M. MD, Pediatric Endocrinologist \(^1\)\(^2\), Naugolani L. MD, Pediatric Endocrinologist \(^1\), Mazor-Aronovitch K. MD, Pediatric Endocrinologist \(^2\), Levin A \(^3\), Dr. Koren-Morag N, Bio-statistician \(^2\), Prof. Bistritzer T. MD, Pediatric Endocrinologist, Head of Pediatric Department \(^1\)\(^2\).

\(^1\)Pediatric Endocrinology Clinic, Assaf Haroffeh Medical Center, Zerifin Israel, 
\(^2\)Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel. 
\(^3\)SonicBone Medical, Rishon Lezion, Israel.
Abstract

**Background:** Bone age (BA) assessment in children is based on interpretation of hand x-ray scans according Greulich and Pyle (GP) standard atlas. The aim was to evaluate an ultrasound based device, SonicBone, for safety, reproducibility and concordance to the current method.

**Methods:** Study population included 150 participants, 74 males, mean age 10.6±3.3 years, attending pediatric endocrinology clinic. X-ray scans were evaluated independently by 4 pediatric endocrinologists according to GP. SonicBone assessments were performed by two observers. Study population was randomly divided to 2 groups. A group of 100 participants, to assess correlation between speed of sound (SOS) and distance (DIS) parameters of SonicBone and BA by GP, and to establish an algorithm for provision of a numeric BA assessment in years. A group of 50 participants to assess concordance between BA based on GP and BA based on SonicBone.

**Results:** The SonicBone has high repeatability performance, 0.73% relative standard deviation (RDS) for SOS and 3.5% RDS for DIS. Pearson correlation between BA by GP, SOS and DIS demonstrated a significantly high correlation in all areas. The algorithm including age, gender, SOS and DIS for each skeletal location, wrist, carpal and phalangeal, has R square of 0.87, p<0.004. BA by SonicBone was highly correlated with BA by GP, with R square of > 0.946 and p value <0.0001 for all locations.

**Conclusion:** SonicBone device is safe, convenient, non painful and highly reproducible. Its BA assessment in a population of children attending pediatric endocrinology clinics is comparable to BA by GP method.

**Introduction**

Skeletal maturity assessment, defined also as bone age (BA), has an important role in pediatric endocrinology, used mainly for evaluating growth and puberty related endocrine disorders. It is agreed that the assessment of skeletal maturity by left hand x-ray is always recommended as part of the routine workup at first presentation of a child with short stature and during assessment of precocious puberty and its subcategories (1, 2). Repeated BA assessments are an important clinical tool during the follow up of those patients, especially when treated by growth promoting medications (1, 2). The method for skeletal maturity determination is based on the understanding that the ossification centers of the skeleton appear and progress in a predictable sequence in normal
children, and skeletal maturation can therefore be compared with normal age-related standards (3). BA is currently assessed according to the progress of the hand bones, by subjective comparison of the shape and size of wrist, carpal and phalangeal bones, to a standard series of representative radiographic films of hands at all ages, according to the Radiographic Atlas of Skeletal Development of the hand and wrist (4). This observation is related to either the published standards of Greulich and Pyle (GP) (1, 4), or the scoring system of each individual bone, Tanner - Whitehouse method (1, 5, 6). This method is the only accepted standard for assessing skeletal maturation. However, it is susceptible to wide inter and intra individual variability of its interpretation and exposure to radiation. Quantitative ultrasound (QUS) technology is a radiation-free method currently used for bone composition assessment, measuring the speed of sound (SOS) of US waves propagating along a specific bone distance (DIS) (7, 8). So far no QUS based device could accurately assess BA (9). A new device, SonicBone (Rishon Lezion, Israel) was developed to allow quantitative measurement of several skeletal components of the hand and wrist in order to objectively assess skeletal maturation. The aims of the study were to assess initially the similarity between BA assessment by radiographic standards based on GP method to the parameters obtained by SonicBone measurements, and to measure the safety, reproducibility and validity of BA by SonicBone compared to BA by GP.

**Patients and Methods:**

**Study design:**

This is a cross sectional study. It was designed to include three phases of data analysis, while all participants were recruited consecutively and randomized for the data analysis sections to two groups of 100 participants and 50 participants, respectively, only after completion of recruitment. The study protocol was approved by the institutional review board and by the national ethics committee for pediatric trials of the Israeli ministry of health. The study was registered as ClinicalTrials.gov number NCT01346618. The study included three phases of data analysis according to study objectives:

First Phase: correlation between SOS and DIS parameters of SonicBone and BA by GP , in a group of 100 children attending Pediatric Endocrinology Clinics. Second Phase: establishment of a algorithm for incorporation of objective patient and SonicBone parameters quantitative data, to provide a numeric result of the BA in years and months, defined as BA by SonicBone. Third phase: comparison of BA by GP and BA by SonicBone, in a similar randomly assigned group of 50 children attending same Pediatric Endocrinology Clinics.

**Study population:**
The study population included all patients ages 4-17 years who attended Pediatric Endocrinology Clinic in Assaf Haroffeh Medical Center, Israel, or seen in ambulatory setting by one of the study investigators, and who performed an x-ray of the left hand as part of their clinical work up within 3 months of clinical visit. Exclusion criteria included children with bone diseases, or taking any medication in a dose which might change bone metabolism or mineralization within the last year. Written informed consent was obtained from a legal guardian, and assent was obtained from the participant. After all participants were recruited, they were randomized to the "Analysis Group" of 100 participants, assigned for correlation analysis between BA by GP and SonicBone parameters, and to the "Validation Group" assigned for analysis of correlation between BA by GP and BA by SonicBone according to the conversion algorithm from quantitative parameters to BA.

**Data collection:**

Medical records of the clinical visit performed within 3 months of x-ray evaluation were reviewed for clinical and demographic information, including: gender, age, reason for clinical assessment, concurrent illnesses and medication use, weight, height, BMI SDS, pubertal stage, BA assessed by GP method and final diagnosis stated for purposes of clinical care.

**BA assessment according to GP method (BA by GP):**

Hand x-ray scans were performed in ministry of health authorized centers in Israel. All hand x-ray scans that were performed were copied (after consent) to a study portable memory disk by one of the study investigators (L.U). All scans were assessed separately and individually, from the study memory disk by additional 3 pediatric endocrinologists (study investigators M.R, L.N, T.B, K.M) without their knowledge of the reason for clinical assessment, patient's diagnosis or the BA assessment by the primary pediatric endocrinologists. Those BA assessments were blindly assessed according to gender and chronological age only. Thus, all study x-ray scans were assessed separately and independently by 4 pediatric endocrinologists, being blinded to each other's assessments. The median of 4 BA assessments was defined as BA by GP and used for study analysis.

**Ultrasonic BA assessment by SonicBone device (BA by SonicBone):**

SonicBone device is a small (50cm X 25cm X 25cm) ultrasound bone sonometer which measures the speed of propagation of inaudible high frequency waves of a short ultrasound pulse, defined as SOS (Speed of Sound – m/sec) through bone and measures the distance (Distance - mm) between a transmitter probe and a receiver probe, located at the edges of the measured bone area, as shown in figure 1. Three different sites of the hand and wrist bones were measured: phalanx III (P), metacarpal bones (M) and wrist (W). All ultrasonic examinations were conducted in the Pediatric
Endocrinology Clinic, Assaf Harofe Medical Center, Israel, performed by trained personal, under physician supervision. The examiners were blinded to the participant clinical reason for investigation and to the BA by GP. Each participant underwent 2 repeated readings in all three sites, by two observers, at the same session. Nine participants, 5 boys and 5 girls, from age groups 6-7 years, 10-11 years and 14-16 years, respectively, performed 8 additional repeated readings, at the same setting for reproducibility assessment.

**Satisfaction Questionnaires:**

Each participant and parent answered together a satisfaction questionnaire regarding satisfaction from both methods of BA assessment. The questionnaire included questions regarding length of exam, degree of inconvenience, and degree of fear from examination. The questionnaire was filled by participant and parent immediately after performance of US examination.

**Statistical Analysis:**

Data was analyzed with SPSS software version 19.0 (SPSS Inc. Headquarters, 233 S. Wacker Drive, 11th floor Chicago, Illinois 60606, USA). The outcome measures of the study included efficacy, by demonstration of $R^2$ correlation between the two methods, safety, by counting the numbers of incidents of safety nature or inconveniences complains while using the device, and repeatability, by measuring the repeatability and accuracy values of device's performance. The significance levels were set at 0.05. Data was presented as mean and standard deviation for continuous variables. We used normal plots as well as non-parametric Kolmogorov-Smirnov tests to check for the normality of the variables. The linear relationships between SonicBone measurements and BA by X-rays were assessed using Pearson correlation coefficient. To establish a algorithm for incorporation SonicBone quantitative data (SOS and Dis) to produce BA assessment, we used a multivariate linear regression analysis followed by R square measure. Reproducibility and the relationship between BA by X-ray and by SonicBone were assessed by the Pearson correlation coefficient. To quantify the agreement between measurement we estimated repeatability coefficient which define by $1.96*sr^2*within subject SD$. The estimation of within subject SD was calculated by one way analysis of variance (ANOVA) model.

**Results**

The study population included a total of 150 subjects (74 females, 76 males) who were recruited during the period June 2011 and March 2012. The mean age was 10.6±3.3 years, median 11.0 years, range 4.1-17.4 years. (The major diagnoses under investigation at the time of recruitment included short stature and failure to thrive (46%), children diagnosed and treated for growth hormone deficiency (9.3%), children with precocious or early puberty (22.7%) and patients with
tall stature, overweight and obesity (8%). Twenty one children (14%) were diagnosed as normal and healthy, not requiring further endocrine assessment. This study population was randomized to the Analysis group and Validation group, as described in the methods section. The clinical, demographic and body composition characteristics of both groups were similar, as presented in Table 1.

The SonicBone performance analysis in the all study population (n=150) showed high repeatability according to repeated measurements conducted by two personal independently and in the same environment. The percents of relative standard deviation (%RSD) for SOS were smaller than 0.73% for all the children with a maximum standard deviation of 13.7. The %RSD for DIS was smaller than 3.5% for all the children with a maximum standard deviation of 1.4. The distribution of SOS and DIS measurements according to skeletal area (W,C and P) in the study population is presented in Figure 2.

Pearson correlation of BA by GP median between 4 pediatric endocrinologists and parameters of SonicBone, SOS and DIS, performed for the Analysis Group demonstrated a significantly high correlation in all areas, especially in the phalanges (P) area, as presented in Figure 3. In the wrist, R=0.58 for the SOS and R=0.81 for DIS, p<0.001, in the carpal area, R=0.66 for the SOS and R=0.80 for DIS, p<0.001, and in the phalangeal area, R=0.82 for the SOS and R=0.83 for DIS, p<0.001.

This significantly high level of correlation between the x-ray based BA estimation and the numerical objective parameters retrieved from the SonicBone allowed us to proceed to phase 2 and establish a algorithm for transforming the numerical SOS and DIS parameters to BA assessment. Linear regression analysis, performed for the entire sample and for each gender separately, detected one model which was adequate for all patients. Four parameters were required for BA assessment using the SonicBone; age, gender, SOS and DIS. The regression coefficients, their standard error and statistical significance for estimating the BA, according to skeletal site, are presented in table 2. The strength of the model was assessed by goodness of fit measure, R square=0.87.

We proved the validity and accuracy of the BA by SonicBone assessment by a comparison of its assessment to the radiographic GP based BA assessment (median of 4 pediatric endocrinologists) in a large similar group of participants, the Validation group. Statistically significant strong linear correlations were demonstrated between both assessments for each area, as presented in figure 4. The correlation coefficient for the BA assessed by the SonicBone device and the BA by GP was 0.95 for the wrist area, 0.91 for the carpal area, and 0.92 for the phalangeal area, p value <0.0001 for each. Those highly significant correlations prove that the actual correlation in a pediatric
population (ages 4-17 years), attending pediatric endocrinology clinics is at least 0.8 with a power of 80% and significance of 5%.

The satisfaction questionnaires demonstrated that participants were similarly satisfied from both methods, x-ray scan and SonicBone. The convenience of being located at the doctor's office was clearly an advantage. Both devices were rapid, 95% reported SonicBone measurement lasted less than 5 minutes, comparable to 88% using x-ray scan. Eighty one percent and 74% reported of minor inconvenience and only minor fear from equipment using the SonicBone, compared to 61% and 71%, using the x-ray, respectively. 99% of all participants expressed their preference to perform bone age examination at the physician's office. Less than one percent of study participants (1\150) complained of local short mild pain at the area of measurement, which resolved within minutes.

**Discussion**

This study presents the high safety, repeatability and efficacy profile of SonicBone, a novel device applying QUS for BA assessment, producing separate results for three measurement areas of wrist, carpal and phalangeal bones, similarly to the currently used x-ray based GP method.

Assessment of skeletal maturation is a basic clinical care requirement for the diagnosis and management of the pediatric population attending Pediatric Endocrinology Clinics for growth, puberty and weight issues (1, 2). It is an obligatory tool since it is the only means of objective assessment of the progression of ossification centers in the growing bones. The current most widely used method for skeletal maturation assessment is estimation of BA by comparison of the size and shape of wrist, carpal and phalangeal bones of a patient to age-related standards of a series of representative radiographic films of hands in the Radiographic Atlas of Skeletal Development of the hand and wrist (4), known as the GP method. The drawbacks of this BA assessment method are: the exposure to ionizing radiation, which is very low (0.00015mSv) (10), but in many cases repeated annually, the obligatory need for using radiology facilities, the requirement of specialized personal to interpret the bones appearance, the considerable rater variability of BA interpretation (11-13), and the range of normal variability of the appearance of the ossification centers during pubertal age, as seen by the standard deviation of mean BA assessment at the 9-12 years age group of 11 months (4).

The SonicBone device implies QUS technology with the hypothesis that velocity of sound through a bony area depends on the amount of cartilage and cortical bone, with longer time as ossification process progresses. It enables BA accurate, objective estimation without the need for radiation exposure and without the subjective inter-observer variability existing in the currently used GP based method. This is not the first attempt to apply QUS technology for skeletal maturation.
assessment during the last decade; however the previously studied methods are not of clinical practice. Castriota-Scanderbeg et al, (14, 15) suggested to assess skeletal maturation by quantification of the overlying layer of cartilage of the femoral head cartilage (FHC). They studied FHC thickness in a small group of healthy Italian population, indicating a decrease in cartilage thickness with age and provision of normal ranges according to age. However, this method is not used clinically since its reliability was not confirmed by large studies, and its comparison with the conventional GP and TW methods was in poor agreement (15). Shimura et al, and Khan et al, (9, 16) suggested to assess skeletal maturation by measurement of SOS through the head of ulna (wrist) by the Sunlight BonAge device using the measurement of SOS of ultrasonic waves transmitted from one side of the distal ulna to the other, depending on wrist width and level of ossification of carpal bones. The BonAge results were highly correlated to the TW method in one study (16), but with more dissimilarity between radiographic and QUS method in the other (9). The device is not used in clinical practice due to lack of consistency, lack of confirmatory data in large groups and due to the reliability only on the ulna and carpal bones, while it is known he phalanx bone age is not always similar to carpal bones, and it was suggested to be more predictive in clinical care (2).

This study demonstrates that SonicBone Device took into consideration most of the drawbacks of both the conventional GP method and the previously suggested QUS based devices.

The algorithm used automatically by the device was produced not only by a mathematical hypothesis or numerical calculation, but mainly according to 100 concordant measurements of DIS, SOS and BA assessment by GP method, among pediatric children attending endocrine clinic. Those parameters, used for algorithm production are reliable since SOS and DIS were measured twice for each participant and the BA assessment according to GP method was based on the median of 4 independent pediatric endocrinologists raters to eliminate inter observer variability. The algorithm was both established and validated separately in the same randomized pediatric population, with high performance reliability and significant concordance of results between the BA assessed by GP and BA assessed by SonicBone. It should be noted that we included only those subjects being evaluated for endocrine issues, including only 14% of healthy population since it is the clinically relevant heterogeneous population, and it more closely reflects most patients who would require bone age estimation in clinical practice.

Unlike the BonAge device, the SonicBone provides information of three areas of the hand, similar to the x ray scan and not just ulnar and carpal, and delivers three independent results, enabling similar clinical judgment as provided by BA by GP assessment. The ability to produce separate information regarding the carpal and phalangeal areas is of major clinical importance (2).
The SonicBone is a small sized portable, non-operator-dependent device enabling performance of the BA assessment at the primary physician's office setting. It is obvious that patients would prefer to perform the BA assessment at their physicians clinic rather than wasting more time in an X ray specialized ambulatory setting, and the similar findings on questionnaires between both methods of no pain and speed of both methods are also important parameters considering new technology. The limitations of the study are the lack of information on healthy population, but it was not the aim of this study to assess healthy population. It was to establish a conversion algorithm and assess if the results may be comparable to the GP method, in a population performing BA assessment in clinical practice. Healthy population does not perform BA assessment regularly, thus performing an additional non required X-ray did not seem to us an ethical request. Consecutive measurements of healthy population for the establishment of normal ranges for the device reports, for all ages and separately for females and males are mandatory and currently underway.

In conclusion, the assessment of BA by SonicBone device in a population of children attending pediatric endocrinology clinics is comparable to the GP based method. It is a safe, radiation free convenient and highly reproducible device. However, establishment of healthy population reference curves is a preliminary requirement for clinical use.

References

**Figure 1: Schematic illustration of Through-Transmission ultrasound Technique**

An ultrasound wave is propagated perpendicularly through a medium containing soft tissue and bone, from transmitter (T) to receiver (R). The parameter primarily used in this method is speed of sound (SOS), i.e., time of flight of the ultrasound wave from transmitter to receiver, over the distance (DIS) between the transmitter and receiver.

**Table 1: Demographic, clinical and body composition parameters of study population.**

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Analysis Group</th>
<th>Validation Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>150</td>
<td>100</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Gender (f)</td>
<td>74</td>
<td>51 (50%)</td>
<td>23 (50%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Pre-puberty*</td>
<td>46</td>
<td>39 (39%)</td>
<td>17 (34%)</td>
<td>0.33</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>0.2±1.4</td>
<td>0.3±1.3</td>
<td>-0.1±1.48</td>
<td>0.09</td>
</tr>
<tr>
<td>Age (years)</td>
<td>10.6±3.3</td>
<td>10.5±3.2</td>
<td>10.9±3.4</td>
<td>0.85</td>
</tr>
<tr>
<td>Mean BA Wrist (years)</td>
<td>10.0±3.4</td>
<td>10.1±3.2</td>
<td>10.0±3.8</td>
<td>0.20</td>
</tr>
<tr>
<td>Mean BA Metacarpal (years)</td>
<td>10.1±3.5</td>
<td>10.1±3.3</td>
<td>10.0±3.8</td>
<td>0.26</td>
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<tr>
<td>Mean BA Phalanges (years)</td>
<td>10.3±3.4</td>
<td>10.3±3.2</td>
<td>10.3±3.7</td>
<td>0.47</td>
</tr>
</tbody>
</table>

*Data is based on n=148 since 2 participants refused pubertal examination, FTT- failure to thrive, GHD – growth hormone deficiency.*
Figure 2: Descriptive data of SonicBone parameters according to the 3 measured areas of the left hand, wrist (W), carpal (C) and phalanx (P), in the all study population (n=150). 2a. Speed of sound in mm/sec (SOS). 2b. Distance in mm (DIS). Lines within boxes, median; limits of boxes, 25th and 75th percentiles; extensions of boxes, minimum and maximum; circles presents outliers.
Figure 3: The correlation between ultrasonographic parameters by the SonicBone and BA by GP in the phalanx site. 1a) Speed of sound (SOS), 1b) Distance (DIS). The scatter plot was performed using the Pearson correlation coefficient.

Table 2: Regression coefficients for BA estimation, using SonicBone results of SOS and DIS, according to skeletal site.

<table>
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<tr>
<th>Site</th>
<th>Parameter</th>
<th>Coefficient b</th>
<th>SE</th>
<th>t</th>
<th>P value</th>
<th>$R^2$</th>
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<tbody>
<tr>
<td>Wrist</td>
<td>Age</td>
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<td>0.061</td>
<td>-3.114</td>
<td>0.002</td>
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<tr>
<td></td>
<td>Gender</td>
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<td>0.267</td>
<td>10.507</td>
<td>0.000</td>
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<tr>
<td></td>
<td>SOS</td>
<td>0.003</td>
<td>0.002</td>
<td>-4.040</td>
<td>0.000</td>
<td>0.87</td>
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<tr>
<td></td>
<td>DIS</td>
<td>0.211</td>
<td>0.030</td>
<td>1.385</td>
<td>0.169</td>
<td></td>
</tr>
<tr>
<td>Carpal</td>
<td>Age</td>
<td>0.629</td>
<td>0.065</td>
<td>-4.096</td>
<td>0.000</td>
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<td></td>
<td>Gender</td>
<td>0.146</td>
<td>0.026</td>
<td>9.700</td>
<td>0.000</td>
<td>0.87</td>
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<tr>
<td></td>
<td>SOS</td>
<td>-0.916</td>
<td>0.286</td>
<td>5.726</td>
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<tr>
<td></td>
<td>DIS</td>
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<td>0.004</td>
<td>-3.205</td>
<td>0.002</td>
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<tr>
<td>Phalanx</td>
<td>Age</td>
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<td>0.070</td>
<td>8.180</td>
<td>0.000</td>
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<tr>
<td></td>
<td>Gender</td>
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<td>0.291</td>
<td>-0.408</td>
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<tr>
<td></td>
<td>SOS</td>
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<td>0.002</td>
<td>3.682</td>
<td>0.000</td>
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</tr>
<tr>
<td></td>
<td>DIS</td>
<td>0.115</td>
<td>0.031</td>
<td>3.667</td>
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SE= standard error, t= statistics value from the independent t-test.
Figure 4: The association between BA by SonicBone device and BA by GP method. These measurements were performed in the subgroup of 50 participants, Validation Group. BA by GP assessment is based on the median of 4 pediatric endocrinologist readings. BA by SonicBone is based on the conversion equation. Statistical significance was assessed according to Pearson correlation coefficient. 1a) wrist area, \( r=0.95 \), \( p<0.001 \)  
1b) carpal area, \( r=0.91 \), \( p<0.001 \)  
1c) phalanx area \( r=0.92 \), \( p<0.001 \).