

Original Article

German Pediatric Reference Data for Quantitative Transverse Transmission Ultrasound of Finger Phalanges

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Abstract. Quantitative ultrasound (QUS) of the finger phalanges is a useful tool in the assessment of disease- or age-related deterioration of bone. For studying the impact of juvenile diseases or growth disorders affecting the skeleton, a reference database for QUS parameters is needed. The aim of this study was to establish a calibrated reference database of parameters of transverse ultrasound transmission through juvenile finger phalanges. A total of 1328 children (650 females, 678 males; ages 3–17 years) were measured in Heidelberg and Kiel in order to establish a German reference database. Highly significant gender-specific correlations ($p < 0.0001$) were found between the QUS parameters amplitude-dependent speed of sound (AD-SoS) and bone transmission time (BTT) versus age, body height and body mass index (BMI). For AD-SoS the correlation coefficients were $R^2 = 0.64$ against age in males and $R^2 = 0.73$ in females, $R^2 = 0.60$ against body height in males and $R^2 = 0.68$ in females, and $R^2 = 0.19$ against BMI in males and $R^2 = 0.23$ in females. For BTT the correlation coefficients were $R^2 = 0.74$ against age in males and $R^2 = 0.79$ in females, $R^2 = 0.75$ against body height in males and $R^2 = 0.77$ in females, and $R^2 = 0.32$ against BMI in males and $R^2 = 0.35$ in females. Age and height were the strongest determinants of QUS results. Gender-specific differences were observed in AD-SoS (significant for ages 11–14 years and for 150–170 cm body height) and in BTT (significant for ages 7 and 11–17 years and for 160–170 cm body height). Tables of QUS parameters versus age and height can serve as a basis for the

evaluation of the impact of skeletal diseases or growth disorders on phalangeal QUS. Depending on the type of disease or growth disorder, measurement results can be compared with age- or height- specific reference data. In this way a simple and radiation-free assessment of juvenile skeletal disorders using quantitative ultrasound might be possible in the future.

Keywords: Bone; Children; Growth; Ultrasound

Introduction

Quantitative ultrasound (QUS) methods have proven to be useful in the assessment of osteoporotic bone changes and in the prediction of future fracture risk [1–4]. However, diseases other than osteoporosis are known to also have an impact on bone properties. The research of their impact on QUS parameters might extend the diagnostic quality of QUS methods. For example, changes in bone properties due to rheumatoid arthritis could be measured using a device for QUS measurements in human phalanges in transverse transmission mode (DBMSonic 1200, Igea, Carpi, Italy) [5,6]. In children hand radiographs are commonly used for the estimation of juvenile bone status, usually expressed as skeletal compared with chronological age. First results indicate that QUS of finger phalanges is also affected by juvenile growth disorders [7]. Due to its lack of ionizing radiation QUS seems to be particularly useful for studying bone status in children. Other QUS methods have been investigated, predominantly at the calcaneus [8,9]; however, little is known about their diagnostic

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potential. There are two main indications: the assessment of disorders of growth and puberty, and knowledge about the attainment of a high peak bone mass, which is an important risk factor for senile osteoporosis [10]. QUS of finger phalanges is a new method for the measurement of the skeletal status of children. Because the device is easy to use, portable and radiation-free, its application is attractive and future studies should examine its diagnostic potential.

However, a validated reference database is needed for the assessment of abnormal ultrasound measurements. In this article we want to introduce the first comprehensive reference database of transverse transmission ultrasound measurements on phalanges of German children. A new parameter, bone transmission time (BTT), offering improved performance for measurements in children, is introduced. We applied quality assurance measures for proper use of this normative database using a cross-calibration phantom, enabling the use of the reference data on all present and future devices.

Materials and Methods

Subjects

Measurements were performed on 1221 children recruited in school classes and kindergartens in Heidelberg in 1997 by three operators using two DBMSonic 1200 devices. In 1998/99 an additional 146 children were measured in Kiel and Heidelberg using two cross-calibrated devices in order to introduce calibration procedures for the devices. Thirty-nine subjects were excluded due to incorrect measurements, e.g., due to incorrect soft tissue measurements (velocity >2000 m/s), incorrect bone tissue measurements (AD-SoS >3000 m/s) caused by noise or missing data of single fingers. No other exclusion criteria were applied. The remaining 1328 children (650 females, 678 males; ages 3–17 years) were measured. Height and weight were also recorded, but no information about pubertal status was available. The study was approved by the local educational administration and the parents of the children gave informed consent.

Measurements of Quantitative Ultrasound

Measurements were performed using the DBMSonic 1200 (IGEA, Carpi, Italy) on proximal phalanges II to V of the right hand of the children. The DBMSonic 1200 measures the transmission of ultrasound through human phalanges using a hand-held caliper with two opposing transducers, one acting as a transmitter and the other as a receiver. Time-of-flight between the probes and the distance between probes is measured and a velocity parameter, amplitude dependent speed of sound (AD-SoS), is calculated [11] as the ratio between transducer separation and the time when the signal received attains a predefined signal amplitude of 2 mV. A new

parameter, bone transmission time (BTT), is calculated as the difference between the time when the first peak of the signal received attains its maximum and the time that would be measured if no bone but only soft tissue were present between the transducers. This parameter is calculated from phalanges II to IV only. Soft tissue velocity is measured between the base of the thumb and the index finger during each session. Thus BTT, unlike AD-SoS, is largely independent of ultrasound attenuation and soft tissue bias. A detailed description of these parameters can be found in the Appendix. The procedure used for measurements in children was exactly the same as for measurements in adults. No adaptation of the probes was necessary.

Cross-calibration

The creation of a reference database requires the use of measurement devices with well-controlled quality. Usually, phantoms are used for measuring the stability of a device and to cross-calibrate different devices against each other. A cross-calibration phantom for the measurement of velocity and amplitude was developed by Igea in 1998 and was not available during the measurements in 1997. At that time only the stability of the time base and the transducer separation were controlled, but not the amplitude. Moreover, the quality control procedure allowed deviations which now are considered too large for measurements in children, who have a population standard deviation substantially lower than in adults. Therefore, we calculated mean values of AD-SoS and BTT of the children for each age and gender and tested for differences between the measurements in 1997 and 1998/99. Age range was 6–14 years; however, the impact of pubertal stage could not be taken into account. The two devices used in 1998/99 were calibrated using the new cross-calibration phantom. Differences between the 1997 and 1998/99 data were calculated for all ages concerned and the mean of these differences was used to adjust the 1997 data to the calibrated level of the 1998/99 data. Thus the database created here can be used on all devices that are calibrated using this cross-calibration phantom.

Statistics

Precision errors were obtained from five measurements on each of 22 children, calculated as the root mean square CV. By taking into consideration the different age-related slopes of AD-SoS and BTT the precision error of BTT was standardized to AD-SoS as reference parameter [12].

By pooling all calibrated measurements in both centers at any time, tables for the ultrasound parameters at different values of age and body height were generated. Correlations of the ultrasound parameters AD-SoS and BTT versus age, height and body mass index (BMI) were calculated using linear, square and

cubic regressions. The regressions with the highest order which were significantly different from regressions with lower orders were selected. For example, when a quadratic regression was significantly better than a linear regression but a cubic regression was not significantly better than the linear or quadratic regression, the quadratic regression was chosen. Gender-specific differences were tested for significance for different ages and different heights using an unpaired double-sided *t*-test.

Results

Statistically significant differences between the 1997 and 1998/99 data of $44.9 \text{ m/s} \pm 3.5 \text{ m/s}$ for AD-SoS and

$0.046 \mu\text{s} \pm 0.014 \mu\text{s}$ for BTT were observed. Data measured in 1997 were corrected for these differences. Precision of the AD-SoS measurements was 0.3%, which was better than reported precision results in adults (0.5–1%). Precision and standardized precision in BTT were 3.5% and 0.4% respectively.

AD-SoS in males increased with age from 1832 m/s at age 3 years to 2071 m/s at age 17 years (Fig.1a). Values for females were similar (1838 m/s to 2064 m/s). Simultaneously the population standard deviation in each year doubled from approximately 30 m/s at age 3 years to 60 m/s at age 17 years. The signal was always triggered on the first peak. Correlations were strongest with age and (slightly lower) with body height while BMI was less predictive (Table 1). AD-SoS and BTT were strongly correlated ($R^2 = 0.88$ in girls and $R^2 = 0.86$

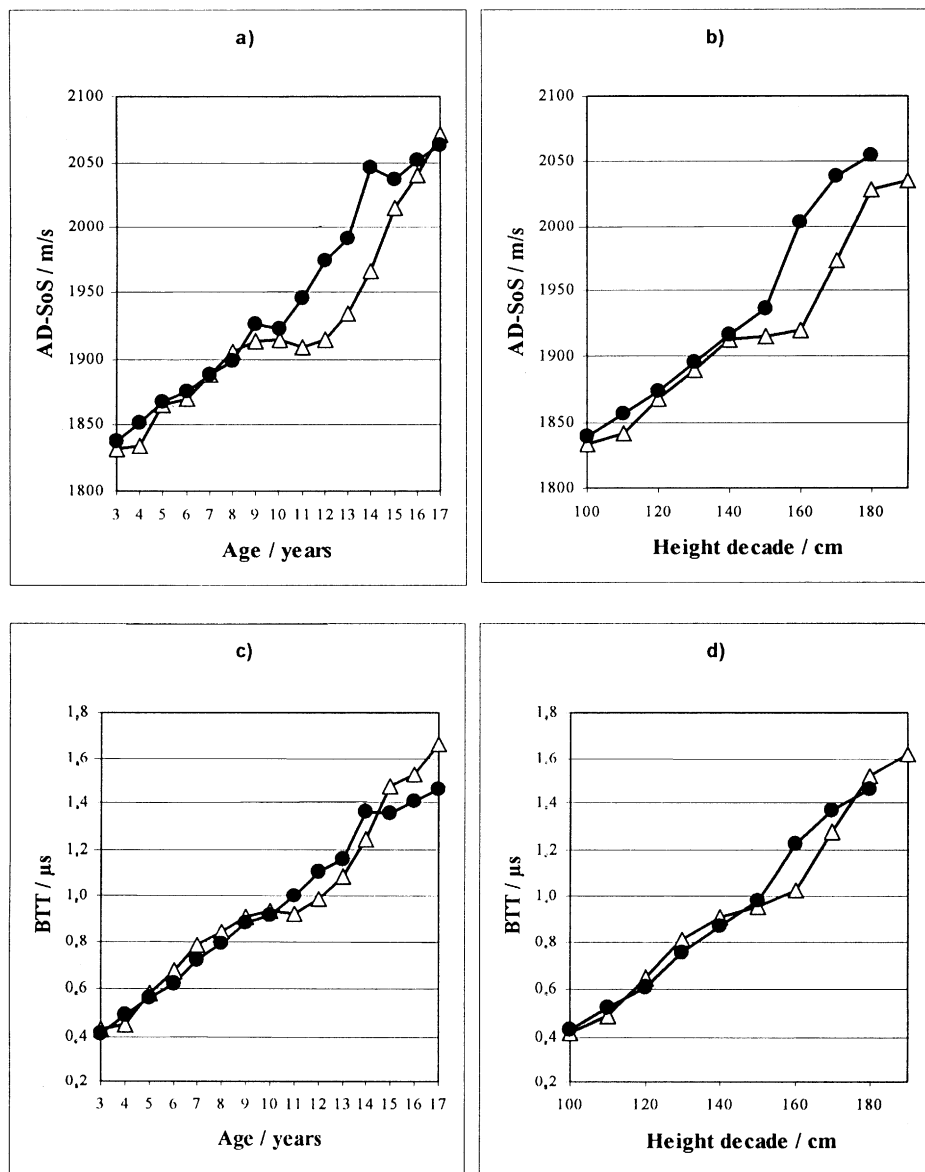


Fig. 1. AD-SoS and BTT in relation to age (a, c) and height (b, d). Depicted are the mean values, for each sex separately (circles, females; triangles, males).

Table 1. Correlation coefficients (R^2) and the best type of regression of QUS parameters against age, body height and body mass index (BMI)

	AD-SoS				BTT			
	Male		Female		Male		Female	
	R^2	Type	R^2	Type	R^2	Type	R^2	Type
Age	0.64	Cubic	0.73	Linear	0.74	Cubic	0.79	Linear
Height	0.60	Cubic	0.68	Square	0.75	Cubic	0.77	Square
BMI	0.19	Linear	0.23	Linear	0.32	Linear	0.35	Linear

All regressions are significant at a level of $p < .0001$.

Table 2. AD-SoS reference data for German children for each age between 3 and 17 years and different values of body height, for each sex separately. Depicted are the number of subjects in each group, mean value of AD-SoS as well as the population standard deviation (SD) and standard error of the estimate (SEM) for each group. Body height is expressed as median value of 10 cm wide ranges, e.g., 90 cm covers all heights between 85 cm and below 95 cm. This database should only be used in combination with a cross-calibration using the IgEA cross-calibration phantom

	Male				Female			
	Number	Mean	SD	SEM	Number	Mean	SD	SEM
<i>Age (years)</i>								
3	28	1832	28	5	27	1838	27	5
4	41	1834	24	4	33	1851	33	6
5	39	1865	29	5	37	1868	30	5
6	47	1870	32	5	53	1876	34	5
7	55	1888	32	4	44	1888	28	4
8	47	1906	32	5	43	1899	36	6
9	62	1913	43	5	66	1926	37	5
10	98	1914	38	4	73	1923	43	5
11	59	1909	40	5	43	1945*	43	7
12	43	1915	33	5	44	1974*	42	6
13	43	1934	47	7	44	1991*	48	7
14	37	1966	55	9	41	2046*	47	7
15	41	2015	60	9	49	2037	40	6
16	21	2040	59	13	38	2051	40	7
17	17	2071	53	13	15	2064	61	16
<i>Height (cm)</i>								
90	1	1809			2	1830	44	31
100	24	1833	30	6	29	1839	23	4
110	53	1841	25	4	49	1856	37	5
120	77	1868	32	4	61	1874	29	4
130	82	1890	33	4	78	1896	35	4
140	129	1913	35	3	104	1916	40	4
150	124	1915	40	4	92	1936*	45	5
160	57	1920	43	6	129	2003*	58	5
170	65	1973	66	8	97	2039*	48	5
180	50	2029	66	9	8	2054	60	21
190	14	2036	46	12	1	1996		
200	2	2114	63	45				

* $p < 0.05$ compared with males.

in boys). Compared with males of the same age, females at ages 11–14 years had significantly higher AD-SoS values ($p < 0.05$; Fig. 1a). Corresponding data for AD-SoS versus height are shown in Fig. 1b. In the height range 150–170 cm AD-SoS was significantly higher in females than males ($p < 0.05$). Stronger correlations were observed for BTT (Table 1). Female values were significantly higher at ages 11–14 years and lower at the age of 7 years and above an age of 14 years ($p < 0.05$)

(Fig. 1c). Only in the range between 155 cm and 175 cm were female values higher than male values ($p < 0.05$) (Fig. 1d). Correlations with BMI were only poor to moderate (Table 1). Mean values, population standard deviations and standard errors of the estimate are depicted in Table 2 for AD-SoS against age and height for both sexes. Table 3 shows the same results for BTT.

In a model combining age, height and BMI, only age and height contributed significantly to the prediction of

Table 3. BTT reference data for German children for each age between 3 and 17 years and different values of body height, for each sex separately. Depicted are the number of subjects in each group, mean value of BTT as well as the population standard deviation (SD) and standard error of the estimate (SEM) for each group. Body height is expressed as median value of 10 cm wide ranges, e.g., 90 cm covers all heights between 85 cm and below 95 cm. This database should only be used in combination with a cross-calibration using the IgEA cross-calibration phantom

	Male				Female			
	Number	Mean	SD	SEM	Number	Mean	SD	SEM
<i>Age (years)</i>								
3	28	0.433	0.123	0.023	27	0.411	0.118	0.023
4	41	0.448	0.092	0.014	33	0.488	0.121	0.021
5	39	0.579	0.129	0.021	37	0.559	0.127	0.021
6	47	0.670	0.152	0.022	53	0.619	0.126	0.017
7	55	0.786	0.136	0.018	44	0.716*	0.122	0.018
8	47	0.843	0.165	0.024	43	0.789	0.158	0.024
9	62	0.905	0.178	0.023	66	0.879	0.154	0.019
10	98	0.934	0.164	0.017	73	0.913	0.160	0.019
11	59	0.923	0.166	0.022	43	1.000*	0.195	0.030
12	43	0.987	0.152	0.023	44	1.104*	0.130	0.020
13	43	1.083	0.214	0.033	44	1.159*	0.175	0.026
14	37	1.240	0.231	0.038	41	1.359*	0.195	0.031
15	41	1.474	0.247	0.039	49	1.356*	0.173	0.025
16	21	1.524	0.271	0.059	38	1.405*	0.166	0.027
17	17	1.665	0.242	0.059	15	1.456*	0.198	0.051
<i>Height (cm)</i>								
90	1	0.284			2	0.374	0.141	0.100
100	24	0.418	0.108	0.022	29	0.428	0.118	0.022
110	53	0.491	0.103	0.014	49	0.520	0.122	0.017
120	77	0.646	0.140	0.016	61	0.608	0.109	0.014
130	82	0.809	0.149	0.016	78	0.749	0.136	0.015
140	129	0.911	0.160	0.014	104	0.866	0.158	0.016
150	124	0.956	0.162	0.015	92	0.979	0.172	0.018
160	57	1.028	0.182	0.024	129	1.224*	0.215	0.019
170	65	1.278	0.279	0.035	97	1.368*	0.184	0.019
180	50	1.520	0.243	0.034	8	1.457	0.218	0.077
190	14	1.615	0.227	0.061	1	1.354		
200	2	1.879	0.247	0.175				

* $p < 0.05$ compared with males.

BTT (both $p < 0.0001$) ($R^2 = 0.80$ in females, $R^2 = 0.73$ in males). In males AD-SoS depended on age ($p < 0.0001$), height ($p < 0.0001$) and BMI ($p < 0.01$) ($R^2 = 0.59$), while in females AD-SoS was significantly associated only with age and BMI (both $p < 0.0001$) ($R^2 = 0.73$).

Discussion

This is to our knowledge the first comprehensive German reference database for AD-SoS in a large pediatric subject group. AD-SoS values in boys and girls correlated both highly significant with age showing different age-related patterns. Especially between the ages of 11 and 14 years male values are lower, which might be interpreted as an effect of a later onset of male puberty. However, it is not clear which properties of the phalanges are responsible for this puberty-related effect. AD-SoS is a mixed parameter depending on signal amplitude and time-of-flight of the signal between the ultrasound probes. An additional analysis of our data, not shown here, revealed that the amplitude of the signal does not depend on age and only slightly on sex.

However, time-of-flight depends on the velocities through bone and surrounding soft tissue and on the ratio between bone width and soft tissue thickness. For example, an *increase* in soft tissue thickness while the bone remains unchanged leads to a *decrease* in AD-SoS because soft tissue velocity is about only one half of bone velocity. The delayed increase in AD-SoS in boys could be due to a later onset of puberty-related bone growth in boys [13] but it could also be due to a potentially stronger reduction in relative soft tissue thickness in females following puberty.

An approach to a selective estimation of growth patterns might be enabled by an analysis of the other QUS parameter evaluated: BTT. BTT is the interval between the arrival of the sound wave when bone tissue is present compared with a wave through soft tissue alone [14]. In the absence of bone (soft tissue only) BTT is equal to zero, independent of soft tissue thickness. Ultrasound velocity in bone is about twice the velocity in soft tissue. Replacing a part of the soft tissue by bone leads to an increase in BTT. BTT increases further when the amount of bone increases. Assuming that soft tissue velocity is fairly constant, BTT depends only on bone properties and not (or only slightly) on soft tissue

thickness. When bone remains unchanged (e.g., in young adults) but soft tissue thickness changes (associated with, e.g., a change in body weight) BTT should remain constant. In growing bone, soft tissue, bone width and BTT all increase. However, the increase in BTT is only associated with the increase in bone properties, not with the increase in soft tissue thickness. AD-SoS and BTT are strongly correlated. However, correlations between BTT and age are higher than those between AD-SoS and age ($R^2 = 0.79$ for BTT and $R^2 = 0.73$ for AD-SoS in females and $R^2 = 0.74$ for BTT and $R^2 = 0.64$ for AD-SoS in males). The better quality of the regression of BTT with age might be due to its ability to compensate for variabilities in soft tissue thickness for a given age. This assumption is also supported by the fact that in a model combining age, height and BMI no significant contribution of BMI to BTT could be observed in either sex. The nature of the correlation of BTT and age, however, might be complex and may be affected by bone mass, geometry and material velocity in the cortex.

To gain further insight into the determination of BTT we looked at its relationship with cross-sections of bone. Gender-specific differences between ages 11 and 14 years are less pronounced in BTT than in AD-SoS. Above the age of 14 years, BTT is higher in boys. In a study of QUS measurements in adult phalanges we found a strong correlation between cortical cross-sectional area and a parameter we named 'normalized SOS' (nSOS) [15]. This parameter was introduced to correct for variations in soft tissue thickness and is strongly correlated with BTT. Although it is not evident that the correlation between cross-sectional area and BTT or nSOS is as strong in children, other results support this assumption:

1. Estimated metacarpal cross-sectional cortical area, calculated from literature data [16], is similar in both sexes up to the age of 14 years. Above the age of 14 years cortical area increases more in boys which is true also for BTT.
2. Using a computer simulation of ultrasound propagation through juvenile cortical bone [15,17] we found a strong and gender-independent relationship between cortical area and BTT [18].

We also calculated age-related growth curves of finger width, which should be related to growth curves of bone width. Up to the age of 12 years, finger width is similar in boys and girls. Above 12 years there is hardly any further increase of finger width in girls, while bone width increases further in boys. On the other hand, BTT increases further in girls, indicating that bone width is not a predominant factor for BTT. Taking all these results into consideration it is very likely that BTT can be used to estimate cortical cross-sectional area of finger phalanges with possible applications in the detection of growth disorders of the cortex.

The correlation of AD-SoS and BTT with height is nearly as good as it is for age. A comparison with height-specific reference data is useful in the examination of

pathologic changes of QUS parameters in relation to bone growth – for example, smaller children might have reduced QUS values, which on the other hand might be normal for their height.

This comprehensive database is useful for examining the impact of juvenile diseases affecting the skeleton on quantitative ultrasound of the finger phalanges. Depending on the type of disease or growth disorder, measurement results could be compared with age- or height-specific reference data. Interpretation of AD-SoS data should be complemented by an analysis of BTT to reduce part of the soft tissue bias. In this way a simple and radiation-free assessment of juvenile skeletal disorders using quantitative ultrasound might be possible in the future. The impact of pubertal status on the QUS results could not be examined in our study. The future addition of these associations might further improve the usefulness of this database for the study of juvenile bone quality.

Appendix

Figure A1 illustrates the signal traces that can be observed in children and the corresponding time intervals. Different time intervals are used for the calculation of different velocities. T(AD-SoS) is the interval between the start time of the transmitted signal (A) and the time the signal received reaches a constant trigger level of 2 mV (C). By dividing transducer separation (TS) through T(AD-SoS), the standard velocity amplitude-dependent speed of sound (AD-SoS) is calculated:

$$AD-SoS = \frac{TS}{T(AD-SoS)}$$

The point in time at which the trigger level is attained depends on the amplitude of the first peak. Therefore, amplitude variability has an impact on AD-SoS.

Another velocity parameter was introduced by our group. We used the very first part of the signal received

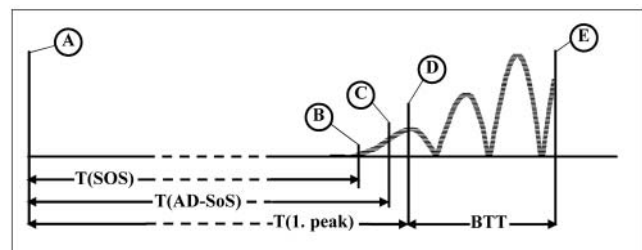


Fig. A1. Received traces and corresponding time intervals in children. Letters refer to points in time: A, start of transmitted signal; B, first part of signal received; C, time when the signal reaches a constant trigger level; D, time when the first peak reaches its maximum; E, time when the signal would have been received after transmission through soft tissue only.

(B) for the calculation of a parameter SOS, as SOS no longer depends on the signal amplitude

$$SOS = \frac{D}{T(Sos)}$$

To compensate for the variability in soft tissue thickness SOS is normalized assuming a constant finger width (nSOS) [15].

The parameter bone transmission time (BTT) was introduced by Igea. BTT is calculated as the interval between the time when the first peak of the signal received reaches its maximum (D) and the time that would be measured if no bone but only soft tissue were present between the transducers (E). BTT depends only on bone properties; it would be equal to zero if no bone were present.

BTT and nSOS are positively correlated ($R^2 = 0.79$) in our group of children. During growth BTT increases while T(SOS) and T(AD-SoS) decrease. Decreased time-of-flight is associated with an increase in the velocity parameters SOS, nSOS and AD-SoS. BTT and velocity parameters all increase with bone growth.

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