Journal of Clinical Densitometry: Assessment & Management of Musculoskeletal Health, vol. 17, no. 2, 243–257, 2014

1094-6950/17:243–257/$36.00
http://dx.doi.org/10.1016/j.jocd.2014.01.002

2013 Pediatric Position Development Conference

Bone Densitometry in Infants and Young Children: The 2013 ISCD Pediatric Official Positions

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Abstract

Infants and children <5 yr were not included in the 2007 International Society for Clinical Densitometry Official Positions regarding Skeletal Health Assessment of Children and Adolescents. To advance clinical care of very young children, the International Society for Clinical Densitometry 2013 Position Development Conference reviewed the literature addressing appropriate methods and skeletal sites for clinical dual-energy X-ray absorptiometry (DXA) measurements in infants and young children and how results should be reported. DXA whole-body bone mineral content and bone mineral density for children ≥3 yr and DXA lumbar spine measurements for infants and young children 0–5 yr were identified as feasible and reproducible. There was insufficient information regarding methodology, reproducibility, and reference data to recommended forearm and femur measurements at this time. Appropriate methods to account for growth delay when interpreting DXA results for children <5 yr are currently unknown. Reference data for children 0–5 yr at multiple skeletal sites are insufficient and are needed to enable interpretation of DXA measurements. Given the current scarcity of evidence in many areas, it is likely that these positions will change over time as new data become available.

Key Words: Bone mineral content; bone mineral density; clinical assessment; dual-energy X-ray absorptiometry; guideline.

Introduction

Currently, clinical assessment of bone health and bone fragility of infants and young children relies predominantly on standard radiography. Evaluation of radiographs involves visual assessment of bone mineral density (BMD) and of characteristics specific to disease conditions (e.g., rickets, sclerosis, fracture). Visual assessment of BMD based on opacity of radiographs is insensitive, subjective, requires appropriate exposures, and large changes in BMD (>25%) must occur before low BMD is visually detected. BMD based on radiographs in conjunction with the use of a metallic reference is primarily restricted to the measurement of extremities, providing a semi-quantitative measure of bone density with limited clinical application. The field of densitometry has evolved to overcome these limitations and provide quantitative methods that have good precision and can reliably assess adequacy and changes in BMD.

There is great interest in using quantitative densitometry for clinical assessment of bone fragility of infants and young children and for evaluating and monitoring changes in bone mineral content (BMC), BMD, and bone structure. Research

Received 01/08/14; Accepted 01/08/14.
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on bone mineral accretion and BMD of the very young has lagged behind that of older children, despite that preterm infants were one of the first populations studied with early densitometric methods beginning with single photon absorptiometry (1). Owing to minimal research in the area, guidelines for densitometry of infants and children <5 yr were not included in the previous 2007 ISCD Positions regarding Skeletal Health Assessment in Children and Adolescents (2). Like older children, adolescents and adults, infants and young children experience myriad diverse chronic medical conditions and/or are treated with pharmaceutical agents that affect bone accretion, increase bone fragility, and may prevent them from reaching their genetic potential for peak bone mass. Improved medical and surgical treatments of complex diseases have extended the lives of many infants and children who previously may not have survived (e.g., extreme prematurity, cancer, congenital heart disease), and their bone health has become a relevant clinical concern. There is also interest in using quantitative densitometry to monitor children receiving bone-altering therapies (such as bisphosphonates), as well as for use in differentiating children who have sustained non-accidental trauma from those with metabolic bone disease.

Low BMC or BMD is associated with increased fracture risk in children (3–8) and adults (9,10). It has been hypothesized that poor bone accrual during growth in humans affects lifelong bone strength (11–13). There is a paucity of data on the relationship between BMC or BMD and fracture risk in the very young. In growing animals, BMC, BMD, and bone area are directly related to bone strength, with BMC the best overall predictor (14). Based on fundamental physical principles, fracture risk will be inversely related to BMC, BMD, and bone strength at any age. The challenge in pediatric bone fragility assessment is how to characterize bone strength of infants and children relative to the expected forces that impact the young growing skeleton in everyday life.

Fractures in healthy infants are uncommon, in part due to their non-ambulatory state and low risk of accidental trauma. With the onset of walking and climbing in the second and third years of life, children place themselves at greater risk of falling and sustaining trauma that may result in fracture. Worldwide, fracture rates increase steadily in childhood from ≈2 yr until their peak in adolescence (15–18). Infants with significant medical conditions (e.g., prematurity, osteogenesis imperfecta, Ehlers-Danlos syndrome) experience higher fracture incidence than their healthy peers (19,20). Whether bone accretion in infancy and early childhood are related to bone health outcomes at older ages is unknown.

Special challenges are encountered when performing densitometry to estimate bone strength in the very young. The most notable technical issues are measurement of bones of small size and low density and preventing movement-related artifacts. Three methods for quantifying BMC and BMD, originally developed for adults, have been used in the very young: quantitative ultrasound (QUS), peripheral quantitative computed tomography (pQCT), and dual-energy X-ray absorptiometry (DXA). Adaptation of these methods has been required to accommodate measurement of small bones with lower density with varying success, and their utility in clinical assessment of bone fragility has not been established.

QUS measurements in infants and very young children have most frequently consisted of axial transmission speed of sound measurements at the mid-tibia, distal radius, or phalanges. This technique is transportable to the bedside for use in infants and young children in whom DXA measurements are not feasible, particularly premature infants in the neonatal intensive care unit. However, results are markedly affected by probe size (21,22) and subcutaneous fat thickness (22), and data suggesting how results from such studies may be clinically interpreted are scarce (23). These limitations dissuaded the task force from considering QUS as a tool for clinical bone health assessment in the very young at this time.

Utilization of pQCT in infants and young children has been very limited, although some studies have been published involving infants and children aged 3–5 yr (24–27). pQCT yields volumetric measures of bone density (vBMD, mg/mm^3) for specific bone compartments (total, trabecular, and cortical bone), as well as geometric measures and biomechanical strength indices. Also, pQCT measurements may inform why DXA measures are affected among children with specific diseases or conditions (28,29). For example, areal BMD (aBMD) may be low due to a thin cortical shell leading to decreased BMC rather than an actual reduction in vBMD. However, there are no standard scan sites, acquisition parameters (voxels size and scan speed), and analysis algorithms. These disadvantages have limited its clinical utility. Additionally, for the very young, positioning an arm or leg in the measurement gantry becomes increasingly challenging with smaller body size. There is little information regarding suitable scan analysis thresholds and algorithms to identify bone edges. Smaller bones have thinner cortices; cortical vBMD cannot be accurately measured at cortical thicknesses <2 mm with voxel size of 0.4 mm (30). Mean cortical thickness at the distal 20% tibia site in 3- to 4-yr-old children was shown to be 1.2 mm thereby excluding the measurement of cortical vBMD. However, total cross-sectional area, cortical area, and cortical thickness could be accurately measured in these children (30). Given the sparse data on use of pQCT in the very young, more information was deemed necessary before pQCT could be evaluated as a tool for clinical bone assessment of infants and young children.

DXA has been the most commonly used method for densitometry in infants and young children, and measurements have been obtained in the context of research studies and clinical situations for more than 20 yr. The accumulated experience and research related to use of DXA provided a starting point for considering DXA as a clinical tool for this age group. To assess the potential clinical utility of DXA in the assessment of bone health in the very young, the task force addressed the following general areas:

- What are appropriate methods and skeletal sites for clinical DXA measurements in infants and young children?
- How should densitometry results be reported and what adjustments should be made to account for skeletal size and growth?

Methodology

The methods used to develop, and grading system applied to the ISCD Official Positions, are presented in the Executive Summary that accompanies this task force document. In brief, all positions were graded on quality of evidence (Good, Fair, Poor: where Good is evidence that includes results from well-designed, well-conducted studies in representative populations; Fair is evidence sufficient to determine effects on outcomes, but strength of the evidence is limited by the number, quality, or consistency of the individual studies; and Poor is evidence that is insufficient to assess the effects on outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or information), strength of recommendation (A, B, C: where A is strong recommendation supported by the evidence; B is a recommendation supported by the evidence; and C is a recommendation supported primarily by expert opinion), and applicability (W = worldwide or L = variable according to local requirements).

What Are Appropriate Methods and Skeletal Sites for Clinical DXA Measurements in Infants and Young Children?

ISCD Official Position

- DXA is an appropriate method for clinical densitometry in infants and young children.
  Grade: Fair-B-W.
- DXA whole body measurements are feasible and can provide reproducible measures of BMC and aBMD for children $\geq$3 yr.
  Grade: Fair-B-W.
- DXA whole body BMC measurements for children $<$3 yr are of limited clinical utility due to feasibility and lack of normative data. aBMD should not be used routinely due to difficulty in appropriate positioning.
  Grade: Fair-C-W.
- DXA lumbar spine measurements are feasible and can provide reproducible measures of BMC and aBMD for infants and young children 0−5 yr.
  Grade: Fair-B-W.
- Forearm and femur measurements are technically feasible in infants and young children, but there is insufficient information regarding methodology, reproducibility, and reference data for these measurement sites to be clinically useful at this time.
  Grade: Fair-C-W.

Rationale

The clinical utility of bone densitometry should ideally be based on its ability to predict fractures during the time period of interest. In the absence of such data, DXA techniques were evaluated for clinical use in infants and young children based on operational and technical criteria, namely, that they should be safe, feasible, reliable, well standardized in the population of interest, and free from undue sources of error. DXA is the preferred method for assessment of bone health in older children and adolescence as outlined in the 2007 ISCD Position Statements owing to its widespread availability, low cost, ease of use, good precision, and safety *(31)*. These advantages hold true for use in infants and young children as well. Also, the ability to perform comparable measurements using the same technique and device across infancy and childhood would be advantageous as it would allow continuity of follow-up and facilitate interpretation of findings over time. However, seamless utilization of DXA measures from infancy through childhood and adulthood remains to be demonstrated. The application of DXA techniques for the very young, as well as limitations of use, are reviewed in support of the position statements above.

DXA scan acquisition and analysis applications for the very young were developed for pencil beam technology in the early 1990's. These applications have been revised for devices using current-generation fan-beam technology. Older data generated from pencil beam densitometers cannot be compared directly with scan results from fan-beam densitometers without adjustment *(32)*. Unlike pencil beam DXA devices, validation of current generation fan-beam devices for small subjects remains limited. The validity of Hologic's fan-beam device for measuring BMC in small animals was demonstrated by comparison of DXA measurements obtained on piglets (0.6−21.1 kg) to chemical carcass analysis *(33,34)*. No similar validation of the GE/Lunar current generation fan-beam devices has been carried out for small subjects.

The main technical challenges encountered using DXA to measure BMC and aBMD in the very young are software that can detect bones of very low density and the need to remain motionless and correctly positioned for the scan duration. Movement in the scanned region results in unpredictable motion-related artifacts that can greatly affect results *(35)*. Current-generation fan-beam DXA machines have enhanced resolution that improves accuracy for measuring small, less dense bones and require much shorter scan times than earlier models, although motion of the scanned region still needs to be avoided. BMC and aBMD measurements in the very young have been obtained at several different skeletal sites including standardized scans of the whole body, lumbar spine, femur and radius, as well as customized femur scans.

Whole-Body Scans

The overall rapid rate of growth and bone mineral accretion in early childhood means the whole-body scan is likely to detect a change in BMC over a short period. However, the major limitation of the whole-body scan in the very young

is the possibility of significant motion artifact that renders the scan un-interpretable. It is possible to obtain satisfactory scans in the majority of infants if there is sufficient time to calm them before DXA scanning or if multiple attempts are made. This may not be feasible in busy DXA facilities or by inexperienced DXA technicians.

There are 2 scan types for acquiring whole-body DXA measurements: the infant whole-body scan and the standard (adult) whole-body scan. On Hologic devices, the infant whole-body scan was developed as a research application for children aged 0 to ≈2 yr. It has been used on premature infants as young as 30 wk gestational age and has been validated on piglets *(33,34)*. The infant whole-body application was originally developed for the pencil beam devices, which have now been replaced by fan-beam technology. The fan-beam applications and software have been modified to better reflect carcass analysis data *(33,34)*. The infant whole-body scan on current generation Hologic DXA devices takes up to 3 min, and bone edge detection algorithms were optimized to detect bone of very low density. Its acquisition and analysis algorithms differ from those in the adult whole-body scan. BMC and aBMD values generated with the infant software do not converge with those from pediatric and adult software *(36)*. This precludes direct comparison of whole-body measurements acquired under the infant and adult whole-body scan types. The regions of interest (ROI) in the 2 whole-body scan types also differ. ROI in infant whole-body scans are user defined general ROIs, whereas ROI in adult whole-body scans are standardized anatomically defined regions.

Infant whole-body scans can also be performed with GE/Lunar Prodigy devices *(37,38)*, with scan times for newborn infants taking up to 6 min *(38)*. The age range for which this software was developed is not clear. Unlike the Hologic infant whole-body scan, the GE/Lunar Prodigy analysis includes standardized anatomically defined regions similar to that for older children. Appropriate positioning to conform to the anatomical ROIs is important for optimal scan analysis. Scans from the GE/Lunar device can also be analyzed with manually drawn ROIs similar to that of the Hologic device. It is unclear whether infant whole-body scan results converge with regular whole-body scan results on the GE/Lunar Prodigy. Presently, there are no studies that have performed head-to-head comparisons of fan-beam devices from different manufacturers and software versions for their impact on infant whole-body bone results. However, whole-body BMC values of newborn infants measured with the GE/Lunar Prodigy have been reported to be 21% higher than those measured by the Hologic Discovery *(38,39)*, whereas whole-body BMC values at 6 mo measured with the GE/Lunar Prodigy were 34% lower than those measured by the Hologic Discovery *(37,40)*. The discrepancies probably reflect the difference between instruments produced by different manufacturers, different scan analysis software versions used, as well as differences in sample characteristics *(37–42)*. These inconsistencies and differences in whole-body BMC values underscore the importance using the same DXA hardware for scan acquisition of repeated measures with software-specific analysis and reference values. Easily accessible information from the manufacturers on the modifications made to various versions of software would facilitate meaningful interpretation of DXA data.

Although whole-body scans and bone detection algorithms have been developed for infants, acquisition can be challenging. Whole-body scans are feasible for newborns and young infants that can be swaddled and remain motionless during scanning. Young infants can be scanned while sleeping. As infants age, becomes stronger and nap less frequently, it becomes more difficult to obtain a movement-free whole-body scan, as swaddling become less effective in preventing motion for the required 3 to 6 min. Waiting until the infant is asleep may not be an option in a busy densitometry facility, and even if the infant is asleep, they may awaken during the scan. Pediatric sedation is not an option in many clinical densitometry settings and with current fan-beam DXA technology it is not feasible to hold a child still or use restraints without interfering with the whole-body scan path. Some investigators have reported using restraints on 6- and 12-mo-old infants scanned with fan-beam densitometers *(37)*. If swaddling or restraints are used, materials must be completely radiolucent or scan results will be affected. Materials of very low density will be considered ''soft tissue'' and affect BMC and aBMD results if they are not uniform throughout the scan region. The effects of swaddling or restraint materials and accessories such as a pacifier on DXA measurements must be assessed since each material has different properties.

For the Hologic fan-beam densitometer, the in vivo precision expressed as the coefficient of variation of BMC and aBMD measured with the infant whole-body software were 1.9% and 1.7%, respectively, from duplicate scans of 40 piglets between 0.6 and 21.1 kg *(36)*. The in vivo precision for infants with repositioning is unknown, but likely to be greater. The in vivo precision of newborn whole-body aBMD measurements obtained on the GE/Lunar Prodigy without repositioning was reported to be 8.2% *(38)*. It is likely that reproducibility would have been worse with repositioning between duplicate scans, a necessity for estimating the exact precision of a given scan. Whole-body scan positioning is difficult to reproduce particularly when bundling or swaddling is used or if the infant is asleep. Positioning affects projected bone areas and therefore aBMD. For this reason, whole-body BMC results are likely to be more reproducible and appropriate than aBMD in infants.

In the event of movement, DXA scans are often repeated with the hope of obtaining a movement-free image. Even with multiple attempts, this is not always successful. Gallo et al reported that when making up to 2 attempts, they obtained movement-free whole-body scans on 99% of infants at 1 mo, compared with 92% at 6 mo and 81% at 12 mo *(40)*. Few studies report success rates obtaining movement-free scans or the number of attempts to obtain one. General guidance is to make up to 3 attempts to obtain a movement-free scan, as further attempts are unlikely to be successful. If movement is significant, the scan is not suitable for comparison with reference or follow-up values. At the 2013 ISCD meeting, Powers et al *(43)* presented 2 approaches

for ''fixing'' DXA scans affected by movement. The first was to piece together movement-free regions of 2 scans to obtain a whole image. The second was to use a reflection or mirroring technique that excludes the region of the scan with movement and substitutes the results from the side of the body without movement. This approach is only feasible when movement is confined to the limbs. They found that the mirroring approach was superior to combining regions from 2 different scans. However, this relies on standardized positioning and may not be feasible for very young infants who are swaddled in various positions. Given the uncertainties in software performance, issues of positioning and movement, and lack of normative data, whole-body scans DXA measurements for children <3 yr are of limited clinical utility at this time. However, with expert interpretation, whole-body assessments may be useful in limited situations where serial measurements are anticipated for monitoring of disease states or therapy effects that may affect BMC.

Standard (adult) whole-body scans with appropriate positioning are feasible for most children by 3 yr who are able to remain motionless during the scan. On Hologic devices, scan duration is 2−3 min, and scan analysis algorithms have been optimized to detect bone for children as young as $\approx$2.5 yr (personnel communications, Tom Kelly, Hologic Inc.). The scan analysis software sets the bone edge detection thresholds depending on the child's weight. GE/Lunar whole-body scans adjust beam characteristics based on height and weight entered into the densitometer. Independent verification of these algorithms is lacking. To our knowledge, reproducibility of whole-body BMC and aBMD measurements using current generation fan-beam technology and analysis software for children 3−5 yr has not been reported.

In 2007, the ISCD recommended that results from the head region be excluded from whole-body scan results to yield total body less head measures due to the large contribution of the head to whole-body BMC at young ages *(31,44)*. At birth, the head contains almost 50% of the whole-body BMC, whereas at age 5, it contains $\approx$34% of whole-body BMC. If disease conditions do not affect the skull and only affect the sub-cranial skeleton, then inclusion of the skull in whole-body results will reduce the sensitivity of the assessment. The opposite is true if disease conditions preferentially affect the head. Studies in older children show that BMC or aBMD of the head is affected by activity level, with an apparent shifting of bone mass from one part of the skeleton to another. For example, the skull has a significant increase in BMC with increasing length of bed rest, whereas the remainder of the skeleton has a decrease *(45,46)*. The opposite appears to occur with young gymnasts who have a lower skull aBMD, whereas the remainder of the skeleton is greater than non-gymnasts *(47)*. The decision to include or exclude the head from the whole-body results for the very young may be affected by head positioning and movement. Standard positioning described by device manufacturers for whole-body scans is that the head is face-up and perpendicular to the DXA bed surface. This head position can be difficult to achieve in infants (especially if they are asleep) as their head may fall to the side, which affects the projected bone area and, therefore, aBMD results, or the head may tilt forward, which makes ROI difficult to set across the shoulders, neck, and head regions. Lastly, the very young often move their head in response to noises resulting in movement-related artifacts. Exclusion of the head region from whole-body results circumvents the aforementioned issues.

Regional DXA Scans

Regional DXA measurements can be generated from the whole-body or region-specific scans. The results obtained by the 2 approaches differ and cannot be used interchangeably *(48)*. Standardized regional scans, such as the lumbar spine or forearm, are acquired with better resolution and, therefore, are preferred over regional measurements from whole-body scans. Furthermore, regional scans are more likely to be movement-free because of the shorter scan time ($<$30 sec) and the possibility for manually securing the child so that the specific region can be scanned without interference with the scan image.

The lumbar spine is the most commonly used regional scan site in infants and young children. It has been successfully obtained in small subjects weighing as little as 1.1 kg and premature infants as young as 27 wk gestation *(49)*. The reported percentage coefficient of variation of pencil beam devices using infant spine software in 49 neonates was $<$1.4% for BMC and $<$0.4% for aBMD *(49)*. Movement during the scan worsens the precision and increases the error 5 to 24-fold *(49)*. Using the current infant spine software on a Hologic device, precision estimates from 76 children between 1 and 36 mo for BMC and aBMD were 2.2% and 1.8%, respectively, and improved as children got older *(50)*.

On Hologic devices, scan acquisition is performed using the standard posterior-anterior spine scan. Recent Hologic software versions (Apex 4) automatically determine the specific algorithm and bone edge detection thresholds needed to analyze spine scans for infants and young children including newborns. Bone edge detection thresholds are set as a function of age for children $\leq$36 mo and by bone map evaluation for children $>$36 mo. The software was developed to optimize bone edge detection algorithms for a smooth transition from infancy through adulthood (personal communications, Tom Kelly, Hologic, Inc.). On Hologic devices, there are multiple scan modes (array, fast array, turbo) for acquisition of spine scans, but data comparing the various modes for infants and young children are lacking. It is recommended that one scan mode be used in repeated assessments of the very young and the mode should be the same as that used to acquire the reference data used for comparison. The GE/Lunar densitometers also have the capability to perform lumbar spine measurements in the very young, but technical support for such applications is currently unavailable.

There are potential pitfalls with the use of lumbar spine measurements. Unlike adults where the spine has a high bone turnover and is commonly involved in pathologic states such as fractures, the major regional growth in infants and children occurs in the extremities and fractures in the spine

are extremely rare. At birth, BMC of the lumbar spine L1−L4 region is about 2 g and increases to about 10 g by 36 mo (50). Proportionately, the increase in spine BMC is even greater from 27 to 42 wk gestation (49). However, lumbar spine BMC is still a small proportion (<3%) of whole-body BMC in infants 1 to 12 mo (40). Even a 20% change in spine BMC corresponds to a very small absolute quantity of bone mineral and its clinical significance remains to be defined.

The forearm was the site assessed in early bone density measurements of infants and children by single beam photon absorptiometry, but there are few data on forearm BMC and aBMD measured by current generation DXAs in children aged <5 yr. Obtaining forearm DXA scans on infants and young children is feasible. Forearm scans have been successfully obtained on infants 12 mo using a Hologic device (Babette Zemel, personal communications). Subjects were scanned while lying supine and the arm restrained by the technician. Despite obtaining technically good scans, there were some software-related analysis issues. The software consistently identified bone edges of the radius, but not the ulna, and the lowest forearm length allowed was 12 cm, which was longer than that of some infants. According to the manufacturer, this latter issue has been corrected in recent software releases. BMC and aBMD results can be generated for the standard ultra-distal, mid-, and 1/3 radius sites, although the precision of these measurements is not known. Hazell et al (51) obtained forearm scans on 57 children 2−5 yr of age and did not report difficulties with analysis of scans to yield standard ultra-distal, mid-, and 1/3 radius BMC and aBMD results. It was sometimes necessary, however, for small children to lie on the DXA table to achieve correct positioning (forearm centered and aligned with the long axis of the table). An important deficit in the literature is information regarding the ability of current generation DXA software to acquire and analyze forearm scans of the very young in a reproducible and precise manner. Furthermore, there are no reference data for the forearm from current generation DXAs for children <5 yr.

Proximal femur scans have been performed on children as young as 2−3 yr (52−55); however, the analysis of these scans is difficult. Standardized scan analysis protocols do not work well due to the shape of the trochanter, short femoral neck, and detection of low-density bone (31,56). These limitations prompted the 2007 ISCD recommendation that the proximal femur scan not be obtained for clinical bone health evaluations in growing children. Since that time, there have been no published advancements in software or analytical approaches, thus this recommendation is maintained.

DXA scans have been obtained of the entire femur using the proximal femur scan in infants up to 12 mo (39,40). On Hologic devices, the length of the scan field is limited to 23.9 cm, thereby restricting the age/or size of the infant being scanned since the entire femur must fit within the scan field. Analysis of the entire femur scan requires manually drawing a bone map so that BMC can be determined. Positioning issues (i.e., rotation of the limb and therefore projected bone area) limit data interpretation to BMC. The reproducibility of an entire femur scan has not been reported. Owing to the non-standardized nature of this measurement, it is not recommended for clinical use at this time.

Discussion

The evolution in DXA technology permits reliable measurement of BMC and aBMD of the lumbar spine in infants and children aged 0 to 5 yr and of the total body in children ≥3 yr. These measures are feasible, reproducible, and appropriate for clinical use. Movement during scanning is a problem, making it difficult to obtain a good whole-body scan for children <3 yr. Although infants may be swaddled to prevent movement, swaddling or restraint materials may affect scan results, as will non-standard positioning (35,41). Regional scans such as the lumbar spine scan have the advantage of allowing the infant or young child to be restrained during scanning without interference with the scan path. Software algorithms have been developed for analysis of lumbar spine scans from birth onwards. Independent verification of the performance of these software algorithms is needed and would make an important contribution to the field. Development of the forearm scan in the very young has potential advantages. The forearm can be easily restrained facilitating attainment of a movement-free scan. Also, the forearm shaft contains cortical bone, which may be advantageous to measure in some clinical situations.

There are no data to determine which skeletal sites are optimal to determine fracture risk or to identify disease or treatment-related effects on bone health in the very young. Studies in other populations, including older children, have demonstrated differences in effects of mechanical loading, diseases, and therapies by skeletal site (53,57,58). Since there are differences in the amount and type of bone in different skeletal regions, there may be greater utility in assessments at some skeletal sites than at others for very young children with specific medical conditions. However, there are insufficient data to recommend assessing one site vs others for particular disease conditions or monitoring at the present time.

Developments in DXA hardware and software over the last 20 yr have affected the absolute values of BMC and aBMD results generated. BMC and aBMD values differ between DXA manufacturers and from different software versions within a given manufacturer. The notable inconsistencies among BMC and aBMD values underscore the importance of obtaining follow-up measurements and using reference data generated with the same DXA platform and software version. Advancement in the field will be greatly enhanced by well-designed validation studies and clear descriptions of changes in analysis algorithms and their effects on BMC and aBMD results.

Although scan acquisition is feasible in the very young, special training and ongoing monitoring of technician performance are critical. Comfort and skill working with infants and young children enhance likelihood of success in obtaining good scans. Due to increased chance of movement, scan

quality should be closely monitored. Likewise, difficulties in positioning may result in poor precision. Regular monitoring of the precision error for each technician will help ensure that good scan results are obtained.

How Should Densitometry Results be Expressed and What Corrections Should be Made for to Account for Skeletal Size, Growth, and Development?

ISCD Official Position

- In infants and children below 5 yr, the impact of growth delay on the interpretation of the DXA results should be considered, but it is not quantifiable presently.
  Grade: Fair-C-W.

Rationale

Age, Sex, and Race

The importance of expressing BMC and aBMD as Z-scores (the number of standard deviations above or below the median according to age-, sex-, and race-specific norms) was identified by the Reporting Task Force in the 2007 ISCD Positions *(31)* and reconfirmed in the 2013 Positions *(59)*. Age-specific values of BMC and aBMD obtained with current-generation fan-beam densitometers from diverse studies are presented in Table 1. In healthy normally growing infants, whole-body BMC and spine BMC and aBMD increase dramatically during the first year of life (Table 1) with bigger increases in BMC compared with aBMD because of the corresponding rapid growth in skeletal size. Gallo et al *(40)* observed that spine BMC increased by 102% but aBMD increased by only 10.8% between 1 and 12 mo. The magnitude of changes in these measures slow as the rate of linear growth slows during infancy. Kalkwarf et al *(50)* found that spine BMC and aBMD increased by 64% and 26%, respectively, between ages 12−24 mo and by 39% and 15% between ages 24−36 mo. These rapid changes in BMC and aBMD underscore the need to account for the age-related gains by presenting results as age-specific Z-scores. Because annual increases in BMC and aBMD are large, especially in the first year of life, it is important that there is sufficient granularity in reference data (i.e., by month not year) used in Z-score calculations. Preterm infants represent a special challenge, as comparison of preterm infants with age-related norms for healthy term infants may not be appropriate until catch-up growth has been obtained. Under no circumstance should traditional T-scores (comparison with young adults at peak bone mass) be used in pediatric densitometry assessments.

The sex of an infant or child is also important to consider when evaluating the appropriateness of BMC and aBMD values. Growth curves for weight and length or height are separate for each sex in recognition of the different growth trajectories and body composition of males and females *(60,61)*. Sex differences in BMC and aBMD are pronounced with the onset of puberty making it important to have sex-specific reference data in older children and adolescents *(62−71)*. Sex differences are smaller in younger children. Females have lower BMC, but not aBMD, of the whole-body as newborns *(38)* and as infants 1 to 12 mo *(39,72)*, and lower spine BMC as infants 1 to 36 mo *(39,50)*. There were no sex differences in spine aBMD likely due to the smaller bone area in females than males. In a sample of 428 children (228 girls) aged 4.5 to 6.4 yr, spine and hip aBMD were lower in girls even when accounting for age, height, and weight *(52)*. Similarly, BMC of the whole body and whole body less head were lower in girls with and without adjustment for age, height, and weight; spine BMC was only lower in girls before body-size adjustment. A lower whole-body BMC was observed in females aged 3−5 yr, and this difference remained significant after adjusting for whole-body bone area *(73)*. Given the presence of sex differences in BMC early in life, DXA reference data used in calculation of Z-scores for infants and young children should be sex-specific.

BMC and aBMD vary by race, and differences between blacks vs non-blacks have been documented in children, adolescents, and adults. Although the data on race differences in infancy are equivocal, most studies of whole-body BMC and spine BMC and aBMD of infants and toddlers failed to identify black vs non-black differences *(50,74,75)*. However, Li et al *(76)* found that forearm BMC measured by single photon absorptiometry was higher in black compared with white children 1−6 yr of age. By age 5 yr, black children had greater spine BMC and aBMD and whole-body BMC *(77)*. These differences are known to increase in older children and adults *(63,65,66,69,70,78)*. Gilsanz et al *(79)* suggest that like sex effects, the differences in vertebral vBMD between black and white children become more apparent after Tanner stage 3. Comparisons among other racial groups are less common. In one report, Asian infants had 29% lower lumbar spine BMC compared with white infants, and Native American newborns had intermediate values *(80)*. Since the age when population ancestry differences in DXA bone measures emerge is unknown, and the samples sizes of studies that have addressed this issue may have been too small to detect meaningful differences, more research is needed to determine the ages when it is important to have race-specific reference data. Race-specific reference data are recommended for older children and adolescents. To prevent confusion for DXA technologists, it is prudent to have consistent recommendations for using race-specific reference data from infancy to adulthood.

Bone Size, Growth, and Body Composition

The need to account for growth and body composition when evaluating bone health in children age >5 yr has been well appreciated *(81−83)*. Throughout infancy and childhood, BMC and aBMD are positively associated with weight and height *(50,84−86)*, due in part to age-related increases in body size, bone thickness, and vBMD. For example, among infants and toddlers 1 to 36 mo,

Table 1
Bone Mineral Content and Areal Bone Mineral Density Values in Healthy Children From Birth to 5 yr From Current Generation Fan-Beam Dual-Energy X-ray Absorptiometers

First author, year (reference)	Mode/software	Number of children aged ≤5 yr	Ethnicity	BMC (g) or aBMD (g/cm^2) by age and skeletal site (n) mean ± SD		
Hologic 4500A						
Specker, 2011 *(123)*	Software N/R (Pediatric option analysis)	n = 239 (124 Male, 115 female)	White 233 (118 male) Other 16 (6 male) (USA)	Age 3−5 yr Male Female	WB BMC 592 ± 81 (124) 561 ± 91 (114)	
Koo, 2003 *(124)*	Fan beam/vKH6	n = 98 (Subgroup measured using 4500A device)	White 48 Black 72 Hispanic 8	Age Newborn 3 mo 6 mo	IWB BMC 89.4 ± 13.9 148.6 ± 24.9 214.7 ± 34.6	IWB BMD 0.238 ± 0.021 0.257 ± 0.023 0.296 ± 0.024
Hammami, 2003 *(41)*	Fan beam beam/vKH6	n = 73 (32 Male, 41 female)	White 26 (11 male) Black 42 (17 male) Hispanic 5 (4 male)	Age Newborn	IWB BMC 89.3 ± 14.1 g	IWB aBMD 0.240 ± 0.022 (72)
Goksen, 2006 *(68)*	Software version N/R		Caucasian (Turkish)	Age 2 yr Male Female 3 yr Male Female 4 yr Male Female	L1−L4 aBMD 0.401 ± 0.046 (8) 0.432 ± 0.061 (12) 0.472 ± 0.062 (12) 0.473 ± 0.072 (14) 0.498 ± 0.051 (12) 0.513 ± 0.055 (17)	
				Age 2 yr Male Female 3 yr Male Female 4 yr Male Female	FN aBMD 0.455 ± 0.059 (7) 0.460 ± 0.055 (11) 0.554 ± 0.111 (11) 0.503 ± 0.049 (11) 0.563 ± 0.050 (12) 0.511 ± 0.043 (17)	
Webber, 2007 *(54)*	QDR v8.26 or v12.3	n = 21	(Canadian)	Data presented graphically and with prediction equations for normal ranges by age and sex for spine BMC, aBMD; femur aBMD		
Wosje, 2010 *(125)*	Fast array Version 12.4	n = 295	Black 56 White 239 (USA)	Age 3.8−4.8 yr	WB BMC 379 ± 50 (295)	

Gallo, 2012 *(39)*	Infant whole body. AP lumbar spine array mode. Femur left hip sub-region array mode. Software QDRv11.2	n = 63 (36 Male, 27 female)	White 41 First Nations 10 Asian 7 Black 2 Other 3 (Canada)	Age Term 6 mo 12 mo Age Term 6 mo 12 mo Age Term 6 mo 12 mo	IWB BMC 75.98 ± 14.17 (52) 169.48 ± 29.01 (35) 227.0 ± 29.73 (11) Femur BMC 2.94 ± 0.54 (61) 5.58 ± 1.46 (60) 8.50 ± 1.84 (54) L1−L4 BMC 2.35 ± 0.42 3.59 ± 0.63 5.37 ± 1.02	 L1−L4 aBMD 0.226 ± 0.044 (62) 0.252 ± 0.031 (62) 0.304 ± 0.44 (57)
Kalkwarf, 2013 *(50)*	Fast array Infant spine	n = 307 Across 1−36 mo age range (158 male, 149 female)	White 225 Black 63 Mixed 15 Asian 4 (USA)	Age 1 mo 3 mo 6 mo 9 mo 12 mo 15 mo 18 mo 21 mo 24 mo 27 mo 30 mo 33 mo 36 mo	L1−L4 aBMD 50th (9th, 91st) percentiles 0.204 (0.171, 0.241) 0.224 (0.188, 0.263) 0.254 (0.215, 0.297) 0.283 (0.241, 0.329) 0.312 (0.267, 0.361) 0.338 (0.291, 0.389) 0.361 (0.312, 0.413) 0.379 (0.330, 0.432) 0.395 (0.345, 0.447) 0.409 (0.360, 0.461) 0.423 (0.375, 0.475) 0.438 (0.390, 0.489) 0.453 (0.406, 0.503)	
Gallo, 2013 *(40)*	Apex 13.2:1 infant whole body; Array mode for regional scans.	n = 132 (76 male, 56 female)	(Canada)	Age 1 mo 3 mo 6 mo 9 mo 12 mo Age 1 mo 3 mo 6 mo 9 mo 12 mo Age 1 mo 3 mo 6 mo 9 mo 12 mo	IWB BMC 100.70 ± 16.93 (131) 134.30 ± 20.26 (113) 175.80 ± 27.61 (99) 201.70 ± 28.72 (86) 236.40 ± 31.70 (79) L1−L4 BMC 2.76 ± 0.62 (132) 2.94 ± 0.55 (116) 3.59 ± 0.63 (107) 4.55 ± 0.86 (100) 5.58 ± 0.98 (97) Total femur BMC 3.57 ± 0.71 (131) 4.92 ± 0.90 (116) 6.46 ± 1.33 (108) 8.19 ± 1.90 (100) 10.21 ± 2.64 (96)	IWBLH BMC 52.87 ± 8.89 (131) 69.01 ± 11.46 (112) 88.30 ± 16.55 (98) 100.80 ± 17.18 (86) 121.70 ± 22.33 (79) L1−L4 aBMD 0.267 ± 0.057 (132) 0.243 ± 0.037 (116) 0.264 ± 0.041 (107) 0.296 ± 0.041 (100) 0.333 ± 0.046 (97)

(*Continued*)

Table 1 (Continued)

First author, year (reference)	Mode/software	Number of children aged ≤5 yr	Ethnicity	BMC (g) or aBMD (g/cm^2) by age and skeletal site (n) mean ± SD		
Lunar prodigy						
Godang, 2010 *(38)*	Software version 12.10	n = 207	(Norway)	Age	WB BMC	
				Newborn		
				Male	95.7 ± 12.0 (112)	
				Female	88.9 ± 12.3 (95)	
				Age	IWB BMC	IWB BMD
				6 mo		
				Males	120.9 ± 23.5	0.55 ± 0.03 (145)
				Females	110.5 ± 20.4	0.55 ± 0.03 (107)
Ay, 2011 *(37)*	Not reported	n = 252 (145 male, 107 female)	(Netherlands)	Age	L2–L4 BMC	BMD
				6 mo		
				Males	2.7 ± 0.5	0.31 ± 0.04 (145)
				Females	2.6 ± 0.4	0.33 ± 0.33 (107)

Abbr: aBMD, areal bone mineral density; BMC, bone mineral content; IBW, infant whole body; IWBLH, infant whole body less head; L1–L4, lumbar spine vertebra 1–4; WB, whole body.

weight-for-age scores and length-for-age Z-scores were associated with spine aBMD Z-scores (r = 0.34 and 0.24, $p < 0.001$) *(50)*. Similarly, spine BMC was related to weight, height, BMI, and body surface area (r > 0.6, $p < 0.0001$) in healthy infants between 1 and 12 mo, and whole-body BMC to weight (r = 0.92, $p < 0.001$) and length (r = 0.84, $p < 0.001$) *(87)*. Furthermore, DXA measures of aBMD are inherently influenced by bone size due to the 2-dimensional nature of DXA (g/cm^2). As such, adjustment of BMC and aBMD for bone size is necessary in situations of advanced or delayed skeletal growth. This is an important consideration in clinical assessment as infants and children with chronic medical conditions undergoing bone health evaluations often have delayed growth.

Different methods have been proposed to adjust size-related effects in a clinical bone health assessment of older children and adolescents. One approach is to calculate a vBMD from DXA measures, namely bone mineral apparent density, which divides BMC by the projected bone area to the power of 1.5 *(88)*. This approach has only been used in a few studies of infants *(37,39,54,68)*. In older children, BMC also has been expressed as a function of bone area *(89)* and corrected for bone size by using height-for-age Z-scores *(77,81)*. Others have recommended a sequential assessment of bone mineralization by evaluating (1) height-for-age, (2) bone area-for-height, and (3) BMC-for-bone area *(90)*. These 3 steps correspond to 3 different causes of reduced bone mass: short bones, narrow bones, and light bones *(90)*. These adjustment approaches have not been evaluated in the very young, and their clinical applicability in this young age group, particularly for children with chronic disease or abnormal growth trajectories is not known.

In older children and adolescents, body composition, especially lean mass, has been found useful when interpreting whole-body BMC measures *(82,83,91,92)*. Few studies have examined the relationship between bone and body composition measures in the very young. Sudhagoni et al recently combined data from 3 separate longitudinal studies involving a total of 362 infants between 1 and 12 mo to determine the influence of changes in fat and lean mass on bone accrual during the first year of life *(72)*. Both lean and fat mass were positively associated with whole-body bone accrual, a finding that remained significant when body length was included as a covariate.

The above findings support the need to adjust for body size and relative growth when determining whether BMC and aBMD are reduced in an individual child. However, the most appropriate way to account for delayed or accelerated growth of in the context of a bone health assessment is not clear. In many clinical situations (especially infants), weight measurements are easier to obtain and more reliable than lengths or heights. Weight standardization is also preferable if stature is affected by fractures or deformity. More research is needed to identify optimal means of correcting or adjusting for growth when interpreting BMC and aBMD results in the very young.

Infant Feeding and Gross Motor Development/Bone Loading

Infant feeding (human milk vs formula) and bone loading activities are both likely to influence bone accretion and aBMD. Infant growth curves are based on the human milk-fed infant, the gold standard for defining normal growth *(93)*. Bone accretion rates vary in the first year of life between human milk-fed and formula-fed infants, with a greater bone accretion among formula-fed infants, especially formula with higher mineral content *(24,94)*. The effect of human milk feeding in infancy on BMC and aBMD in childhood and adulthood is variable *(95–97)* because many other factors (e.g., post-weaning diet, physical activity, and genetics) play increasingly important roles over time. Given the variability in duration and exclusivity of human milk feeding during infancy, there is no recommendation regarding standardization of densitometry results according to type of infant feeding.

Large changes in gross motor skills occur between birth and age 5 yr with the onset of crawling, standing, walking, hopping, and running with skill. These developmental changes influence physical activity and patterns of mechanical loading throughout the skeleton. Skeletal development follows functional requirements, and bone-loading activity promotes bone accrual among children and adolescents *(27,98–101)*. This issue may be relevant for infants and toddlers with chronic medical conditions associated with delayed gross motor skill development. Even among healthy children, the age of achievement of gross motor milestones varies. For example, the median age when children walk alone is 12.0 mo but the 5th and 95th percentiles are 9.4 and 15.3 mo *(102)*. Interpretation of BMC and aBMD measures in the context of the achieved stages of gross motor development is analogous to considering the stage of puberty of older children. Past position statements have not included adjustment for lack of or limited ambulation in older children. Given the lack of data regarding BMC and aBMD in relation to motor development, above and beyond that captured by age, there is no recommendation regarding standardization of densitometry results according to motor skills.

Discussion

Interpretation of BMC and aBMD values in infants and young children requires robust age-, sex-, and race-specific reference data. As outlined in the 2007 ISCD Official Positions for older children, an appropriate reference data set must include a sample of the general healthy population that is sufficiently large to characterize the normal variability in bone measures and takes into consideration age, sex, and race/ethnicity *(31)*. Data should be collected with well-described and standardized protocols and be appropriate for the DXA hardware and software and skeletal site. Reference data for several bone sites would be useful since different parts of the skeleton may not be similarly affected by medical conditions, medications, and genetic and environmental factors. There are no reference data included in current generation GE/Lunar devices for infants and children <5 yr. On Hologic devices, reference data are included for children according to age, sex, and Caucasian/African ancestry beginning at age 3 yr for the whole-body aBMD and spine aBMD. The representativeness of these data is unclear.

There are few published DXA reference data that meet all of the aforementioned criteria obtained on current generation fan-beam densitometers. Nonetheless, there are published comparative data on healthy infants and children (Table 1), but data are limited by small sample sizes within a chronological age/sex category. The extent to which these samples are representative of the general population is not known. Most studies reporting normative data have been based on convenience samples and have been composed of predominantly white children. The largest studies providing age-specific reference data of the lumbar spine for infants and toddlers (a recommended site) are those of Gallo et al (n = 79–131, aged 1–12 mo) *(40)* and Kalkwarf et al (n = 308, aged 1–36 mo) *(50)*. Use of published data even for comparative purposes should be done with care.

The importance of using reference data valid for the hardware and software being used also was emphasized in the 2007 ISCD Official Positions for children aged 5–20 yr *(31)* and is likewise true for the very young. There are significant differences among published values for BMC and aBMD in healthy pediatric samples, in part due to differences in the machines and software used, as well as reported skeletal sites. For example, some studies report spine results for the region L1–L4, whereas others only report values for L2–L4.

Attained growth and body size affect BMC and aBMD results. Infants and young children with chronic conditions that affect the skeleton may have delayed growth, complicating interpretation of their BMC and aBMD results. Validation of methods to adjust for body size and relative growth (i.e., weight and length) in the context of a bone health assessment of an individual infant or young child are needed. There is no recommendation regarding standardization of densitometry results according to human milk feeding or gross motor skill development. This information however may provide insight in some situations when BMC and aBMD results are lower than expected.

Clinical Indications for Assessment of BMC and aBMD in Infants and Young Children

As a guiding principle, DXA measurements should only be obtained when results are interpretable and they will affect clinical management. There are many diverse clinical care situations where either single or serial BMC and aBMD assessments in children under the age of 5 are desired despite a paucity of reference data. Examples include children with genetic disorders such as osteogenesis imperfecta *(103)*, Marfan syndrome *(104)*, Noonan syndrome *(105)*, osteopetrosis *(106)*, Duchene muscular dystrophy, Ehlers Danlos syndrome, phenylketonuria *(107)*, cerebral palsy *(108,109)*, neuromuscular disorders *(110)*, rheumatic diseases *(111)*, and cancer

(112,113). Measurement of BMC and aBMD may also be part of efficacy and safety assessments of therapies designed to improved bone mass and/or palliate for pain. There are many articles in the literature that include DXA assessments in very young children on a variety of bone-altering treatment regimens including bisphosphonate treatments for osteogenesis imperfecta (114,115) and other diseases (116,117), other therapies ranging from enzyme replacement therapy for Gaucher (118) to oxandrolone treatment of severely burned children (119) and calcium and vitamin D fortified snacks given to malnourished children (120). Despite these numerous examples, there is insufficient information to provide recommendations regarding clinical indications requiring DXA assessments on infants and young children. Bone status measures, BMC, or aBMD Z-scores may be useful in assessments of children for the ''normalcy'' of their bone mass during investigations of suspected non-accidental trauma, although there are no well-designed studies that have established appropriate DXA use in this area.

In modern neonatology, the need to assess aBMD in preterm infants before initial discharge from the hospital after birth is extremely uncommon. The high fracture incidence of 20−30% reported in the 1970s and 1980s is rarely seen in neonatal intensive care units today due to improvements in dietary management of preterm infants. The American Academy of Pediatrics recently published guidance-related to assessment and dietary management of bone status in preterm infants (121). In former preterm infants, catch-up mineralization generally occurs by 2 yr (122), and there is no current recommendation to routinely assess bone mineral status in most former preterm infants. However, former preterm children with severe growth failure, a history of clinical and radiological rickets, severe intestinal failure or clinical conditions that may have been exacerbated by prematurity may be candidates for assessment of bone mineral by DXA during the first 2 yr of life.

Areas for Future Research

DXA has mainly been used as a research tool on infants and young children. Additional information is needed to facilitate use of DXA as a diagnostic tool and inform clinical management related to bone health in the very young. Research on the topics below would greatly advance development of evidenced-based guidelines regarding clinical use of bone densitometry for children <5 yr.

- Verification of the ability of different DXA platforms and current software to provide seamless serial measures from birth to adulthood for the whole-body and regional measurements.
- Robust reference data for all skeletal sites that enable calculation of Z-scores for both BMC and aBMD.
- Development and validation of measures to use for adjustment for body size.
- Precision studies that allow calculation of least significant change over time and monitoring time intervals to guide recommendations on when follow-up measures should be obtained.
- Studies to help determine whether BMC or aBMD measures are more clinically useful.
- Studies to help guide which skeletal sites to measure in specific disease conditions.
- Studies among infants and toddlers to understand the magnitude of bone deficits in specific diseases affecting bone.
- Studies evaluating fracture prediction and the long-term impact of bone deficits early in life.

In summary, the ISCD Official Positions reported herein are a step toward consolidation of data and expert opinion on use of bone densitometry for clinical bone health assessment of infants and young children. Difficulties in obtaining movement-free images and technical challenges measuring smaller bones have slowed research on this young age group. Challenges in bone densitometry of the very young remain, although positions and guidelines described herein provide a reasonable starting point for the use of bone densitometry in clinical practice. There are no studies that have directly evaluated bone densitometry for fracture prediction in children <5 yr, and the long-term impact of bone deficits early in life have been inadequately investigated. There are sparse data for many questions that arise regarding the use of bone densitometry for infants and young children, and it is anticipated that positions will evolve over time as new data become available.

References

1. Greer FR, McCormick A. 1986 Bone growth with low bone mineral content in very low birth weight premature infants. Pediatr Res 20:925−928.
2. Baim S, Leonard MB, Bianchi M-L, et al. 2008 Official positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Pediatric Position Development Conference. J Clin Densitom 11:6−21.
3. Clark E, Ness AR, Bishop NJ, Tobias JH. 2006 Association between bone mass and fractures in children: a prospective cohort study. J Bone Miner Res 21:1489−1495.
4. Ferrari SL, Chevalley T, Bonjour JP, Rizzoli R. 2006 Childhood fractures are associated with decreased bone mass gain during puberty: an early marker of persistent bone fragility? J Bone Miner Res 21:501−507.
5. Goulding A, Cannan R, Williams SM, et al. 1998 Bone mineral density in girls with forearm fractures. J Bone Miner Res 13: 143−148.
6. Goulding A, Jones IE, Taylor RW, et al. 2001 Bone mineral density and body composition in boys with distal forearm fractures: a dual-energy x-ray absorptiometry study. J Pediatr 139: 509−515.
7. Kalkwarf HJ, Laor T, Bean J. 2011 Fracture risk in children with a forearm injury is associated with volumetric bone density and cortical area (by peripheral QCT) and areal bone density (by DXA). Osteoporos Int 22:607−616.
8. Manias K, McCabe D, Bishop N. 2006 Fractures and recurrent fractures in children; varying effects of environmental factors as well as bone size and mass. Bone 39:652−657.

9. Johnell O, Kanis JA, Oden A, et al. 2005 Predictive value of BMD for hip and other fractures. J Bone Miner Res 20: 1185−1194.
10. Marshall D, Johnell O, Wedel H. 1996 Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. [see comments]. BMJ 312:1254−1259.
11. Rizzoli R, Bianchi ML, Garabedian M, et al. 2010 Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly. Bone 46:294−305.
12. Hernandez CJ, Beaupré GS, Carter DR. 2003 A theoretical analysis of the relative influences of peak BMD, age-related bone loss and menopause on the development of osteoporosis. Osteoporos Int 14:843−847.
13. Amin S, Melton JL, Achenback SJ, et al. 2013 A distal forearm fracture in childhood is associated with an increased risk for future fragility fractures in adult men, but not women. J Bone Miner Res 28:1751−1759.
14. Koo M, Yang K, Begeman P, et al. 2001 Prediction of bone strength in growing animals using noninvasive bone mass measurements. Calcif Tissue Int 68:230−234.
15. Thandrayen K, Norris SA, Pettifor JM. 2009 Fracture rates in urban South African children of different ethnic origins: the Birth to Twenty Cohort. Osteoporos Int 20:47−52.
16. Hedstrom EM, Svensson O, Bergstrom U, Michno P. 2010 Epidemiology of fractures in children and adolescents. Acta Orthop 81:148−153.
17. Mayranpaa MK, Makitie O, Kallio PE. 2010 Decreasing incidence and changing pattern of childhood fractures: a population-based study. J Bone Miner Res 25:2752−2759.
18. Cooper C, Dennison EM, Leufkens HGM, et al. 2004 Epidemiology of childhood fractures in Britain: a study using the general practice research database. J Bone Miner Res 19: 1976−1981.
19. Lucas-Herald A, Butler S, Mactier H, et al. 2012 Prevalence and characteristics of rib fractures in ex-preterm infants. Pediatrics 130:1116−1119.
20. Bar-Yosef O, Polak-Charcon S, Hoffman C, et al. 2008 Multiple congenital skull fractures as a presentation of Ehlers−Danlos syndrome type VIIC. Am J Med Genet A 146A: 3054−3057.
21. Koo WW, Bajaj M, Mosely M, Hammami M. 2008 Quantitative bone US measurements in neonates and their mothers. Pediatr Radiol 38:1323−1329.
22. Bajaj M, Koo W, Hammami M, Hockman EM. 2010 Effect of subcutaneous fat on quantitative bone ultrasound in chicken and neonates. Pediatr Res 68:81−83.
23. Fewtrell M, Loh K, Chomtho S, et al. 2008 Quantitative ultrasound (QUS): a useful tool for monitoring bone health in preterm infants? Acta Paediatr 97:1625−1630.
24. Viljakainen H, Korhonen T, Hytinantti T, et al. 2011 Maternal vitamin D status affects bone growth in early childhood—a prospective cohort study. Osteoporos Int 22:883−891.
25. Viljakainen H, Saarnio E, Hytinantti T, et al. 2010 Maternal vitamin D status determines bone variables in the newborn. J Clin Endocrinol Metab 95:1749−1757.
26. Holmlund-Suila E, Viljakainen H, Hytinantti T, et al. 2012 High-dose vitamin D intervention in infants—effects on vitamin D status, calcium homeostasis, and bone strength. J Clin Endocrinol Metab 97:4139−4147.
27. Specker B, Binkley T. 2003 Randomized trial of physical activity and calcium supplementation on bone mineral content in 3- to 5-year-old children. J Bone Miner Res 18:885−892.
28. Binkley T, Johnson J, Vogel L, et al. 2005 Bone measurements by peripheral quantitative computed tomography (pQCT) in children with cerebral palsy. J Pediatr 147:791−796.
29. Samra HA, Specker B. 2007 Walking age does not explain term versus preterm difference in bone geometry. J Pediatr 151: 61−66. e2.
30. Binkley TL, Specker BL. 2000 pQCT measurement of bone parameters in young children: validation of technique. J Clin Densitom 3:9−14.
31. Gordon CM, Bachrach LK, Carpenter TO, et al. 2008 Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: the 2007 ISCD Pediatric Official Positions. J Clin Densitom 11:43−58.
32. Koo WW, Hammami M, Hockman EM. 2003 Interchangeability of pencil-beam and fan-beam dual-energy X-ray absorptiometry measurements in piglets and infants. Am J Clin Nutr 78:236−240.
33. Koo WW, Hammami M, Hockman EM. 2002 Use of fan beam dual energy x-ray absorptiometry to measure body composition of piglets. J Nutr 132:1380−1383.
34. Chauhan S, Koo WW, Hammami M, Hockman EM. 2003 Fan beam dual energy X-ray absorptiometry body composition measurements in piglets. J Am Coll Nutr 22:408−414.
35. Koo WW, Walters J, Bush AJ. 1995 Technical considerations of dual-energy X-ray absorptiometry-based bone mineral measurements for pediatric studies. J Bone Miner Res 10:1998−2004.
36. Hammami M, Koo W, Hockman EM. 2004 Technical considerations for fan-beam dual-energy x-ray absorptiometry body composition measurements in pediatric studies. JPEN J Parenter Enteral Nutr 28:328−333.
37. Ay L, Jaddoe VW, Hofman A, et al. 2011 Foetal and postnatal growth and bone mass at 6 months: the Generation R Study. Clin Endocrinol (Oxf) 74:181−190.
38. Godang K, Qvigstad E, Voldner N, et al. 2010 Assessing body composition in healthy newborn infants: reliability of dual-energy x-ray absorptiometry. J Clin Densitom 13:151−160.
39. Gallo S, Vanstone CA, Weiler HA. 2012 Normative data for bone mass in healthy term infants from birth to 1 year of age. J Osteoporos 2012:672403.
40. Gallo S, Comeau K, Vanstone C, et al. 2013 Effect of different dosages of oral vitamin D supplementation on vitamin D status in healthy, breastfed infants: a randomized trial. JAMA 309: 1785−1792.
41. Hammami M, Koo WW, Hockman EM. 2003 Body composition of neonates from fan beam dual energy X-ray absorptiometry measurement. JPEN J Parenter Enteral Nutr 27:423−426.
42. Koo WW, Hammami M, Shypailo RJ, Ellis KJ. 2004 Bone and body composition measurements of small subjects: discrepancies from software for fan-beam dual energy X-ray absorptiometry. J Am Coll Nutr 23:647−650.
43. Powers CL, Fan B, Shepherd JA, et al. Analyzing infant whole body DXA scans—reflection or fusion? Annual meeting of the International Society for Clinical Densitometry. Tampa, FL. 2013: poster presentation.
44. Taylor A, Konrad PT, Norman ME, Karcke HT. 1997 Total body bone mineral density in young children: influence of head bone mineral density. J Bone Miner Res 12:652−655.
45. Bikle DD, Halloran BP. 1999 The response of bone to unloading. J Bone Miner Metab 17:233−244.
46. Arnaud SB, Powell MR, Vernikos-Danellis J, Buchanan P. 1988 Bone mineral and body composition after 30 day head down tilt bed rest. J Bone Miner Res 3:S119.
47. Courteix D, Lespessailles E, Obert P, Benhamou C. 1999 Skull bone mass deficit in prepubertal highly-trained gymnast girls. Int J Sport Med 20:328−333.
48. Zia-Ullah M, Koo WW, Hammami M. 2002 Lumbar spine bone measurements in infants: whole-body vs lumbar spine dual X-ray absorptiometry scans. J Clin Densitom 5:17−25.

49. Koo WW, Hockman EM. 2000 Physiologic predictors of lumbar spine bone mass in neonates. Pediatr Res 48:485−489.
50. Kalkwarf HJ, Zemel BS, Yolton K, Heubi JE. 2013 Bone mineral content and density of the lumbar spine of infants and toddlers: influence of age, sex, race, growth and human milk feeding. J Bone Miner Res 28:206−212.
51. Hazell TJ, Vanstone CA, Rodd CJ, et al. 2013 Bone mineral density measured by a portable X-ray device agrees with dual-energy X-ray absorptiometry at forearm in preschool aged children. J Clin Densitom 16:302−307.
52. Willing MC, Torner JC, Burns TL, et al. 2005 Percentile distributions of bone measurements in Iowa children: the Iowa Bone Development Study. J Clin Densitom 8:39−47.
53. Ausili E, Rigante D, Salvaggio E, et al. 2012 Determinants of bone mineral density, bone mineral content, and body composition in a cohort of healthy children: influence of sex, age, puberty, and physical activity. Rheumatol Int 32:2737−2743.
54. Webber CE, Beaumont LF, Morrison J, et al. 2007 Age-predicted values for lumbar spine, proximal femur, and whole-body bone mineral density: results from a population of normal children aged 3 to 18 years. Can Assoc Radiol J 58:37.
55. Zanchetta J, Plotkin H, Filgueira M. 1995 Bone mass in children: normative values for the 2−20-year-old population. Bone 16:S393−S399.
56. Mckay HA, Petit MA, Bailey DA, et al. 2000 Analysis of proximal femur DXA scans in growing children: comparisons of different protocols for cross-sectional 8-month and 7-year longitudinal data. J Bone Miner Res 15:1181−1188.
57. El Hage R, Moussa E, El Hage Z, et al. 2011 Influence of age and morphological characteristics on whole body, lumbar spine, femoral neck and 1/3 radius bone mineral apparent density in a group of Lebanese adolescent boys. J Bone Miner Metab 29:477−483.
58. Gahlot M, Khadgawat R, Ramot R, et al. 2012 The effect of growth hormone deficiency on size-corrected bone mineral measures in pre-pubertal children. Osteoporos Int 23:2211−2217.
59. Crabtree NJ, Arabi A, Bachrach LK, et al. 2014 Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD Pediatric Official Positions. J Clin Densitom 17:225−242.
60. Onis M. 2006 WHO Child Growth Standards based on length/-height, weight and age. Acta Paediatr 95:76−85.
61. Butte N, Heinz C, Hopkinson J, et al. 1999 Fat mass in infants and toddlers: comparability of total body water, total body potassium, total body electrical conductivity, and dual-energy X-ray absorptiometry. J Pediatr Gastroenterol Nutr 29:184−189.
62. Arikoski P, Komulainen J, Voutilainen R, et al. 2002 Lumbar bone mineral density in normal subjects aged 3−6 years: a prospective study. Acta Paediatr 91:287−291.
63. Bachrach LK, Hastie T, Wang M-C, et al. 1999 Bone mineral acquisition in healthy Asian, Hispanic, Black and Caucasian youth: a longitudinal study. J Clin Endocrinol Metab 84: 4702−4712.
64. Del Rio L, Carrascosa A, Pons F, et al. 1994 Bone mineral density of the lumbar spine in white Mediterranean Spanish children and adolescents: changes related to age, sex, and puberty. Pediatr Res 35:362−365.
65. Ellis KJ. 1997 Body composition of a young, multiethnic, male population. Am J Clin Nutr 66:1323−1331.
66. Ellis KJ, Abrams SA, Wong WW. 1997 Body composition of a young, multiethnic female population. Am J Clin Nutr 65: 724−731.
67. HasanoĞlu A, Tümer L, Ezgü FS. 2004 Vertebra and femur neck bone mineral density values in healthy Turkish children. Turk J Pediatr 46:298−302.
68. Goksen D, Darcan S, Coker M, Kose T. 2006 Bone mineral density of healthy Turkish children and adolescents. J Clin Densitom 9:84−90.
69. McCormick DP, Ponder SW, Fawcett HD, Palmer JL. 1991 Spinal bone mineral density in 335 normal and obese children and adolescents: evidence for ethnic and sex differences. J Bone Miner Res 6:507−513.
70. Kalkwarf HJ, Zemel BS, Gilsanz V, et al. 2007 The bone mineral density in childhood study: bone mineral content and density according to age, sex, and race. J Clin Endocrinol Metab 92:2087−2099.
71. Southard RN, Morris JD, Mahan JD, et al. 1991 Bone mass in healthy children: measurement with quantitative DXA. Radiology 179:735−738.
72. Sudhagoni RG, Wey HE, Djira GD, Specker BL. 2011 Longitudinal effects of fat and lean mass on bone accrual in infants. Bone 50:638−642.
73. Specker BL, Johannsen N, Binkley T, Finn K. 2001 Total body bone mineral content and tibial cortical bone measures in preschool children. J Bone Miner Res 16:2298−2305.
74. Koo WW, Bush AJ, Walters J, Carlson SE. 1998 Postnatal development of bone mineral status during infancy. J Am Coll Nutr 17:65−70.
75. Rupich R, Specker B, Lieuw-A-Fa M, Ho M. 1996 Gender and race differences in bone mass during infancy. Calcif Tissue Int 58:395−397.
76. Li J-Y, Specker BL, Ho ML, Tsang RC. 1989 Bone mineral content in black and white children 1 to 6 years of age: early appearance of race and sex differences. Arch Pediatr Adolesc Med 143:1346−1349.
77. Zemel BS, Kalkwarf HJ, Gilsanz V, et al. 2011 Revised reference curves for bone mineral content and areal bone mineral density according to age and sex for black and non-black children: results of the bone mineral density in childhood study. J Clin Endocrinol Metab 96:3160−3169.
78. Nelson DA, Simpson PM, Johnson CC, et al. 1997 The accumulation of whole body skeletal mass in third- and fourth-grade children: effects of age, gender, ethnicity, and body composition. Bone 20:73−78.
79. Gilsanz V, Roe TF, Mora S, et al. 1991 Changes in vertebral bone density in black girls and white girls during childhood and puberty. N Engl J Med 325:1597−1600.
80. Weiler HA, Fitzpatrick-Wong SC, Schellenberg JM. 2008 Bone mass in First Nations, Asian and white newborn infants. Growth Dev Aging 71:35−43.
81. Zemel BS, Leonard MB, Kelly A, et al. 2010 Height adjustment in assessing dual energy x-ray absorptiometry measurements of bone mass and density in children. J Clin Endocrinol Metab 95:1265−1273.
82. Crabtree NJ, Kibirige MS, Fordham JN, et al. 2004 The relationship between lean body mass and bone mineral content in paediatric health and disease. Bone 35:965−972.
83. Hogler W, Briody J, Woodhead H, et al. 2003 Importance of lean mass in the interpretation of total body densitometry in children and adolescents. J Pediatr 143:81−88.
84. Salle BL, Braillon P, Glorieux FH, et al. 1992 Lumbar bone mineral content measured by dual energy X-ray absorptiometry in newborns and infants. Acta Paediatr 81:953−958.
85. Koo WW, Walters J, Bush AJ, et al. 1996 Dual-energy X-ray absorptiometry studies of bone mineral status in newborn infants. J Bone Miner Res 11:997−1002.
86. Kurl S, Heinonen K, Jurvelin JS, Lansimies E. 2002 Lumbar bone mineral content and density measured using a Lunar DPX densitometer in healthy full-term infants during the first year of life. Clin Physiol Func Imaging 22:222−225.

87. Unal A, Gur E, Arvas A, et al. 2000 Bone density values in healthy Turkish infants. Indian Pediatr 37:497−503.
88. Carter DR, Bouxsein ML, Marcus R. 1992 New approaches for interpreting projected bone densitometry data. J Bone Miner Res 7:137−145.
89. Prentice A, Parsons TJ, Cole TJ. 1994 Uncritical use of bone mineral density in absorptiometry may lead to size-related artifacts in the identification of bone mineral determinants. Am J Clin Nutr 60:837−842.
90. Molgaard C, Thomsen BL, Prentice A, et al. 1997 Whole body bone mineral content in healthy children and adolescents. Arch Dis Child 76:9−15.
91. Schoenau E. 2005 From mechanostat theory to development of the ''Functional Muscle-Bone-Unit''. J Musculoskelet Neuronal Interact 5:232−238.
92. Schoenau E, Frost HM. 2002 The ''muscle-bone unit'' in children and adolescents. Calcif Tissue Int 70:405−407.
93. de Onis M, Garza C, Victora CG, et al. 2004 The WHO Multicentre Growth Reference Study: planning, study design, and methodology. Food Nutr Bull 25:15S−26S.
94. Specker BL, Beck A, Kalkwarf H, Ho M. 1997 Randomized trial of varying mineral intake on total body bone mineral accretion during the first year of life. Pediatrics 99:E12.
95. Harvey NC, Robinson SM, Crozier SR, et al. 2009 Breastfeeding and adherence to infant feeding guidelines do not influence bone mass at age 4 years. Br J Nutr 102:915−920.
96. Fewtrell MS, Kennedy K, Murgatroyd PR, et al. 2013 Breastfeeding and formula feeding in healthy term infants and bone health at age 10 years. Br J Nutr 110:1061−1067.
97. Pirila S, Taskinen M, Viljakainen H, et al. 2011 Infant milk feeding influences adult bone health: a prospective study from birth to 32 years. PLoS One 6:e19068.
98. Bailey DA, McKay HA, Mirwald RL, et al. 1999 A six-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: the University of Saskatchewan Bone Mineral Accrual Study. J Bone Miner Res 14:1672−1679.
99. Janz KF, Eichenberger JM, Levy SM, et al. 2007 Physical activity and femoral neck bone strength during childhood: the Iowa bone development study. Bone 41:216−222.
100. Janz KF, Gilmore JM, Burns TL, et al. 2006 Physical activity augments bone mineral accrual in young children: the Iowa bone development study. J Pediatr 148:793−799.
101. Specker BL, Mulligan L, Ho M. 1999 Longitudinal study of calcium intake, physical activity, and bone mineral content in infants 6−18 months of age. J Bone Miner Res 14:569−576.
102. Onis M. 2006 WHO Motor Development Study: windows of achievement for six gross motor development milestones. Acta Paediatr 95:86−95.
103. Rauch F, Lalic L, Roughley P, Glorieux FH. 2010 Relationship between genotype and skeletal phenotype in children and adolescents with osteogenesis imperfecta. J Bone Miner Res 25: 1367−1374.
104. Grover M, Brunetti-Pierri N, Belmont J, et al. 2012 Assessment of bone mineral status in children with Marfan syndrome. Am J Med Genet A 158:2221−2224.
105. Choudhry KS, Grover M, Tran A, et al. 2012 Decreased bone mineralization in children with Noonan syndrome: another consequence of dysregulated RAS MAPKinase pathway? Mol Genet Metab 106:237−240.
106. Kaste SC, Kasow KA, Horwitz EM. 2007 Quantitative bone mineral density assessment in malignant infantile osteopetrosis. Pediatr Blood Cancer 48:181−185.
107. de Groot MJ, Hoeksma M, van Rijn M, et al. 2012 Relationships between lumbar bone mineral density and biochemical parameters in phenylketonuria patients. Mol Genet Metab 105:566−570.
108. Henderson RC, Berglund LM, May R, et al. 2010 The relationship between fractures and DXA measures of BMD in the distal femur of children and adolescents with cerebral palsy or muscular dystrophy. J Bone Miner Res 25:520−526.
109. Mergler S, Rieken R, Tibboel D, et al. 2012 Lumbar spine and total-body dual-energy X-ray absorptiometry in children with severe neurological impairment and intellectual disability: a pilot study of artefacts and disrupting factors. Pediatr Radiol 42: 574−583.
110. Bergqvist AG, Schall JI, Stallings VA, Zemel BS. 2008 Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet. Am J Clin Nutr 88:1678−1684.
111. Rodd C, Lang B, Ramsay T, et al. 2012 Incident vertebral fractures among children with rheumatic disorders 12 months after glucocorticoid initiation: a national observational study. Arthritis Care Res 64:122−131.
112. Kohler JA, Moon RJ, Sands R, et al. 2012 Selective reduction in trabecular volumetric bone mineral density during treatment for childhood acute lymphoblastic leukemia. Bone 51:765−770.
113. Alos N, Grant RM, Ramsay T, et al. 2012 High incidence of vertebral fractures in children with acute lymphoblastic leukemia 12 months after the initiation of therapy. J Clin Oncol 30: 2760−2767.
114. Plotkin H, Rauch F, Bishop NJ, et al. 2000 Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. J Clin Endocrinol Metab 85:1846−1850.
115. DiMeglio LA, Ford L, McClintock C, Peacock M. 2004 Intravenous pamidronate treatment of children under 36 months of age with osteogenesis imperfecta. Bone 35:1038−1045.
116. Paksu MS, Vurucu S, Karaoglu A, et al. 2012 Osteopenia in children with cerebral palsy can be treated with oral alendronate. Childs Nerv Syst 28:283−286.
117. Pastore S, Londero M, Barbieri F, et al. 2012 Treatment with pamidronate for osteoporosis complicating long-term intestinal failure. J Pediatr Gastroenterol Nutr 55:615−618.
118. Ciana G, Deroma L, Franzil AM, et al. 2012 Long-term bone mineral density response to enzyme replacement therapy in a retrospective pediatric cohort of Gaucher patients. J Inherit Metab Dis 35:1101−1106.
119. Porro LJ, Herndon DN, Rodriguez NA, et al. 2012 Five-year outcomes after oxandrolone administration in severely burned children: a randomized clinical trial of safety and efficacy. J Am Coll Surg 214:489−502.
120. Ekbote V, Khadilkar A, Chiplonkar S, et al. 2011 A pilot randomized controlled trial of oral calcium and vitamin D supplementation using fortified laddoos in underprivileged Indian toddlers. Eur J Clin Nutr 65:440−446.
121. Abrams SA, Bhatia JJ, Corkins MR, et al. 2013 Calcium and vitamin D requirements of enterally fed preterm infants. Pediatrics 131:e1676−e1683.
122. Schanler RJ, Burns PA, Abrams SA, Garza C. 1992 Bone mineralization outcomes in human milk-fed preterm infants. Pediatr Res 31:583−586.
123. Specker B, Namgung R, Tsang R. 2001 Bone mineral acquisition in utero, during infancy, and throughout childhood. Osteoporos 1:599−620.
124. Koo WW, Hammami M, Margeson DP, et al. 2003 Reduced bone mineralization in infants fed palm olein-containing formula: a randomized, double-blinded, prospective trial. Pediatrics 111:1017−1023.
125. Wosje KS, Khoury PR, Claytor RP, et al. 2010 Dietary patterns associated with fat and bone mass in young children. Am J Clin Nutr 92:294−303.