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Evaluation of bone mineralization in former preterm born children: Phalangeal quantitative ultrasound cannot replace dual-energy X-ray absorptiometry

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ABSTRACT

Background: Preterm infants are at risk of impaired bone health in later life. Dual-energy X-ray absorptiometry-scan (DXA) is the gold standard to determine bone mineralization. Phalangeal quantitative ultrasound (pQUS) is an alternative technique that is inexpensive, easy to use and radiation-free. The aim of this study was to investigate whether both techniques reveal equivalent results.

Materials and methods: Sixty former preterm infants (31 boys; 29 girls) received a DXA and pQUS at age 9 to 10 years. DXA measured bone mineral content (BMC) and bone mineral density (BMD) for total body and lumbar spine (L1-4), while pQUS measured the amplitude dependent speed of sound (AD-SoS) and bone transit time (BTT) at metacarpals II-IV providing continuous values and *Z*-scores based on age and sex. Four statistical methods evaluated the association between both techniques: Pearson's correlation coefficients, partial correlation coefficients adjusted for gestational age, height and BMI, Bland-Altman analysis and cross tabulation.

Results: Both techniques showed a statistically significant weak correlation for continuous values as well as *Z*-scores (0.291–0.462, $p < 0.05$). Boys had significant and relatively high correlations (0.468–0.585, $p < 0.05$). In comparison, the correlations for girls were not significant. Correlation coefficients further decreased while calculating the partial correlations. The Bland-Altman plots showed poor agreement. Sensitivity ranged from 33% to 92% and specificity from 16% to 68%. Positive and negative predictive values ranged from 4% to 38% and 82% to 97%, respectively.

Conclusions: We found statistically significant weak correlations and poor agreement between DXA and pQUS measurements. DXA is not equivalent to pQUS and therefore not replaceable by this technique in former preterm born children at the age of 9 to 10 years.

1. Introduction

Bone development is one of the key processes during fetal, neonatal and infant development (Schoenau et al., 2004). Mineralization of bone mainly starts during the third trimester of pregnancy based on active placental transfer of calcium and phosphorus to the fetus. Up to 80% of the body calcium of a term infant is accrued during the last trimester (Kovacs, 2014). Preterm infants miss out the active fetal bone development and therefore are at risk of reduced bone mineralization and development of osteopenia (Harrison et al., 2008). Inadequate bone mineralization is seen as a risk factor for the development of osteoporosis in later life, which is an important cause of morbidity and mortality in elderly people and a considerable factor of healthcare expenditure (Kannus et al., 1999; Javaid and Cooper, 2002; Leppälä et al.,

Abbreviations: AD-SoS, amplitude dependent speed of sound; *BMC*, bone mineral content; *BMD*, bone mineral density; *BTT*, bone transit time; *DXA*, dual-energy X-ray absorptiometry-scan; *pQUS*, phalangeal quantitative ultrasound; *QUS*, quantitative ultrasound; *SOS*, speed of sound; *ISCD*, International Society of Clinical Densitometry

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1999). The peak bone mass is attained before skeletal maturity (Bonjour et al., 1991). Any factor that influences the acquisition of peak bone mass may represent a mechanism to affect later osteoporosis risk. The evaluation of bone development in preterm born children is relevant for the determination of the individual health risk as well as the evaluation of medical treatment that aimed at improvement in bone development.

Currently, there are two techniques available to determine bone mineralization, either dual-energy X-ray absorptiometry-scan (DXA) or quantitative ultrasound (QUS). DXA is the most commonly used technique for assessing bone mineralization in children and adolescents (Wren and Gilsanz, 2006). Although DXA is a non-invasive and standardized method, it is not available for all medical centers and it uses a low amount of radiation. In recent years, QUS has been proposed as an alternative method to replace DXA for the evaluation of bone status, especially since it is relatively inexpensive, fast, easy to use, portable and radiation-free (Baroncelli, 2008; Gianni et al., 2008; Tansug et al., 2011; Tuna et al., 2008).

Studies investigating the association between the measurements of DXA and QUS revealed inconsistent results. While a number of studies showed a significant positive correlation between DXA and QUS (Van Rijn et al., 2000; Di Mase et al., 2012; Falcini et al., 2000; Gonçalves et al., 2014; Hartman et al., 2004a; Pluskiewicz et al., 2002; Sani et al., 2011; Sundberg et al., 1998; Xu et al., 2014; Bąk-Drabik et al., 2016; Catalano et al., 2017; Olszynski et al., 2016; Zuckerman-Levin et al., 2007; Mora et al., 2009; Weeks et al., 2016; Halaba et al., 2005; Catalano et al., 2013), others found a discrepancy between the measurements of the two methods (Gianni et al., 2008; Halaba et al., 2005; Chong et al., 2015; Christoforidis et al., 2010; Christoforidis et al., 2011; Hartman et al., 2004b; Williams et al., 2012; Alwis et al., 2010). This could be a result of the different QUS measurement sites or different patient categories investigated. Only a limited number of studies used the phalangeal QUS (Di Mase et al., 2012; Gonçalves et al., 2014; Pluskiewicz et al., 2002; Bąk-Drabik et al., 2016; Catalano et al., 2017; Olszynski et al., 2016; Halaba et al., 2005; Catalano et al., 2013) and only one study looked at the specific group of former preterm born children (Gianni et al., 2008).

The aim of this study was to investigate whether the measurements of dual-energy X-ray absorptiometry scan (DXA) and phalangeal quantitative ultrasound (pQUS) performed in preterm born children aging from 9 to 10 years reveal comparable results. We hypothesized that both techniques were equivalent in diagnosing the state of bone mineralization. Equivalent results would mean that the pQUS could replace the DXA for evaluation bone mineralization as a diagnostic tool.

2. Materials and methods

2.1. Study design

This study was a cross-sectional study using the data collection of the study “Long-term follow up of growth and bone mineralization of former preterm infants” (FoBoMin). This study was approved by the Ethics committee (CMO nr 2013/594) of the Radboud University Medical Center. Informed consent was obtained from all parents after approval by the local ethics committee.

2.2. Study population and procedure

The study included 60 former preterm infants at the age of 9 to 10 years. All subjects participated in the FoBoMin-study. This long-term follow-up study evaluated two cohorts of very preterm infants with a birth weight below 1500 g and gestational age < 34 weeks. The cohorts differed by nutritional intake during the first two weeks of life. The second cohort received higher intake of protein, energy as well as calcium and phosphate. This was associated with improved weight gain during the early postnatal period (Christmann et al., 2013). The aim of the FoBoMin-study was to compare long-term growth and bone mineralization in relation to early nutritional intake in preterm born children at age 9 to 10 years. All participants of the studies were evaluated by DXA and pQUS. The measurements were performed on the same day for the individual participant. Four statistical methods were used to compare both methods.

2.3. Measurement instruments and variables

Bone mineralization of the total body and lumbar spine (L1-L4) was determined using the QDR Discovery A S/N 85606 (Hologic, Inc., USA). According to the International Society for Clinical Densitometry (ISCD), the lumbar spine (L1-L4) and whole body scan are the preferred skeletal sites for measurement in children (Lewiecki et al., 2008). The measurements of the DXA were analyzed using the APEX-system software version 13.3. The DXA uses a low dose of radiation depending on measurement site. The effective dose, reflecting the real radiation risk for children of 10 years old, for the whole body is 4.8 μSv and for the lumbar spine 7.1 μSv (Blake et al., 2006). According to the ‘Rijksinstituut voor Volksgezondheid en Milieu’ (RIVM) the yearly averaged ambient dose equivalent rate for the NMR station in the area of Nijmegen is 74 nSv/h (Knetsch, 2013), resulting in a daily exposure in Nijmegen of 1.78 μSv. Therefore, the radiation dose of DXA can be regarded as very low and is negligible. Results of the DXA were expressed as Bone Mineral Content (BMC; g), Bone Mineral Density (BMD; g/cm^2), representing the ratio between BMC and bone area (cm^2), and *Z*-scores, representing the number of standard deviations above or below the mean for the patients' sex and age. The *Z*-scores were calculated by the DXA software on the basis of reference values for sex and age obtained from a large U.S. population provided by the manufacturer. The *Z*-scores of the whole body were calculated using the reference data of the National Health and Nutrition Examination Survey (NHANES, 2008) (Kelly et al., 2009), while lumbar spine *Z*-scores were based on the reference data of the Bone Mineral Density in Childhood Study (BMDCS) (Zemel et al., 2011). A Z-score less than or equal to −2.0 SD is considered to indicate ‘low bone mineral status’ (Lewiecki et al., 2008).

The quantitative ultrasound (pQUS) was performed on the second to the fifth metacarpals of the phalangeal bones using a DBM Sonic Bone Profiler (IGEA, Carpi, Italy). The mean value of the measurements per person was calculated. The transmitter of the pQUS generated a sound frequency of 1.25 MHz. This technique measured the amplitude dependent speed of sound (AD-SoS) and bone transit time (BTT), which were both expressed in continuous values and in *Z*-scores. The AD-SoS (m/s) was the ultrasound velocity inside the finger and was derived from the measurement of the time interval between emission and reception of the ultrasound signal, considering the first signal with a minimum amplitude of 2 mV at the receiver probe. The BTT (μsec) reflected the bone characteristics without the interference of the soft tissue by calculating the difference between transmission time in soft tissue and bone and transmission time in soft tissue (Di Mase et al., 2012). The *Z*-scores were determined on the basis of the reference values related to sex and age (AD-SoS Z score (age); BTT- Z-score (age)) or sex and height (AD-SoS Z score (height); BTT Z-score (height)). The Z-scores were obtained from a large Italian population provided by the manufacturer (Baroncelli et al., 2006).

Additionally, age, sex, gestational age at birth, weight, height, BMI and pubertal development were recorded. Weight (kg) was measured using an electronic digital scale (SECA MOD701) to the nearest 0.1 kg. Height (cm) was determined using a vertical stadiometer (SECA MOD240) to the nearest 0.1 cm. Body mass index (BMI; kg/m^2) was calculated by dividing weight (kg) by the square of height (m^2). Pubertal development was self-assessed from pictures showing the different Tanner stages (Tye, 2016). The children were asked to indicate which picture most resembled their current appearance.