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Presented by
The Johns Hopkins University
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for Johns Hopkins Nursing

Supported by an Educational
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eNeonatal Review



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December 2008: VOLUME 6, NUMBER 4

Neonatal Osteopenia and Bone Mineralization

In this Issue...

With major advances in life-support measures, nutrition has become one of the most debated issues in the care of very low birth weight (VLBW) infants, with the explicit goal of providing postnatal nutrient delivery and retention equivalent to the intrauterine gain of a normal, healthy fetus. Mineral homeostasis and skeletal mineralization are multifaceted mechanisms that are not solely dependent on adequate mineral supplies. During fetal development, optimal bone growth and mineralization appear to be the result not only of adequate nutrient (ie, amino acids and minerals) and energy transfer throughout the placenta, but are also influenced by several factors related to the environment, maternal status, and/or fetal well-being.

Following birth, dramatic physiologic changes occur, which may interfere with optimal postnatal bone growth and mineralization. The continuous maternal transfer must be replaced rapidly by developing intestinal absorption. Birth stress and disruption in cord nutritional supply induce a hormonal storm, resulting in a dramatic decrease in mineral levels and subsequent calciotropic hormone stimulation. In VLBW infants, factors influencing skeletal growth and mineralization include the neonatal intensive care unit (NICU), clinical status (including mechanical ventilation), infection, and medications, as well as the progressive introduction of parenteral and enteral nutrition.

In this issue, we examine the major factors influencing fetal and early neonatal bone growth and mineralization, review current nutritional recommendations and best practices regarding screening, and report on suggested treatments for reducing the incidence of osteopenia and risk fracture in VLBW infants.



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Release Date

December 19, 2008

Expiration Date

December 18, 2010

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Guest Faculty Disclosure

Dr. Rigo has no relevant financial relationships to disclose.

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Dr. Rigo does not reference any off-label indications in this publication.

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Describe the physiologic changes occurring at birth that influence bone growth and metabolism in pre-term and term infants
- Identify the various risk factors influencing the development of metabolic bone disease in VLBW infants
- Discuss the biologic markers and use of the various investigative tests for monitoring at-risk infants

COMMENTARY

Premature infants, particularly those born at <28 weeks' gestation, are at significant risk for reduced bone mineral content (BMC) and subsequent bone disease, variably termed metabolic bone disease (MBD), osteomalacia, osteopenia, or neonatal rickets.^{1,2} Reduction in BMC and the development of MBD of prematurity are quite common among VLBW infants. However, due to the lack of widely adopted diagnostic criteria, the true incidence has not been determined. Fractures in premature infants typically occur several weeks after delivery and prior to the postnatal age of 6 months.^{3,4} Rib fractures, the most common type, usually occur silently and are diagnosed only if x-rays are performed. Therefore, the true incidence of fractures is difficult to determine, varying between 2.1% and 25% in 3 previous studies^{3,4} conducted without the use of prospective, systematic skeletal surveys.

The risk factors commonly associated with fractures include extremely low birth weight, late (> 30 days) establishment of full enteral feeds or prolonged parenteral nutrition, exclusive use of unfortified human milk, necrotizing enterocolitis, conjugated hyperbilirubinemia, chronic lung disease, use of various medications, utilization of passive

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respiratory physiotherapy (ie, chest percussion), and lack of physical activity, which may be enhanced by sedatives. Recent data on fractures among VLBW infants are still lacking, but some clinical evidence suggests that the risk for fracture is greatly reduced with the use of parenteral and enteral nutrition adapted to the special nutritional needs of the premature infant.

Fetal accretion of calcium and phosphorus in the last trimester of pregnancy is approximately 20 g and 10 g, respectively, representing accretion rates of 100 to 120 mg/kg/day for calcium and 50 to 65 mg/kg/day for phosphorus. This transfer is fairly stable and relatively independent of the mother's nutritional status.¹ By contrast, 25-hydroxyvitamin D [25(OH)D] from the mother is the major source of vitamin D for the fetus as well as for the newborn, until the infant receives vitamin D from other dietary sources, such as formula or supplements. Fetal vitamin D concentration is directly related to the mother's vitamin D status and thus to the season, the mother's skin pigmentation, sunlight exposure, and vitamin D supplementation. Several recent studies have reported a high prevalence of vitamin D insufficiency among pregnant women and their offspring, suggesting that the resurgence of rickets in the United States and several other nations worldwide is related to maternal deficiencies.^{5,6}

1,25-Dihydroxyvitamin D [1,25-(OH)₂D], the physiologically active metabolite of vitamin D, does not cross the placenta. However, the ability of the placenta to synthesize 1,25-(OH)₂D directly is important in the transfer of phosphate to the fetus and contributes to the infant's circulating level of 25(OH)D.⁷ Thus, as a result of placental insufficiency, some pre-term infants born with severe growth restriction are phosphate-deficient, which increases their risk for MBD. In addition to the effect of vitamin D on numerous other non-skeletal health outcomes, emerging data demonstrate that vitamin D regulates placental development and function, suggesting that maternal vitamin D status may be associated with such adverse pregnancy outcomes as miscarriage, preeclampsia, and pre-term birth.^{5,6}

Risk factors for MBD are commonly encountered in the pre-term infant. The majority of bone mineralization, along with calcium and phosphorus accretion, occurs during the third trimester of pregnancy. Infants born before this time thus have depleted stores of these minerals.⁴ Data from bone density scans (dual-energy x-ray absorptiometry [DEXA]) performed at birth in pre-term and term infants suggest that bone mineral accretion during the last trimester of gestation is higher than needed, with growth in bone volume leading to a continuous increase in skeletal density.¹ Pre-term infants therefore have a large mineral deficit compared with term infants. Several factors increase the risk for severe MBD among VLBW infants, with the most important appearing to be an inadequate supply of calcium and phosphorus associated with the use of an enteral vs transplacental route. Newborn premature infants experience a diminished mineral uptake required for proper bone accretion, due, in part, to the reduced availability and to their compromised gastrointestinal (GI) absorption. Relative calcium absorption, which depends on calcium bioavailability and vitamin D intake, appears to be significantly higher in pre-term infants fed fortified human milk (\pm 50% to 60%) than in those fed formula (35% to 50%).⁸ By contrast, phosphorus intake is generally well absorbed (\pm 90%) in either group.⁸ The retention of calcium and inorganic phosphate is interrelated, based on the calcium to phosphate ratio of hydroxyapatite and the inorganic phosphate to nitrogen retention ratio. Thus, metabolic balance studies⁸ have reported that maximal calcium retention values may reach 60 to 90 mg/kg/day and maximal inorganic phosphate retention values may reach 50 to 75 mg/kg/day. The retention rates are relatively low compared with the fetal accretion rates. In total parenteral nutrition, similar data could be obtained with the use of organic phosphate supply and highly soluble calcium salt. In our unit, we use calcium glycerophosphate, which allows us to provide up to 105 mg of calcium and 80 mg of inorganic phosphate/kg/day.

Decreased bone mineralization and the development of osteopenia are the balanced result between 2 different bone matrix growth factors, directly related to energy balance and nitrogen retention on the one hand, and mineral accretion on the other hand.¹ Data from DEXA scans^{1,8} performed during the first weeks after birth in both pre-term and term infants suggest that bone growth, estimated by increase in bone area, is relatively higher than bone mineral accretion, leading to a continuous decrease in skeletal density.

Nevertheless, after a few weeks or months, with the continuous reduction in growth velocity, the balance is progressively reversed and the bone mass accrual compensates slowly for the early peak bone growth during the first few months of life.

Physical activity appears to play a significant role in bone mineralization. During the neonatal period, mechanical strain on bone and joints stimulates bone formation and growth, whereas inactivity leads to bone resorption. This might be equally valid for pre-term infants in incubators during the first weeks of life, who lack the *in utero* mechanical stimulation associated with regular kicks against the confining uterine wall. During the initial hospitalization, the movements of pre-term infants usually occur without much resistance. While in the NICU, these infants are handled with little tactile stimulation in order to reduce stressful events. Moreover, the use of drugs to reduce pain aggravates the reduction in mechanical stimulation during their stay. In order to obviate the effects of reduced mechanical stimulation, systematic physical activity programs administered several times a week by nurses, therapists, and parents have been evaluated. A number of recent studies, including one by Moyer-Mileur and colleagues (reviewed herein), agree that physical activity either improves bone mineralization, as determined by single-photon absorptiometry, or increases bone formation, as estimated by the measure of serum collagen C-terminal propeptide. These regimens either increased bone strength or attenuated its decrease, as evaluated by quantitative measurement of bone ultrasound transmission speed. Nevertheless, the last Cochrane review of this subject (Schulzke et al. discussed in this issue), concluded that additional studies are needed before the general use of such physical activity programs can be promoted.

A number of other factors may also play a significant role in bone mineralization, including genetic polymorphism, mechanical stimulation, or the use of various medications that interfere with mineral absorption or retention, such as diuretics, caffeine, and corticosteroids.

Neonatal screening for MBD in pre-term infants is still controversial.^{2,4} Serum calcium levels are carefully regulated by hormonal secretion and are not a useful screening tool. However, a low serum phosphorus concentration (<1.8 mmol/L) that is below the renal phosphate threshold has been related to insufficient phosphorus intake and to an increased risk for osteopenia. Urinary excretion of calcium and phosphorus has been proposed as a marker of adequate postnatal mineralization when doses >1.2 mmol/L of calcium and >0.4 mmol/L of inorganic phosphorus are excreted simultaneously. However, these values are more appropriate for estimating the adequacy of the calcium to phosphate ratio than for estimating mineral accretion, especially when data on the mineral absorption rate are lacking.

In infants, 90% of alkaline phosphatase (ALP) is of bone origin and thought to reflect bone turnover. ALP concentrations usually increase during the first 2 to 3 weeks of life and may peak further if there are insufficient mineral supplies. Elevated levels of ALP have been reported in association with severe undermineralization based on radiologic evidence, low bone speed of sound (SOS) using quantitative ultrasound, or severe bone mineral density (BMD) deficit revealed on DEXA scans. Nevertheless, ALP is probably more sensitive for evaluating fracture risk than for assessing MBD or osteopenia.

Various radiologic investigations have been proposed for assessing bone mineralization and osteopenia among pre-term infants. Plain radiography is poorly sensitive, detecting only a decrease of >20% to 40% of bone mineralization.⁴ By contrast, DEXA technology, reviewed by Pieltain and colleagues in this issue, is sensitive, accurate, and precise, and its use has been validated in both pre-term and term infants.^{1,8} Normative data on bone mineral content, projected bone area, and BMD in healthy pre-term and term infants close to birth were established in order to obtain surrogate intrauterine reference values. In addition, various indices have been proposed for reducing the anthropometric dependency of the various parameters and for facilitating group or individual comparison. Thus, data obtained from various groups allow for the determination of major changes in bone mineralization during the fetal life and postnatally in pre-term and term infants. These results are in agreement with the predicted time course of volumetric bone mineral density in mature newborns and premature babies, according to mechanostat theory.²

The use of ultrasound has been proposed for the evaluation of bone mineralization in newborn infants.⁸ It is a simple, non-invasive, relatively inexpensive bedside procedure. Some machines have been designed to measure broadband ultrasound attenuation or SOS, commonly on the tibia. The propagation of sound waves in bone is determined by a number of factors, including mineral density, cortical thickness, elasticity, and micro-architecture, possibly providing a more complete picture of bone strength than measurements of BMD alone. In pre-term and term infants at birth, there is a significant correlation among tibial SOS and gestational age, birth weight, birth length, and tibial length. However, the changes in SOS values during the last trimester of gestation are relatively small, accounting for only about 130 m/sec. This value is only ± 1.5 times higher than the interindividual variability (standard deviation [SD]=95 m/sec). After birth, a rapid decline in bone SOS occurs during the first days of life that cannot be completely explained by a nutritional deficit. Therefore, these data suggest that measurement of bone SOS has a lower sensitivity than DEXA for evaluating the various factors influencing bone mineralization during the neonatal period.

In contrast to fetal bone metabolism, in which modeling is the main process inducing high net bone formation, with a rapid increase in trabecular thickness, neonatal bone metabolism is the result of a prevailing remodeling activity, defined as the cyclical succession of bone resorption and formation on the same bone surface.^{1,2} Therefore, the relative MBD of prematurity could be the result of a postnatal physiologic metabolic adaptation instead of the expression of a transitory MBD. Indeed, the relative osteopenia observed in pre-term infants appears to be similar to that observed in healthy term infants during the first weeks after delivery or to that observed in early adolescence at the time of a growth spurt.

Currently, calcium and phosphorus requirements in pre-term infants are usually based on demands for matching intrauterine bone mineral accretion rates. Recent recommendations from North America¹ suggest that mineral requirement in VLBW infants are as high as 120 to 220 mg/kg per day for calcium and 60 to 140 mg/kg per day for phosphorus. However, a recently acquired understanding of bone physiology suggests that the mere adaptation of the neonate to its extrauterine environment could modify the calcium requirements, as the stimulation of the remodeling process might contribute to the mineral requirements for postnatal bone turnover. In addition, in spite of their low absorption rate, the high-calcium formulas used in pre-term infants might pose a risk for VLBW infants. Therefore, new recommendations have been proposed by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition, based on the fact that a calcium retention level ranging from 60 to 90 mg/kg/day ensures appropriate mineralization, decreases the risk for fracture, and reduces the clinical symptoms of osteopenia. Thus, an intake of 100 to 160 mg/kg/day of highly bioavailable calcium salts, 60 to 90 mg/kg/day of phosphorus, and 800 to 1000 IU/day of vitamin D have been recommended.¹

In summary, after birth, the development of relative osteomalacia or osteopenia is a physiologic event resulting from a mismatch of the mineral supply and the persistent growth velocity on the one hand, and from the stimulation of bone turnover as an adaptation to extrauterine life on the other. This phenomenon is enhanced in pre-term infants born with low mineral stores, an immature GI tract, and reduced physical activity, who demonstrate higher growth rates than do term infants. Several of the conditions discussed above and in the articles reviewed in this issue might increase the severity of MBD, leading to the development of severe osteopenia and the risk for fracture. Early optimal parenteral and oral nutritional support, combined with biologic neonatal screening and measurement of serum phosphorus and ALP concentrations, as well as mineral urinary excretion, appears to be helpful for the prevention of MBD. When available, DEXA is more sensitive than ultrasound for quantifying osteopenia in VLBW infants.

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QUANTITATIVE ULTRASOUND (QUS) FOR MONITORING BONE HEALTH IN PRE-TERM INFANTS

Fewtrell MS, Loh KL, Chomtho S, Kennedy K, Hawdon J, Khakoo A. **Quantitative ultrasound (QUS): a useful tool for monitoring bone health in preterm infants?** *Acta Paediatr.* 2008;97(12):1625-1630.

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Fewtrell et al. sought to assess longitudinal changes in tibial speed of sound (SOS) in pre-term infants during the neonatal period and identify the factors influencing these changes. The authors were also interested in the relationships between SOS and biochemical markers of metabolic bone disease (MBD), in order to determine whether SOS measurements early in the postnatal period have any predictive value for the development of MBD.

SOS was measured at least once in the tibia in 99 preterm infants (mean [SD] gestation, 29.7 [3.6] weeks; birth weight, 1340 [550] g), with longitudinal measurements performed in 75 of the subjects. Mean age at the time of the first quantitative ultrasound (QUS) was 2.6 [2.6] weeks. SOS z scores were generated internally using cross-sectional reference data for infants of the same sex and gestational age. Plasma phosphate and alkaline phosphatase (ALP) concentrations were recorded to evaluate the development of MBD. High peak ALP concentrations (>420 IU/L) and/or low phosphate concentrations <1.2 mmol/L) were used as biochemical markers for the detection of MBD.

The median SOS at baseline was 2950 m/sec (25th/75th percentiles; 2821/3038), with a machine-derived median SOS z score of -0.40 (2.01/-0.93). When infants whose first scan was performed at >3 weeks of age were excluded, the median SOS was 2976 m/sec (2855/3066), with an SOS z score of -0.1 (-0.85, 0.65). Baseline SOS for the 43 infants with their initial measurement performed at <1 week of age showed a significant positive correlation with gestational age ($r=0.33$; $P=.03$) but not with birth weight ($r=0.05$; $P=.8$). Baseline SOS z score was not significantly correlated with gestational age or birth weight.

In the longitudinal evaluation, the median SOS for baseline and final scans was 2964 (2847/3046) m/sec and 2877 (2766/2975) m/sec, respectively, with a median change in SOS of -77 (-150/+16) m/sec. In a multivariate model, the only factor significantly associated with the decline in SOS z score was the number of scans performed (ie, the number of scans performed and the postnatal age are interrelated). Peak ALP and minimum plasma phosphate concentrations were not associated with the decrease in SOS z score. After adjusting for potential confounders using logistic regression analysis, neither initial SOS nor SOS z score was predictive of MBD, as identified by high peak ALP or low phosphate concentrations.

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This study illustrates the relatively poor sensitivity of QUS for the evaluation of MBD in pre-term infants. Indeed, studies evaluating baseline SOS values during the first few days of life reported a positive linear relationship between SOS and gestational age, birth weight, or body length. The mean SOS increase was about 100 m/sec between 30 and 40 weeks of gestational age. In addition, in longitudinal studies, an SOS decrease of similar magnitude was observed during the first 2 to 3 weeks of life (60 to 80 m/sec). Therefore, it is not surprising that when studying patients in whom baseline SOS was obtained during the third week of life (mean age, 2.6 weeks; range, 0 to 12 weeks), no relationships were observed between SOS and gestational age or anthropometric parameters. The design of the longitudinal study led to only 2 significant results: (1) median decline in SOS of -77 m/sec between baseline and final scan; and (2) a significant association between decrease in SOS z score in the final scan and the number of scans performed.

As biochemical markers for detecting MBD, phosphate levels <1.2 mmol/L were observed frequently (27/96 infants), but the duration of low phosphate concentration, which can be more predictive of MBD, was not reported. Similarly, high peak ALP concentrations were reported (51/96 infants), but the duration of elevated ALP concentrations was also not presented. The data from this study are in contrast to those from a prior study evaluating longitudinal evolution of ALP and SOS in VLBW infants, which reported a negative correlation between SOS and ALP at the conclusion of the evaluation period.¹ Therefore, this study also suggests that the sensitivity and specificity of the biochemical markers of MBD require further investigation.

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QUANTITATIVE ULTRASOUND FOR ASSESSING SKELETAL DEVELOPMENT IN PRE-TERM AND TERM INFANTS

Ritschl E, Wehmeijer K, de Terlizzi F, Wipfler E, Cadossi R, Douma D, et al. **Assessment of skeletal development in preterm and term infants by quantitative ultrasound**. *Pediatr Res*. 2005;58(2):341-346.

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Ritschl and coworkers assessed skeletal development via quantitative ultrasound (QUS) of the second metacarpus using cross-sectional data from 132 pre-term or term infants within 24 hours of birth and from 142 term infants up to the age of 18 months. In addition, longitudinal measurements were obtained from 150 pre-term infants up to the age of 14 months. Cross-sectional data were used to devise reference curves for fetal metacarpal speed of sound (mcSOS) and metacarpal bone transmission time (mcBTT), assuming that measurements performed within 24 hours of birth reflect *in utero* bone status.

Results of this study suggest that both parameters - mcSOS and mcBTT - increase during the last trimester of gestation. mcBTT and mcSOS were both significantly associated with gestational age ($r=0.55$ and 0.84 , respectively); body weight ($r=0.52$ and 0.80 , respectively); and body length ($r=0.47$ and 0.76 , respectively). The increase in mcSOS during the last trimester of pregnancy (28 to 40 weeks) was relatively small (1645 to 1680 m/sec, or 2.1%), in contrast to the increase in mcBTT values (0.50 to 0.85 μsec , or 70%). After birth, in term infants, mcSOS declined up to 6 months of age and then increased up to 18 months of age. In contrast, mcBTT measurements remained stable after birth.

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At birth, mcSOS and mcBTT values in pre-term infants were lower than those in term infants. In the longitudinal study, mcSOS declined during the first 2 to 3 postnatal months in pre-term infants (<32 weeks) and reached a nadir close to corrected term. Thereafter, mcSOS increased so that between 3 and 4 months post-corrected term, it reached a mean value in term infants of similar postconceptional age and exceeded that value by the end of the survey. In pre-term infants, mcBTT increased less than expected (based on *in utero* reference values) and reached a mean value at corrected term that was 30% lower than that of infants born at term. Thereafter, mcBTT values in premature infants increased rapidly to a mean value equivalent to that of term infants of similar postconceptional age at 4 months.

This study illustrates the relative poor sensitivity of mcSOS measurements for evaluating MBD in pre-term infants. This may be augmented by the fact that mcSOS may be influenced by body composition and body mass index. In contrast, since mcBTT values depend on the thickness and mineralization of the cortical bone, and appear to be largely independent of soft tissue, they may provide more accurate information on bone tissue. This study further suggests that it is possible to follow skeletal development and maturation using mcBTT evaluation in pre-term infants. Since this method is safe, repeatable, reliable, and easily available, additional studies are needed to compare QUS with mcBTT measurements vs DEXA for the evaluation of MBD in preterm infants.

PHYSICAL ACTIVITY IS A MAJOR DETERMINANT OF BONE MINERALIZATION AND GROWTH IN PRE-TERM INFANTS

Moyer-Mileur LJ, Ball SD, Brunstetter VL, Chan GM. **Maternal-administered physical activity enhances bone mineral acquisition in premature very low birth weight infants.** *J Perinatol.* 2008;28(6):432-437.

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Schulzke SM, Trachsel D, Patole SK. **Physical activity programs for promoting bone mineralization and growth in preterm infants.** *Cochrane Database Syst Rev.* 2007;18:CD005387.

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The objective of the study by Moyer-Mileur and colleagues was to determine if physical activity administered by an infant's mother would be as effective in promoting bone mineral acquisition in pre-term VLBW infants as the same intervention administered by a trained therapist. A total of 33 pre-term VLBW infants were randomized to receive daily physical activity administered by the infant's mother (MOM, $n=11$) or a trained therapist (OT, $n=11$), versus a control group ($n=11$). Physical activity consisted of range of motion movements against passive resistance to all extremities for 5 to 10 minutes daily. All infants were fed mother's milk with fortification to 24 kcal/oz. Peripheral DEXA of the forearm bone area (BA, cm^2); bone mineral content (BMC, g); and bone mineral density (BMD, g/cm^2), as well as proxy measurements of bone formation (bone-specific alkaline phosphatase, BAP) and resorption (urine pyridinium crosslinks of collagen, Pyd), were obtained at study entry and when the infant reached a weight of 2.0 kg.

Forearm BA and BMC gains were greater in MOM and OT infants compared with control infants, despite similar postnatal growth rates and nutrient intake. Serum BAP levels decreased in controls, but remained unchanged in MOM and OT infants. Urine Pyd levels were similar at baseline to 2.0 kg in all 3 groups.

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This limited study suggests that a physical activity program administered by an infant's own mother is equally as effective as therapist-administered physical activity with respect to bone size and mineralization. Based on peripheral DEXA, physical activity promotes greater bone growth and mineral acquisition in pre-term VLBW infants.

A search on the effects of physical activity programs on bone mineralization was conducted in September 2006 and was evaluated in a 2007 *Cochrane Database of Systematic Reviews*. Six trials enrolling 169 pre-term infants (gestational age, 26 to 34 weeks) were included in this review. All trials were small ($n=20$ to 49), single-center studies evaluating daily physical activity for 3.5 to 4 weeks during initial hospitalization. The methodological quality and reporting of all trials were poor.

The reported outcomes of 3 trials, from the same group, included bone mineralization by peripheral absorptiometry (single-photon absorptiometry and DEXA), biochemical markers of bone metabolism, and growth. Outcomes of 3 additional trials from another unique group included short-term growth, biochemical markers of bone and fat tissue metabolism, and bone ultrasound measurements as SOS in m/sec.

The studies generated contradictory findings. Two trials ($n=55$) demonstrated moderate short-term benefits of physical activity on bone mineralization at completion of the physical activity program. The only trial ($n=20$) assessing long-term effects on bone mineralization showed no effect of physical activity administered during initial hospitalization on bone mineralization at 12 months corrected age. Meta-analysis from 3 trials ($n=78$) demonstrated an effect of physical activity on daily weight gain (2.77 g/kg/d). Data from 2 trials ($n=58$) showed no effect on linear growth or head growth during the study period.

The investigators concluded that there is weak evidence that physical activity programs might promote moderate short-term weight gain and bone mineralization in pre-term infants, and that current evidence does not justify the standard use of such programs in this patient population.

In our opinion, the use of peripheral absorptiometry has not been clearly validated for assessing MBD or minimal changes in bone mineralization secondary to nutritional intervention. Similarly, SOS was found to have a poor sensitivity for detecting MBD in pre-term infants. Large, multicenter, randomized, controlled studies are needed before the use of physical activity programs in pre-term infants can be recommended. The recent study by Moyer-Mileur and associates, discussed above, does not justify revising the current Cochrane recommendations.

BIOLOGICAL MARKERS OF BONE MINERAL HOMEOSTASIS: THE USE OF URINARY MINERAL EXCRETION IN PRE-TERM NEONATES

Giapros VI, Papaloukas AL, Andronikou SK. **Urinary mineral excretion in pre-term neonates during the first month of life.** *Neonatology*. 2007;91(3):180-185.

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A prospective, longitudinal, hospital-based study by Giapros and associates evaluated the variability in and modifiers of renal excretion of calcium and phosphate in formula-fed pre-term infants during the first month of life. A total of 34 healthy infants <32 weeks gestational age were evaluated during 3 time periods (at 7 to 10, 14 to 17, and 21 to 26 days of life). Fractional excretion of phosphorus (FEP) and urinary calcium to urinary creatinine ratio (UCa/UCr) were evaluated. The median 24-hour calcium excretion values at the 3 different time intervals were 0.027, 0.030, and 0.031 mmol/kg, respectively; the median 24-hour phosphorus excretion values were 0.26, 0.29, and 0.41 mmol/kg,

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respectively. Calcium and phosphorus intake was significantly lower during the second week of life (2.25 mmol/kg/d and 1.32 mmol/kg/d, respectively) than during the following 2 time periods (4.1 mmol/kg/d and 4.3 mmol/kg/d, respectively, for calcium; 2.56 mmol/kg/d and 2.72 mmol/kg/d, respectively, for phosphorus). Serum calcium remained stable, whereas serum phosphorus increased progressively during the 3 time periods. By contrast, UCa/UCr and FEP remained stable during the 3 periods.

This study demonstrated that renal excretion of calcium and phosphorus in formula-fed pre-term infants is stable during the first month of life. Renal maturation and increased mineral bone deposition may lead to higher mineral deposition, balancing the higher intake during the third and fourth weeks of life so that the renal excretion remains unchanged. Low calcium and high phosphorus excretion has been described as the pattern of formula-fed pre-term infants. This is the result of a relative imbalance in the calcium to phosphorus ratio in the formula. Indeed, a low calcium absorption rate in contrast to a high phosphorus absorption rate leads to an excess of phosphorus for mineral and nitrogen deposition.

These results suggest that careful monitoring of urinary mineral excretion allows for individualized supplementation, with the goal of being able to maintain calcium and phosphorus urinary concentrations >1.2 and >0.4 mmol/L, respectively, as previously described by Trotter and coworkers.¹ We would like to emphasize that during the first weeks of life, the imbalance between calcium and phosphorus supplies could be the result of fetal phosphate deficiency, as seen in severe growth retardation with placental insufficiency and reduced 1,25-(OH)₂ vitamin D production, or the effect of inadequate parenteral mineral balance associated with mineral solubility.

References

1. Trotter A, Pohlandt F. [Calcium and Phosphorus retention in extremely preterm infants supplemented individually](#). *Acta Paediatr.* 2002;91(6):680-683.

IS WHOLE BODY DEXA THE GOLDEN STANDARD OF MBD EVALUATION?

Pieltain C, De Curtis M, Gérard P, Rigo J. **Weight gain composition in pre-term infants with dual energy X-ray absorptiometry**. *Pediatr Res.* 2001;49(1):120-124.

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Pieltain and coworkers investigated whole body composition using DEXA in 54 healthy pre-term infants (birth weight <1750 g) who were fed fortified human milk ($n=20$) or pre-term formula ($n=34$). Measurements were obtained when full enteral feeding was attained and then again 3 weeks later, at around the time of discharge. The authors recorded bone mineral content (BMC) and bone area (BA).

BMC and BA were similar in the 2 groups at the initial measurement (19.5 ± 3.1 g vs 18.0 ± 3.5 g for BMC and 157 ± 17 cm² vs 153 ± 18 cm² for BA in fortified human milk-fed and formula-fed infants, respectively). BMC and BA increased at the time of the second measurement and were significantly higher in formula-fed than in fortified human milk-fed infants (31.3 ± 5.4 g vs 28.0 ± 3.5 g for BMC [$P<.05$] and 225 ± 22 cm² vs 210 ± 15 cm² for BA [$P<.05$]). Formula-fed infants showed a greater BMC gain (289 ± 99 mg/kg/d vs 214 ± 64 mg/kg/d [$P<.05$]) and a greater increase in BA (1.6 ± 0.4 cm²/kg/d vs 1.3 ± 0.3 cm²/kg/d [$P <.05$]) compared with the fortified human milk group.

A power analysis for the minimal detectable changes in mineral metabolism parameters over time according to the variance of the population (within groups of 20 infants) and the minimal detectable changes according to the dietary intervention (between 2 groups of 20

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infants) was performed at the 5% level of significance and 80% power. The power analysis suggested that minimal increases of 3.1 g in BMC and of 13.9 cm²; in BA between the 2 measurement points are needed to be detectable in a longitudinal study that includes 20 infants. These values represent the mean weekly increase observed in the current study.

In order to achieve significance in 2 groups of 20 infants following 3 weeks of evaluation, dietary intervention must achieve minimal differences of 4.1 g in BMC and 17.1 cm²; in BA, representing approximately 1 SD of the value obtained at the second evaluation. With respect to mineral gain and bone growth, the minimal differences required to reach significance are 76 mg·kg⁻¹·d⁻¹ for BMC and 0.32 cm²·kg⁻¹·d⁻¹ for BA, also representing 1 SD of the mean difference between the mineral gain and bone growth. Comparing the 2 measurements to fetal references, there was a significant change in BMC (–1.9 SD in both groups) and in BMC related to BA (–2.1 SD in the fortified human milk–fed group vs –2.4 SD in the formula–fed group), confirming the insufficient postnatal mineral supply and retention in orally fed pre-term infants.

In order to estimate the relative development of osteopenia, bone mineral density index (BMDI), calculated as BMC (mg)/BA(cm²)^{1.71}, was evaluated. BMDI represents a density index independent of anthropometric parameters in the fetal reference data obtained at birth in pre-term and term infants. Thus, BMDI decreased similarly during the study, from 3.4 ± 0.3 to 3.0 ± 0.2 in fortified human milk–fed infants and from 3.3 ± 0.3 to 3.0 ± 0.3 in formula-fed infants. At the end of the study, no fractures were observed, but osteopenia (defined as –2 SD of the fetal reference value) was detected in almost 30% of the VLBW infants.

In conclusion, whole body DEXA is a useful technique for evaluating mineral metabolism parameters in pre-term infants. The sensitivity for detecting significant within-group differences in a longitudinal study and between groups in a parallel study appears to be relatively high, allowing for risk determination of MBD and evaluation of the potential benefit of preventive nutritional strategies in pre-term infants during the first weeks of life. However, because of the low threshold level for bone detection, the BMC measurement does not represent bone mineral mass exclusively, and therefore cannot be directly converted to calcium content and accretion.

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At the conclusion of this activity, participants should be able to:

- Describe the physiologic changes occurring at birth that influence bone growth and metabolism in pre-term and term infants
- Identify the various risk factors influencing the development of metabolic bone disease in VLBW infants
- Discuss the biologic markers and use of the various investigative tests for monitoring at-risk infants

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- **Edward E. Lawson, MD** has indicated a financial relationship of grant/research support from the National Institute of Health (NIH). He also receives financial/material support from Nature Publishing Group as the Editor of the *Journal of Perinatology*.

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- **Christoph U. Lehmann, MD** has received grant support from the Agency for Healthcare Research and Quality and the Thomas Wilson Sanitarium of Children of Baltimore City.
- **Lawrence M. Noguee, MD** has received grant support from the NIH.
- **Mary Terhaar, DNSc, RN** has indicated no financial relationship with commercial supporters.

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