Assessment of bone status in preterm infants by tibial quantitative ultrasound

JUSTyna CZECH-KOWALSKA1, ANNA DOBRZAŃsKA1, KATARZYNA MARIA KORNACKA2, DARIUSZ GRUSZFELD1

Abstract

Aim: To assess the bone strength of preterm infants by tibial quantitative ultrasound before and at term gestation in comparison to term neonates taking into consideration influence of total parenteral nutrition, mechanical ventilation and postnatal steroids treatment. Methods: There was the speed of sound (SOS) along the tibia measured in 40 infants (18F, 22M) by quantitative ultrasound. The median age at the moment of examination was 34 days (range 4-121) for 21 preterm infants born below 33 week of gestation (mean birth weight 1111 ± 346 g; mean gestational age 28.3 ± 2.5 wk) and 4 days (range 1-7) for 19 term newborns (mean birth weight 3308 ± 488 g; mean gestational age 39.3 ± 1 wk). Results: The tibial SOS results were similar in males and females, respectively 2917 ± 152 m/s and 2976 ± 183 m/s (p = 0.277). Tibial SOS was significantly lower in preterm (2852 ± 155 m/s) compared to term infants (3044 ± 115 m/s), even in those preterm in corrected age corresponding to term gestation (2800 ± 142 m/s) (p < 0.0001). There was a negative correlation between tibial SOS and duration of total parenteral nutrition (R = -0.58, p = 0.012), mechanical ventilation (R = -0.57, p = 0.013), steroids treatment (R = -0.74, p = 0.0007) and postnatal age (R = -0.65, p = 0.0014). Conclusion: Diminished bone strength of preterm infants born before 33rd week of gestation is still present at the age of full-term gestation. Further studies are needed to assess timepoint of bone strength recovery in preterm infants. Prolonged parenteral nutrition, mechanical ventilation and steroids treatment may play a role in this unfavourable process.

Key words: Quantitative ultrasound, SOS, metabolic bone disease, premature infants, steroids, mechanical ventilation, total parenteral nutrition

Introduction

Intensive growth of fetal skeletal system and its mineralization occurs in the third trimester of pregnancy. At that time ample provision of calcium, phosphorus and other nutrients by placental flux takes place [1, 2]. The preterm delivery stops that process, and preterm born infants are in high risk to develop metabolic bone disease of prematurity (MBDP). The incidence of the disease is inversely related with gestational age and birth weight, and is as high as 50-60% among babies with birth weight less than 1000 g [3-5]. Insufficient calcium and/or phosphorus supply is the main etiological factor. But other well-known risk factors are as follows: chronic lung disease, steroids and diuretic treatment, prolonged parenteral nutrition, immobilization and mechanical ventilation [3, 5, 6]. The diagnostic methods available in revealing metabolic bone disease of prematurity are still unsatisfactory. Promising method of assessing bone strength in newborns seems to be quantitative ultrasound (QUS) of the tibia measuring ultrasound velocity (speed of sound – SOS) along the cortical layer of the tibia [7-9]. The attractiveness of QUS technique for bone status measurement lies in ease of use, short time of examination, portability and lack of radiation. The bone mineral density is a main determinant of bone strength. But bone mineral density does not fully explain the variance of bone strength. Quantitative ultrasound of the tibia gives also information about other properties of bone such as elasticity, microstructure and cortical thickness, thus providing a more complete picture of the bone [10-12]. Because of its advantages QUS technique could be an useful tool in assessing and monitoring bone strength in preterm infants.

The aim of the study was to assess the bone strength in preterm infants by tibial quantitative ultrasound before and at term gestation in comparison to full-term neonates. The influence of etiological factors of metabolic bone disease like duration of parenteral nutrition, mechanical ventilation and postnatal steroids on bone strength was also analysed.

1 Department of Neonatology and Neonatal Intensive Care, The Children’s Memorial Health Institute, Warsaw, Poland
2 Department of Neonatology, Warsaw Medical University, Poland
Patients and methods

Patients characteristics

A total number of forty infants (18 female, 22 male) were enrolled into the study. Twenty-one preterm infants (6 female, 15 male) born before 33rd week of gestation as a study group and 19 healthy full-term infants (12 female, 7 male) as controls were characterised in Table 1. According to the study protocol (inclusion criteria), the body weight of all infants was appropriate for gestational age and the gestational age of preterm infants was less than 33 weeks. Gestational age was determined by the history of the mother’s last menstrual period, by fetal ultrasound examination and thorough neonatal evaluation (Dubovitz score). There were following exclusion criteria: intrauterine growth retardation, major congenital abnormalities, inborn metabolic disorders and renal and liver dysfunction.

Clinical data about risk factors of MBD

Premature infants received total parenteral nutrition in the first weeks of life. Median time of total parenteral nutrition was 28.3 days (range 4-66 days). When tolerated, the infants received enteral nutrition. They were fed with either fortified human milk (Bebilon BMF-Nutricia) or with special preterm formula (Bebilon Nenatal-Nutricia) up to the weight of 3000 g. Mechanical ventilation was used for preterm infants mainly due to following respiratory problems: respiratory distress syndrome, chronic lung disease, and pneumonia. Median time of ventilation was 14.5 days (range 0-55 days). Chronic lung disease was diagnosed in seven preterm infants (33.3%) and parenteral steroids were used in all these cases. The median duration of steroids treatment was 6d (range 3-11d).

SOS measurements

The tibial SOS was measured by QUS (Sunlight Omnisense 7000P – Sunlight, Israel), a method designed to measure SOS at multiple skeletal sites by an axial transmission. This technique takes advantage of the fact that ultrasound waves propagate more rapidly through dense tissue such as bone than through soft tissue. The system measures the time that elapses between transmission and the first reception of signal. These elapsed time periods, sometimes called the shortest propagation time, are used to calculate the SOS. It performs a sequence of transmissions from the transmitters in the probe to be received by the receivers in the probe. The ultrasound device consists of desktop unit (computer, monitor, keyboard) with multiple probes in different sizes giving possibility to measure many skeletal sites. The smallest probe with center frequency 1.25 MHz used for adults to evaluate small bones (e.g. metacarpal bones, phalanges) is appropriate for assessing tibia of newborns and young infants. The location of measurement site was defined as the midpoint of the knee – sole length determined by special calipers and then marked just by eyeliner pencil. The probe was moved across the mid-tibial plane and the result was shown on the screen. After that two more separate measurements were done. The mean of these 3 measurements were used for further statistical analysis. One physician performed all examination.

The precision for the study population (coefficient of variation – CV%) based on 3 separate consecutive measurements performed in all of 40 infants was 0.8% (23.55 m/s). CV% for full – term infants was 0.7% (21.3 m/s) and 0.89% (25.37m/s) for preterm infants.

Statistical analysis

In order to establish whether preterm infants at the same corrected age as full-term neonates achieve similar bone strength they were divided into 2 groups. Group 1 consisted of 12 infants with corrected age below 37 weeks while group 2 contained 9 preterm infants with corrected age corresponding to full term gestation. There were no differences between groups in birth weight, birth length and gestational age. The comparison of both groups is shown in Table 1.

The data were analyzed using Statistica 5 statistical software (Stat Soft). An unpaired – T test was used to compare SOS results in term and preterm infants and between male and female. A paired T-test was used to determine differences in SOS values between first and control examination. A Mann-Whitney U test or an unpaired T-test was used to compare anthropometrics features and age (gestational, corrected) between studied groups. The Spearman correlation was used to evaluate the relationship between tibial SOS results and age, anthropometrics features and risk factor of metabolic bone disease in preterm infants. Multiple stepwise regression analysis was used to determine the relative contribution of these variables (birth weight, birth length, current weight, gestational age, corrected age, postnatal age, duration of total parenteral nutrition, mechanical ventilation and steroids treatment) in SOS result. P < 0.05 was considered to be statistically significant.

The study was approved by Ethics Committee of The Children’s’ Memorial Health Institute and written informed consent was obtained from the parents.
Table 1. Birth weight, birth length, gestational age, current weight, corrected age and tibial SOS results of study participants. Data presented as mean ± SD

<table>
<thead>
<tr>
<th></th>
<th>Term infant (n = 19)</th>
<th>Preterm infants (n = 21)</th>
<th>Preterm infants Corrected age &lt; 37 Hbd (n = 12)</th>
<th>Preterm infants Corrected age ≥37 Hbd (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>39.3 ± 1.1</td>
<td>28.3 ± 2.5</td>
<td>27.9 ± 2.4</td>
<td>28.9 ± 2.6</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3308 ± 488</td>
<td>1111 ± 346</td>
<td>1083 ± 311</td>
<td>1149 ± 403</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>53.7 ± 2.9</td>
<td>39.4 ± 4.8</td>
<td>39.2 ± 4.1</td>
<td>39.8 ± 6.5</td>
</tr>
<tr>
<td>Birth weight (g)</td>
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<td>1111 ± 346</td>
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<td>28.9 ± 2.6</td>
</tr>
<tr>
<td>Current weight (g)</td>
<td>3261 ± 487</td>
<td>1724 ± 535</td>
<td>1453 ± 460</td>
<td>2211 ± 358</td>
</tr>
<tr>
<td>Corrected age</td>
<td>–</td>
<td>35 ± 4</td>
<td>32.4 ± 2.4</td>
<td>39.3 ± 2.88</td>
</tr>
<tr>
<td>SOS (m/s)</td>
<td>3044 ± 115</td>
<td>2852 ± 155</td>
<td>2895 ± 140</td>
<td>2800 ± 142</td>
</tr>
</tbody>
</table>

*a p < 0.0001 (significant difference in tibial SOS between preterm and full-term infants);

*b p < 0.0001 (significant difference in tibial SOS between preterm infants at corrected age of term gestation and term neonates);

*c p < 0.001 (significant difference in current body weight between groups of preterm infants);

*d p < 0.001 (significant difference in corrected age between groups of preterm infants).

Results

The median age of tibial SOS measurements was 4 days (range 1-7 days) in full-term newborns and 34 days (range 4-121 days) in preterm infants. The tibial SOS results were similar among males and females in the study population, respectively 2917 ± 152 m/s and 2976 ± 183 m/s (p = 0.277). There were also no gender differences in the group of term infants (males – 3026 ± 86 m/s vs. female – 3055 ± 132 m/s, p = 0.61) nor preterm infants (males – 2867 ± 151 m/s vs. female – 2817 ± 173 m/s, p = 0.52). The comparison of tibial SOS results of term and preterm infants is summarised in Table 1. Tibial SOS results in preterm infants were still significantly lower than in full term neonates even at the corrected age corresponding to full term gestation as shown in Table 1.

We found a positive correlation between tibial SOS and gestational age (R = 0.5, p = 0.019) in preterm infants but there were no significant correlations with corrected age (R = 0.4, p = 0.07) and anthropometrics features such birth weight (R = 0.29, p = 0.195), birth length (R = 0.21, p = 0.43) and current weight (R = -0.31, p = 0.16). There was also a significant inverse correlation between tibial SOS results in preterm infants and theirs postnatal age (R = -0.65, p = 0.0014).

The influence of risk factors of metabolic bone disease of prematurity on bone strength was established in preterm infants. There was a high negative correlation between tibial SOS results and duration of total parenteral nutrition (R = -0.58, p = 0.012), duration of mechanical ventilation (R = -0.57, p = 0.013) and duration of steroids treatment (R = -0.74, p = 0.0007).

Multiple stepwise regression analysis was used to determine the relative contribution of examined variables to the measurements of tibial SOS. The significant remained variables were gestational age (b = 0.65) and corrected age (b = -0.2), R² = 0.48, p = 0.0146. Other variable had to be excluded because of colinearity.

Discussion

The present study demonstrates that tibial SOS measurements can be easily performed in preterm infants even for those with very low birth weight during mechanical ventilation. The obtained tibial SOS results indicate that there is no gender differences in bone strength. Other studies with QUS technique did not find relation with sex and bone strength in newborns and infants, as well [8, 13]. We found a positive correlation between tibial SOS and gestational age but not with anthropometrics features at birth (such weight and length). While others found correlations not only with gestational age but also with birth anthropometrics [14-16]. This differencies are difficult to explain.

The lower tibial SOS values in the group of 21 preterm infants of 24-33 weeks of gestation compared to term infants give evidence of worse bone strength in that population what was proved also by other researchers [17, 18]. Probably, the diminished bone strength in these infants is caused not only by insufficient mineralization but also worsening of other properties of the
bone because bone QUS results depend on the degree of the mineralization of skeletal tissue and their elasticity, microstructure and thickness of cortical layer [10-12].

The infants born before 33nd week of gestation have smaller and less mineralised bones because they were not exposed to the period of the most intensive growth and mineralization of the skeletal system that is the 3rd trimester of gestation. But despite providing high standard of neonatal care bone strength of these children even at corrected age corresponding to full-term gestation does not on the level of term neonates as shown by our study. The worse bone strength in preterm infants is related to the lower provision of calcium and phosphorus comparing to the third trimester of pregnancy and to the changes in environmental conditions for bone growth and mineralization from uterus with amniotic fluid to extrauterine space [19]. These disadvantages could be proved by negative correlation between tibial SOS results and postnatal age of infants born before 33rd week of gestation obtained in our study. Decling of SOS measurements of the tibia during several weeks after birth was shown in many other papers [7-9, 20-23]. This fall of SOS values in Tomlinson et al. study was greater in the 24- to 27-week gestation cohort compared with those > 28 weeks [15]. The most immature infants are at greatest risk of MBD. Additionally, physical activity program in VLBV preterm infants prevented fall of SOS values remained them stable [7, 23].

The negative influence of well-known risk factors of metabolic bone disease of prematurity on growth and mineralization of the skeletal system should be considered. Our data show negative correlation between bone strength and the number of days of total parenteral nutrition, mechanical ventilation and postnatal steroids treatment. Also others found a negative correlation between SOS and duration of total parenteral nutrition (TPN) but not mechanical ventilation and postnatal steroids treatment [15, 18].

It is very difficult to achieve calcium and phosphate accumulation close to intrauterine retention in parenterally fed preterm infants. It is mainly due to growing risk of calcium-phosphate salts precipitation in nutritional fluid with rising concentration of these minerals [24, 25]. The additional unfavourable effect of aluminium present in alimental fluids on bone mineralization should also be taken into account [26, 27].

Prolonged mechanical ventilation is one of very important risk factor of MBDP because of diminished physical activity of ventilated infants due to severe general condition and/or influence of sedatives. Prolonged dependence on mechanical support is often related to chronic lung disease. As a method of treatment of chronic lung disease is restriction of fluid therapy, which as a result, causes decreased mineral supply for bone mineralization. Our data show disadvantages of prolonged mechanical ventilation on bone strength in preterm infants. The inverse correlation between duration of mechanical ventilation and bone density was proved also by DEXA technique [28]. The results of the study of Bowden et al. [29] are even more vivid, because number of days of mechanical ventilation significantly correlates with reduction of bone mineral content measured by DEXA in 8 years old preterm children. Prolonged unfavourable influence of mechanical ventilation on skeletal mineralization should be emphasized.

Steroids play important role in perinatal medicine although they have many side effects including disturbance of bone metabolism and calcium-phosphorus homeostasis. Steroids by decreasing intestinal calcium absorption and increasing urine calcium lose cause reduction of calcium provision for bone matrix mineralization and secondary hyperparthyroidism [30, 31]. Primary negative influence of steroids on skeletal system depends on a suppressive effect on osteoblastogenesis in the bone marrow and promotion the apoptosis of osteoblasts and osteocytes, thus leading to decreased bone formation. Additionally, suppressed activity of chondrocytes with longer state of response contributes in slowing down bone elongation and growth [30, 32]. Experimental study underline that negative influence of dexametason treatment on bone density is not restricted to trabecular bone but also cortical bone is affected [31, 33]. As far as tibial QUS measure sound velocity in cortical layer of the tibia is concerned it could be sensitive technique to reveal any changes in bone during steroids treatment. Our data showing inverse correlation between tibial SOS results with duration of steroids treatment are consistent with this thesis. The negative effect of steroids is more pronounced if we take into account a very short time of treatment.

In conclusion, unfavourable quantitative and qualitative changes in skeletal system of preterm infants born before 33rd week of gestation are observed and worsen bone strength is still present despite correction for gestational age. Prolonged parenteral nutrition, mechanical ventilation and steroids treatment may play a role in this unfavourable process. Tibial QUS could be a reliable and non-invasive diagnostic method for bone growth and mineralization.
strength assessment just after birth, but further studies are needed to assess the timepoint of bone strength recovery in preterm infants.

References


Justyna Czech-Kowalska
Department of Neonatology and Neonatal Intensive Care
Children’s Memorial Health Institute
Aleja Dzieci Polskich 20, 04-736 Warsaw, Poland
e-mail: j.kowalska@czd.pl