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ORIGINAL ARTICLE

Feasibility of quantitative ultrasound measurements on the humerus of newborn infants for the assessment of the skeletal status

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Abstract Quantitative ultrasound (QUS), although widely used in adults has, so far, been scarcely employed in newborn infants and children. This study aimed to evaluate the feasibility of the use of QUS in newborn children and the factors influencing QUS parameters. In 140 consecutive healthy full-term newborn babies (76 male and 64 female; gestational age: 39.5 ± 1.5 weeks) QUS parameters were assessed within 3 days of the child's birth at the distal diaphysis of the humerus by use of Bone Profiler, after an appropriate modification of caliper and software. In all subjects we evaluated the amplitude-dependent speed of sound (AD-SoS) (meters per second), the characterizing graphic trace parameters [signal dynamic (SDy), fast wave amplitude (FWA) and bone transmission time (BTT)], SoS (meters per second), that is, the speed of sound calculated on the first peak, and hBTT, that is, the interval time between the first peak of the ultrasound and when this reaches the speed of 1,570 m/s, which is the velocity of ultrasound in the soft tissue. This latter parameter allows one to measure bone tissue independently of soft tissue. QUS measurements were also performed at the phalanges on all mothers (age range 24–38 years), who also completed a self-report questionnaire on their obstetric history, smoking and dietary habits and family history of osteoporosis. In 73 mothers and their children QUS was repeated after 12 months. All QUS parameters were slightly higher in male than in female newborn infants but the difference was not significant. BTT and hBTT of neonates showed a significant relationship with birth weight ($r = 0.20$; $P < 0.05$ and $r = 0.37$; $P < 0.01$, respectively) and with cranial circumference ($r = 0.22$; $P < 0.05$ and $r = 0.36$; $P < 0.01$, respectively). In newborn infants none of the QUS parameters was significantly influenced by maternal QUS or by maternal smoking and calcium intake. In a model of multiple regression analysis the cranial circumference was the only parameter entered into the model, explaining approximately 15% of hBTT value. At month 12 AD-SoS and SoS were slightly lower than at birth (−11% and −0.1%, respectively), whereas both BTT and hBTT showed a significant ($P < 0001$) increase. The present study demonstrated the feasibility of the use of QUS, as assessed by a new measurement approach at the humerus, in the evaluation of skeletal status in neonates. BTT and, above all, hBTT, appears to be the best parameter for both evaluation of skeletal status at birth and monitoring of bone growth in the first year of life.

Keywords Bone growth · Newborn infants · Quantitative ultrasound · Skeletal status

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Introduction

Since skeletal mass in adulthood is the result of both the amount of bone gained during growth and its consequent rate of loss, the maximization of bone mass during skeletal growth has become the goal of primary prevention of osteoporosis [1, 2]. Therefore, any factor that might influence the peak bone mass attained at skeletal maturity is important in determining the individual's risk of developing osteoporosis in later life [3, 4]. Peak bone mass acquisition is under a genetic influence from both parents, and maternal bone mass was found to be associated with skeletal characteristics of pre-pubertal children. However, recent studies suggest that the risk of osteoporosis later in life may be determined in part by environmental influences during intrauterine or early postnatal life.

The mechanisms underlying the long term effect of the intrauterine environment are not known but include the "fetal programming" of endocrine systems that influence skeletal metabolism and persistent effects of altered skeletal growth and development in utero [5]. Other studies have reported that osteopenia is recognized with increasing frequency in low-birth weight newborn infants and that former pre-term infants are at increased risk for suboptimal growth and bone mineralization in comparison with infants born at term [6, 7, 8]. On this basis, it can be derived that the evaluation of skeletal status in neonates and infants may be important for both the early detection of the conditions characterized by defects in bone mass or mineralization and for the monitoring of the bone development process.

For the assessment of bone mineralization in the early stages of life, dual X-ray absorptiometry (DXA) is currently the most extensively employed method [1]. However, the use of DXA in neonates suffers from some important limitations, such as the problem of cumulative radiation dosage and that of motion artifacts. Moreover, the inability of DXA to account for the important changes in body and skeletal size that occur during growth, limits its use in longitudinal studies in children. In fact, in growing children bone mineral content and bone area increase at different rates [9]. Quantitative ultrasound (QUS) methods have proven to be useful in the assessment of osteoporosis and in the prediction of fragility fracture risk in adults [10]. The attractiveness of the use of QUS for bone measurements in children lies in its low cost, portability, ease of use and, above all, its lack of ionizing radiation.

QUS bone measurements in children were obtained mainly at the calcaneus, the patella, the tibia and the fingers. Several studies have demonstrated the suitability of QUS for measuring bone status in infants aged less than 3 years [11] and for the detection of bone growth and gender differences in children of more than 3 years of age [12]. Recently, it has been reported that phalangeal QUS is a useful tool for assessing bone status and fracture risk in children and adolescents with bone and mineral disorders [13]. These last studies highlighted the notable limitations of commercially available equipment, when used on infants, and pointed out the need for the development of transducers and software dedicated to this population.

Very few studies have reported that transmission QUS can also be used for the assessment of bone status in premature and full-term infants [14, 15]. No longitudinal studies are present in the literature on the pattern of QUS during the first year of a child's life.

The aims of the present study were:

A To determine the feasibility of the use of QUS, as assessed by a new measurement approach in the evaluation of skeletal status in newborn infants.
B To evaluate QUS changes in bone growth during a child's first year of life.
C To assess how mothers' QUS patterns and anthropometric and gestational characteristics influence QUS parameters in neonates.

Subjects and methods

One hundred and forty consecutive healthy full-term newborn infants (gestational age 39.5 ± 1.5 weeks) were enrolled from the neonatal department nursery at the University of Siena between October 2000 and September 2001, after informed consent had been received from their parents. Neonates with birth weights of less than 2,300 g and those suffering from major congenital malformations or metabolic diseases were excluded. In addition, the mothers were asked to fill in a questionnaire so that we could obtain information about their menstrual and obstetric history, their smoking and dietary habits and their family history of osteoporosis. In particular, dietary calcium intake was estimated from a validated questionnaire that considered any foods that accounted for the majority of calcium in the diet.

Neonatal anthropometric data, such as weight, length, head circumference and Apgar score at the 3rd and 5th minute after birth, were collected from the case sheet.

The infants whose mothers were not able to complete the questionnaire were excluded.

In both mothers and children QUS was performed within 3 days of the birth.

QUS measurements in the mothers

Measurements in the mothers were performed with Bone Profiler (IGEA, Carpi, Italy) on proximal phalanges II to IV of the left hand, which obtained the amplitude-dependent speed of sound (AD-SoS), calculated as the ratio between transducer separation and the time when the received signal attains a predefined signal amplitude of 2 mV.

Soft tissue velocity is usually measured between the base of the thumb and the index finger before each measurement session.

QUS measurements in the neonates

Neonatal QUS parameters were obtained by measurement at the distal diaphysis of the humerus. The humerus was chosen because a previous study of ours and of others had suggested the possibility that bone status in children could be assessed by use of Bone Profiler at the humerus [11].

For the present study the caliper and the software of the original Bone Profile device were modified by the manufacturer. In particular, caliper tension was reduced and the software was set to read the QUS signal up to a velocity of 1,570 m/s instead of 1,700 m/s. With the use

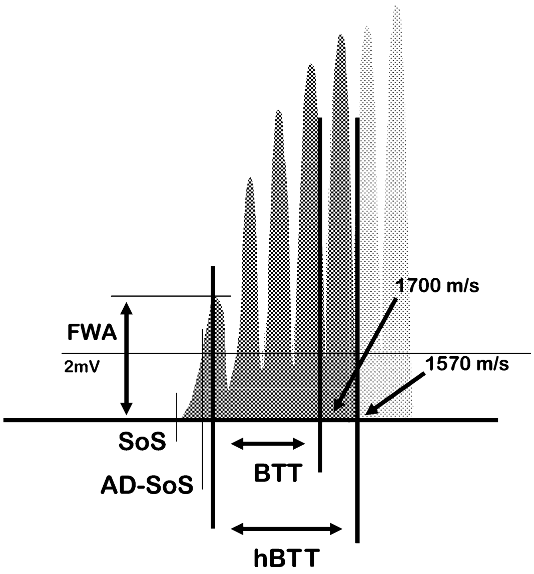

Fig. 1 Schematic representation of the graphic trace of QUS

of the modified device we obtained the AD-SoS, the pure speed of sound (SOS) calculated at the arrival of the first US signal, and bone transmission time (BTT; in microseconds). The BTT is the interval between the time when the first peak of the received signal attains its maximum and when the US signal reaches the velocity of 1,700 m/s. It has been demonstrated by mathematical calculation that BTT is independent of the amount of soft tissue and depends mostly on bone properties [11, 16]. The humerus BTT, calculated with a threshold of 1,570 m/s and not 1,700 m/s, was named hBTT. In addition, by analysis of graphic trace, the fast wave amplitude (FWA; in millivolts), which is the maximum amplitude of the fastest peak of the received US signal, and the signal dynamic (SDy; in millivolts per microsecond squared), which expresses the second derivative of the amplitude versus time of the fastest peak, were evaluated (Fig. 1). The procedure for the performance of measurements in newborn infants consisted of some standardized steps: first, the operator placed the two transducers on the two opposite sides of the humerus; second, the operator let the caliper run along the humerus to meet a repere point given by the two humerus condyles; third, the operator, with minimal upward and downward movements and moving around the humerus, searched for the best QUS signal, which was then measured. The final values of the QUS parameters were calculated as the mean of four repeated measurements.

Both the children and the mothers were recalled 12 months after the first examination in order to undergo repeat QUS measurements by the same procedure as was used in the first control. Only 73 mothers and their children, of those measured at birth, agreed to repetition of the QUS measurements at month 12. In the month-12 visit other information, in addition to QUS parameters assessment, was collected, regarding lactation period and weight gain.

During the study period quality assurance measurements were performed on a weekly basis and showed good coefficients of variation. Moreover, the Bone Profiler device did not undergo changes in hardware or software during the whole study period.

All mothers gave written informed consent to their participation in the study, and the research protocol was approved by our local ethics committee.

Statistical analysis

Clinical and instrumental parameters were expressed as means and SDs.

We used the two-tailed Student's *t*-test to evaluate genderspecific differences.

Linear regression analysis was used for assessment of the relationships between QUS in neonates and other parameters taken into account. The independent effects of variables significantly associated with QUS parameters in children were examined by multiple regression analysis.

The absolute changes in QUS parameters during the child's first year of life were expressed as a percentage of the baseline value. The comparison of the changes at month 12 with baseline values was carried out with one-way analysis of variance (ANOVA). A P value lower than 0.05 was considered statistically significant.

The study of precision of QUS in neonates was carried out on seven infants who underwent six measurements over 3 consecutive days. The coefficients of variation (CVs) were calculated as SD to mean ratio. In addition, standardized CV (sCV) was calculated for each QUS parameter taken into account in the study, according to the formula: sCV = CV%/(dynamic range/mean), where dynamic range was defined as the difference between the maximum and minimum value on the whole population. The precision of QUS parameters at phalanxes in adults has been previously reported [17].

Table 1 The normal CVs and standardized sCVs) of QUS parameters in newborn infants

Parameter	AD-SoS	SoS	FWA	BTT	hBTT	SDy
CV (%)	0.8	1.0	15.0	7.0	7.5	20.1
sCV (%)	6.2	6.1	14.0	5.3	2.3	18.0

Table 2 Demographic and auxological characteristics of the study population (140 newborn infants)

Characteristic	Mean ± SD	Minimum	Maximum
Gestational age (weeks)	39.5 ± 1.5	37	42
Length at birth (cm)	49.8 ± 2.0	45	58
Weight at birth (kg)	3.3 ± 0.47	2.2	4.7
Head circumference (cm)	34.6 ± 1.1	31.5	37.4

Table 3 QUS parameters in the neonates (*NS* not significant)

Parameter	Male ($n=76$)	Female ($n=64$)	*P*
AD-SoS (m/s)	1,757.4 ± 33.8	1,745.4 ± 34.9	NS
SoS (m/s)	1,727.0 ± 25.7	1,721.5 ± 24.8	NS
FWA (mV)	4.0 ± 1.4	4.2 ± 1.9	NS
SDy (mV/μs^2)	830.7 ± 2,075.2	747.0 ± 1,956.6	NS
BTT (μs)	0.26 ± 0.11	0.22 ± 0.10	NS
hBTT (μs)	0.93 ± 0.14	0.87 ± 0.10	NS

Results

The normal and the standardized coefficients of variation for QUS parameters in newborn infants are reported in Table 1.

Table 2 gives the anthropometric characteristics of the 140 healthy full-term neonates.

The values of all QUS parameters in newborn children (divided on the basis of the gender) are shown in Table 3. All QUS parameters were slightly higher in the male babies than in the female ones; however, the difference between the genders did not reach statistical significance for any QUS parameters.

Among all QUS parameters, only BTT and hBTT significantly correlated with some anthropometric data. In particular, both BTT and hBTT showed a closer relationship with the weight at birth ($r=0.20$; $P<0.05$ and $r=0.37$; $P<0.01$, respectively) and with the cranial circumference ($r=0.22$; $P<0.05$ and $r=0.36$; $P<0.01$, respectively) (Fig. 2). A positive, but not significant, correlation ($r=0.18$) was found between hBTT and length at birth. Moreover, in the neonates none of the QUS parameters that were measured was influenced by maternal smoking, calcium intake or by a positive history of osteoporosis.

No significant relationship was found between QUS parameters measured in the mothers and those obtained in the children.

By a model of multiple regression analysis, taking into account all anthropometric parameters as independent variables, and BTT and hBTT as dependent variables, we found that head circumference was the only parameter entered into the model, explaining approximately 15% of hBTT value ($R=0.362$; $P<0.01$), whereas BTT was not predicted by the same model.

In 73 children (39 male and 34 female) QUS parameters were repeated after 12 months. Unexpectedly, AD-SoS values were slightly lower at month 12 than at birth (1,734.5 ± 32.1 m/s vs 1,752.0 ± 34.7 m/s) (Table 4). A similar pattern was also observed for SoS. In contrast, both BTT and hBTT showed a significant ($P<0.001$) increase with respect to the values at birth (0.33 ± 0.1 μ/s and 0.40 ± 0.2 μ/s, respectively) (Table 4).

The percentage increase of BTT and hBTT evidenced a moderate but significant relationship with the weight gain observed in the same period ($r=0.46$; $P<0.01$ for BTT and $r=0.52$; $P<0.01$ for hBTT).

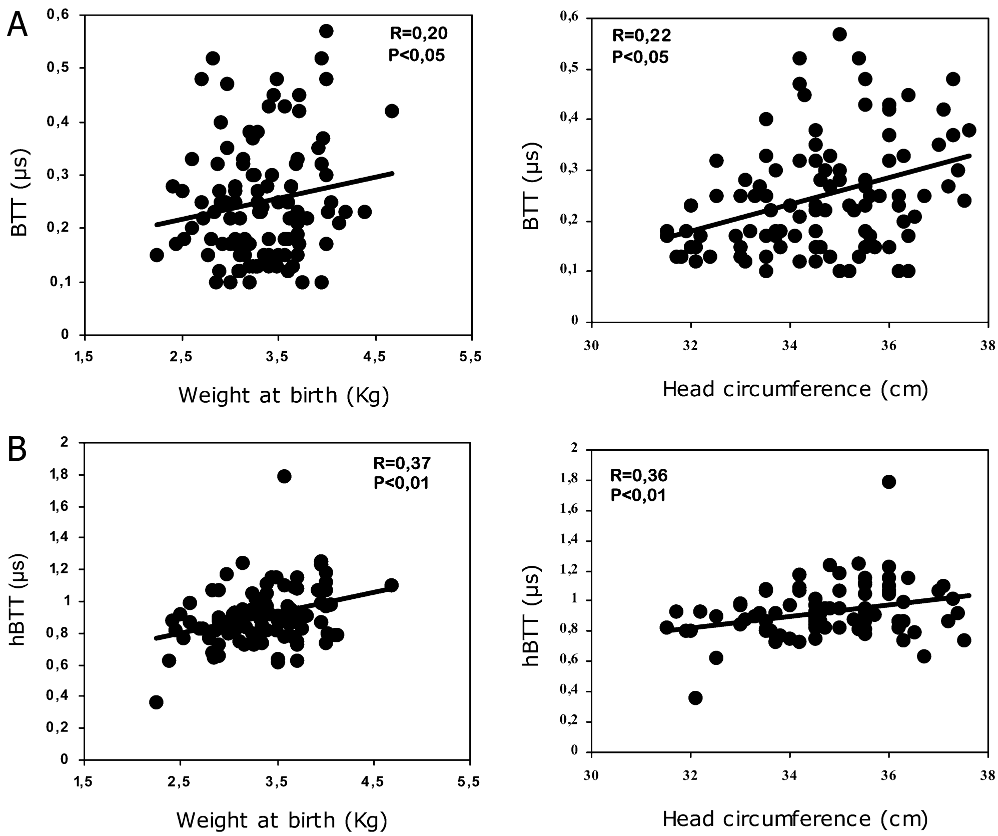

Fig. 2 Correlations of BTT (**A**) and hBTT (**B**) vs weight at birth and cranial circumference measurement in neonates ($n=140$)

Table 4 Bone transmission time (mean ± SD), read up to a velocity of 1,700 m/s (*BTT*) and 1,570 m/s (*hBTT*), and velocity parameters (AD-SoS and SOS) at birth and after 12 months (*NS* not significant)

Parameter	At birth	At month 12	Difference	%	*P*
BTT (μs)	0.25 ± 0.1	0.58 ± 0.3	0.33 ± 0.1	+ 136.1	< 0.001
hBTT (μs)	0.9 ± 0.4	1.30 ± 0.6	0.40 ± 0.2	+ 57.3	< 0.001
AD-SoS (m/s)	1,734.5 ± 32.1	1,714.8 ± 45.1	−19.7 ± 5.6	−1.1	NS
SOS (m/s)	1,724.8 ± 25.3	1,722.6 ± 23.4	−2.2 ± 0.3	−0.1	NS

Discussion

This study has demonstrated the feasibility of the use of QUS as assessed by a new measurement approach in the evaluation of skeletal status in newborn infants. Moreover, it has shown that BTT and, above all, hBTT, are the best QUS parameters for QUS assessment at birth and monitoring of bone growth in the first year of the child's life. The attractiveness of QUS for bone measurements in children lies in its low cost, portability, ease of use and, above all, its lack of ionizing radiation.

The first studies, which employed bone ultrasonography in neonates, clearly demonstrated that devices commonly used in adults were not adequate for use on children [1]. In this study we used a modified caliper and carried out measurements on a bone segment, the humerus, different from those segments normally measured. The humerus was chosen on the following basis: (a) to avoid the risk of scanning skeletal sites that have not yet undergone endochondral ossification [18]; (b) the humerus of the newborn child presents a cross-sectional size comparable to that of an adult phalanx; (c) a previous study by ourselves and others suggested the possibility of assessing bone status in children by QUS at the humerus [11]. This latter study indicated that the traditional method, QUS assessed at phalanxes, was not suitable for taking measurement in infants.

In our study QUS evaluation of the humerus failed to show significant gender-related differences in skeletal status, either at birth or after 1 year of life. The gender effect on mineral status is well described for older age groups. Thus, the gender effect on bone status appears to be age dependent [19, 20]. Whether gender differences in bone mass or density exist in early life is not clear. Inconsistent findings have been reported and may reflect differences in the bone site measured, the use of different devices, or sample sizes insufficient for gender differences to be detected. Even though a higher total body bone mass was observed in male infants than in female infants 1 to 18 months of age [21], the majority of studies failed to find gender differences [5, 8, 22]. Previous studies using QUS reported that the difference between the genders becomes significant after the onset of puberty [12, 16].

The precision of some QUS parameters (FWA and SDy) does not allow their use in a clinical setting, whereas BTT, hBTT, AD-SoS and SOS showed an adequate precision for clinical use in neonates. These findings seem to be in agreement with the data reported by Barkmann et al., who, on a large population of children (3–17 years old), reported that AD-SoS and BTT were the best parameters in detecting bone growth in children [16].

In our study BTT and hBTT were the only parameters that correlated with child anthropometric indices. Namely, BTT and hBTT presented positive correlations with weight at birth and cranial circumference. A different pattern between neonates and adults is evident, in fact, in adults the most effective QUS parameter obtained by Bone Profiler is AD-SoS. The lack of relationship between anthropometric characteristics of newborn babies and parameters measuring speed of sound may be explained by the fact that these latter are strictly related to the ratio between bone width and soft tissue thickness. Some previous studies have shown that body weight and, above all, circumference of head, which represents the major component of body weight at birth, were the best predictors of bone mineral density and bone area [5, 8, 19, 22]. In agreement with these data, we found that cranial circumference was the only anthropometric parameter that entered into a multiple regression model, considering hBTT as a dependent variable. The better correlation between anthropometric parameters and hBTT, in comparison with BTT, may be explained by the fact that this latter, which uses 1,700 m/s as threshold, is less able to discriminate between bone, cartilage and soft tissue.

Instead, in disagreement with a previous study, we did not find any significant correlation between calcium intake and the smoking attitude of expectant mothers and bone status in neonates [5]. This is probably because, in our population, the number of smoking expectant mothers was much lower than 25%, as reported by Godfrey et al. [5].

Our study is the first that has evaluated longitudinally by QUS the development of the skeleton from the child's birth to the end of its first year of life. At month 12, AD-SoS and SoS values were lower than at birth, whereas both BTT and hBTT showed a similar and significant increase. This finding could be explained by the significant influence of soft tissue on SOS and AD-SoS. Instead, the different pattern of BTT might be explained by the fact that it depends only on bone properties and not (or only slightly) on soft tissue thickness. Therefore, in growing bone, BTT is associated only with the increase in bone properties and not with the increase in soft tissue thickness.

The fact that BTT and, above all, hBTT, was correlated with body weight and with the weight gain during the first period of life, seems to confirm that these parameters are strictly correlated to cortical bone area and to cortical width, as reported by an in vitro study [23]. This finding may be reinforced by the observation that the BTT value tends to increase from between 3 years of age and maturity in both genders [16]. Thereafter, it shows a negative trend in women [11], where subcortical reabsorption prevails, while it remains stable in men [24], in whom the subcortical reabsorption is balanced by a periosteal bone apposition [25]. Our study shows some limitations, namely the lack of a reference method, the low number of subjects who completed the longitudinal study and the lack of any comparison with DXA.

In conclusion, further studies are needed before the use of QUS in neonates and infants can be recommended in a clinical setting. These studies should clarify the precision of different QUS devices and confirm their ability to supply specific information on bone development. Once these points are better clarified, QUS could be considered a useful screening tool for early detection of bone status in newborn infants and a valid method for the longitudinal assessment of bone in growing children.

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