Daily Physical Activity Program Increases Bone Mineralization and Growth in Preterm Very Low Birth Weight Infants

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ABSTRACT. *Objective.* **A study of daily physical activity was performed with 32 preterm infants to evaluate changes in body weight and bone mineralization.**

Study Design. **Subjects were matched by birth weight and gestational age and randomly assigned to the physical activity (PA; $n = 16$) or to the control (C; $n = 16$) program. PA consisted of range of motion against passive resistance to all extremities for 5 to 10 minutes daily. Peripheral dual-energy x-ray of the right forearm (ulna and radius); biomarkers of bone formation (serum type I collagen C-terminal propeptide [PICP]) and resorption (urine pyridinoline cross-links of collagen [Pyd]); serum calcium, phosphate, alkaline phosphatase, parathyroid hormone (PTH), and 1,25-$(OH)_2$ vitamin D; and urine levels of calcium, phosphate, and creatinine were obtained. All measurements were made at study entry and at 2.0 kg of body weight.**

Results. **Despite a similar nutrient intake at advised levels for preterm infants, gains in body weight (g) and forearm bone length (cm), bone area (BA; cm^2), bone mineral content (BMC; mg), and fat-free mass (g) were greater in PA infants. Forearm bone mineral density and fat mass gains did not differ between groups. Serum PICP levels remained constant in PA infants but decreased in C infants suggesting a slower rate of bone formation. Urine Pyd or bone resorption activity was similar between groups. A higher level of serum PTH was observed in PA infants at 2.0 kg of body weight; however, the change from study entry to completion did not differ between groups. All other serum and urine values were similar and within normal limits.**

Conclusion. **A daily PA program promotes greater gains in body weight, forearm length, BA, BMC, and fat-free mass in premature infants.** *Pediatrics* **2000;106: 1088–1092;** ***bone mineralization, physical activity, preterm infants.***

ABBREVIATIONS. PA, physical activity; VLBW, very low birth weight; DEXA, dual energy x-ray absorptiometry; pDEXA, peripheral dual energy x-ray absorptiometry; C, control; PICP, serum type I collagen C-terminal propeptide; PTH, parathyroid hormone; Pyd, urine pyridinoline cross-links of collagen; BMC, bone mineral content; BA, bone area; BMD, bone mineral density; SD, standard deviation; ANCOVA, analysis of covariance; SPA, single photon absorptiometry.

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Infants born prematurely are at risk of developing osteopenia of prematurity and rickets because of limited accretion of bone mass in utero, a greater need for bone nutrients than in infants delivered at term, and decreased ex utero calcium retention.[1–6] Provision of bone-related nutrients at advised levels increase bone mineralization; however, ex utero mineralization rates do not equal in utero mineralization rates despite normal body weight gain.[1,3] Bone mineralization in preterm infants does not approach normal ranges until after the first year of life[7] and may continue to be inadequate into childhood, further increasing the risk of fracture.[8]

Mechanical loading on bones and joints stimulates bone formation and growth.[9] Osteoblasts, the cells responsible for bone formation, increase activity in response to mechanical loading in vitro.[10] Mechanical loading or weight-bearing activity increases bone mass in children, young adults, and older individuals.[11–13] Absence of mechanical loading, as seen in spaceflight and bedridden adults, increases bone resorption and hypercalcuria and decreases bone mass.[14] Standard care of hospitalized, preterm infants includes swaddling or nesting and decreased sensory and physical stimulation.[15] Thus, hospitalized, preterm infants experience limited physical activity (PA), which may increase bone resorption and demineralization. We have previously shown a positive effect on radius bone mineralization by single photon absorptiometry in preterm, very low birth weight (VLBW; ≤1500 g) infants who received daily physical activity.[16] Dual energy x-ray absorptiometry (DEXA), a more precise and accurate method, has been used successfully for total body and site-specific bone measurements in older children and adults. Validation of the use of DEXA in infants with low body weight supports its use in neonatal populations.[5,6] Recently, a portable DEXA (pDEXA) with the ability to measure peripheral sites has become available for clinical use. Therefore, the purpose of this prospective, randomized trial was to evaluate the effect of daily PA on weight gain and bone mass using pDEXA in preterm VLBW infants.

METHODS

Study Design

Subjects consisted of healthy, preterm infants recruited from the newborn intensive care unit at the University Hospital (Salt Lake City, UT). Infants were eligible for study under the following criteria: birth weight 800 to 1600 g; gestational age range 26 to 32 weeks; appropriate body size; tolerating enteral feedings at ≥110

kcal/kg of body weight/day; absence of medications other than appropriate vitamin supplements; and informed parental consent. Subjects were removed from study for incomplete data because of illness, hospital discharge, or transfer to another medical facility. This study was approved by the institutional review board of the University of Utah.

Subjects were stratified by birth weight and gestational age and randomly assigned to the PA or control (C) group. The stratification levels were 800 to 1200 g and 26 to 29 weeks and 1201 to 1600 g and 30 to 32 weeks. Randomization was accomplished by selecting envelopes containing group codes. PA infants received daily range of motion exercises with gentle compression and extension/flexion against the infant's passive resistance to both upper and lower extremities. Five repetitions of each movement were performed at the wrist, elbow, shoulder, ankle, knee, and hip. Because tactile stimulation might have influenced growth and development, control subjects had a daily interactive period of holding and stroking but no range of motion activity. Both activity protocols were administered by the same, trained occupational therapist. The activity protocols were initiated when the subject was tolerating enteral feeding at ≥110 kcal/kg of body weight/day and continued until a body weight of 2.0 kg (± 150 g). Subjects were fed human milk with powdered fortification (Human Milk Fortifier, Mead Johnson Nutritional, Evansville, IN) or preterm infant formula (Enfamil Premature Formula®, Mead Johnson Nutritional, Evansville, IN) at an equal caloric density of 24 kcal/oz.

Data collected at study entry included birth weight, length, head circumference, gestation or weeks premature, gender, medial history before study, and type of feeding. Measurements taken at study entry included length and head circumference; serum type I collagen C-terminal propeptide (PICP), calcium, phosphorus, alkaline phosphatase, intact parathyroid hormone (PTH), and 1,25-$(OH)_2$ vitamin D; urine pyridinoline cross-links of collagen (Pyd), calcium, phosphorus and creatinine; and DEXA of the right forearm (ulna and radius) using pDEXA (Norland Medical Systems, Fort Atkinson, WI). Infants were placed in a prone position with the right arm extended palm down at 45 degrees. The forearm was stabilized with Velcro straps at the wrist and elbow. The ulna and radius bone or forearm scan encompassed the entire length of the 2 bones. Forearm bone length was determined by measurement of the radius bone from the distal to proximal endplates and was recorded in millimeters. Quality control scans were performed daily on a manufacturer-supplied phantom. The day-to-day variation for bone mineral content (BMC), bone area (BA), and bone mineral density (BMD) measurements were <.6% for the pDEXA scanner. The coefficient of variation for repeated and repositioned measurements performed on term infants for BMC, BA, and BMD was <1.5% for pDEXA in our laboratory. All pDEXA measurements were performed by a certified technician who was unaware of the infants' group assignment. Body weight (g), intake and output, and study interventions were recorded daily. NEONOVA (Ross Laboratories, Columbus, OH) was used to analyze dietary intakes. Data collected at study completion consisted of anthropometric measurements, forearm pDEXA, and serum and urine measures of bone mineral status.

The projected number of subjects needed was calculated by selecting a power of .80 and a 1-tailed significance of .05. The projected difference in BMC during the study period was 13 mg/cm and the projected standard deviation (SD) for BMC was 10 mg/cm.[16] Sample size was estimated to be 16 subjects in the PA and C groups for a total of 32 subjects. Descriptive statistics, independent *t* test, analysis of covariance (ANCOVA), and correlations and linear regressions were used to examine data from baseline to study completion. Because body weight has been shown to influence bone mass, birth weight and body weight at study entry and completion were treated as covariants. Enteral feeding source (fortified human milk or preterm formula) was treated as a cofactor because of potential differences in fat and calcium and absorption.[17] Ad hoc comparison of growth rate and nutrient intake during 4 phases (birth to study entry, study entry to 1.5 kg, 1.5–1.8 kg, and 1.8–2.0 kg) was performed to decide whether weight gain was the result of PA or other factors, such as catch-up growth in response to weight loss or growth delays before study entry. Because of multiple analyses of the data, the Holm procedure was used to eliminate error from multiple comparisons.[18] Data were analyzed using *SPSS-PC+* (SPSS, Inc, Chicago, IL).

RESULTS

Thirty-two infants were enrolled for study after obtaining informed parental consent with 16 infants assigned to each group. Gestational age, birth weight, length, head circumference, gender distribution, ethnicity, and adjusted age were similar at study entry. The number of study days was similar between groups. Type of feeding and mean energy, protein, calcium, phosphorus, and vitamin D intake did not differ before study entry or during the study and met recommended needs for preterm infants (Table 1).[3,19]

Body weight, length, and head circumference are presented in Table 2. Mean values for body weight, length, or head circumference at study entry or completion did not differ between groups. The rate of change for length and head circumference was similar and showed an overall positive trend. We again found that despite equal energy and nutrient intake,

TABLE 1. Subject Characteristics and Nutrient Intake During Study

	PA (n = 16)	C (n = 16)
Gestation (wk)	29.6 (1.6)	29.8 (1.5)
Birth weight (g)	1258 (230)	1283 (199)
Length (cm)	37.3 (2.5)	37.6 (2.3)
Head circumference (cm)	26.8 (1.8)	26.7 (2.0)
Gender	7 M/9 F	10 M/6 F
Ethnicity	11 white, 2 Asian, 2 biracial, 1 Hispanic	12 white, 2 biracial, 2 Hispanic
Adjusted age at study entry (wk)	31.9 (1.5)	31.9 (1.1)
Days on study	26.8 (9.6)	23.8 (8.0)
Feeding	8 fortified human milk/8 preterm formula	9 fortified human milk/7 preterm formula
Energy (kcal/kg/d)		
Birth to study entry	78.0 (11.0)	82.0 (13.0)
Entry to 1.5 kg	113.0 (10.9)	115.4 (7.4)
1.5–1.8 kg	113.0 (8.7)	123.2 (7.4)
1.8–2.0 kg	113.8 (6.7)	117.4 (5.3)
Study entry to 2.0 kg	115.3 (11.5)	119.3 (10.1)
Protein (g/kg/d)	3.3 (.3)	3.5 (.3)
Calcium (mg/kg/d)	167 (17)	174 (18)
Phosphorus (mg/kg/d)	84 (7.2)	88 (7.1)
Magnesium (mg/kg/d)	6.2 (.4)	6.4 (.4)
Vitamin D (IU/d)	312 (14)	323 (24)

Mean (SD).

TABLE 2. Anthropometric Changes During Study

	PA	C	*P* Value
Body weight (g)			
Entry	1294 (231)	1340 (145)	NS
2.0 kg	1989 (83)	1988 (43)	NS
Gain (g/kg/d)			
Birth to study entry	5.0 (5.1)	4.9 (5.3)	NS
Entry to 1.5 kg	15.9 (3.5)	14.9 (5.0)	NS
1.5–1.8 kg	16.2 (3.4)	15.7 (2.8)	NS
1.8–2.0 kg	22.3 (6.8)	14.7 (4.8)	.04 (MANCOVA)
Entry to 2.0 kg	16.3 (2.6)	14.6 (2.0)	.02 (ANCOVA)
Length (cm)			
Entry	38.5 (2.7)	40.3 (2.0)	NS
2.0 kg	44.2 (1.5)	43.5 (1.6)	NS
Gain (cm/wk)	1.4 (.5)	1.0 (.5)	NS
Head circumference (cm)			
Entry	28.6 (1.8)	28.2 (2.2)	NS
2.0 kg	32.4 (1.4)	32.1 (.9)	NS
Gain (cm/wk)	1.0 (.4)	1.1 (.4)	NS

Mean (SD).
NS indicates not significant; MANCOVA, multivariate analysis of variance.

PA infants had a greater increase in average daily weight from study entry to 2.0 kg, compared with C infants (16.3 ± 2.6 vs 64.6 ± 2.0 g/kg of body weight/day; PA vs C; $P < .02$, ANCOVA). Growth rates were similar from birth to study entry and from study entry to 1.8 kg. While C infants maintained a steady growth rate from study entry to 2.0 kg, PA infants had a significant increase from 1.8 to 2.0 kg ($P = .04$, multivariate analysis of variance; Table 2). Energy and nutrient intakes from birth to study entry and from study entry to 2.0 kg did not differ between groups (Table 1).

Table 3 provides the forearm (ulna and radius) measurements at study entry and 2.0 kg of body weight. Mean values of the forearm at study entry did not differ between groups. However, PA infants had greater forearm length, BA, and BMC at 2.0 kg ($P \leq .05$, *t* test) and significant gains over time for forearm length ($P = .03$), BA ($P = .02$), BMC, and fat-free mass ($P = .05$, all ANCOVA). Feeding source, ie, fortified human milk or preterm formula, was found to be a significant cofactor for the change in BMD over time ($P = .05$, ANCOVA). Fat mass gains were similar between groups.

TABLE 3. Forearm Bone and Body Mass Change During Study

	PA ($n = 16$)	C ($n = 16$)	*P* Value
Length (cm)			
Entry	33.4 (2.0)	32.2 (2.2)	NS
2.0 kg	37.2 (1.6)	35.3 (1.4)	.05 (*t* test)
Gain	4.0 (2.2)	3.1 (1.5)	.02 (ANCOVA)
BA (cm^2)			
Entry	6.4 (1.1)	6.2 (1.4)	NS
2.0 kg	8.6 (1.3)	7.4 (1.4)	.01 (*t* test)
Gain	2.0 (1.4)	1.0 (1.2)	.02 (ANCOVA)
BMC (mg)			
Entry	519 (148)	529 (156)	NS
2.0 kg	763 (145)	660 (185)	.05
Gain	231 (136)	131 (159)	.05 (ANCOVA)
BMD (mg/cm^2)			
Entry	8.2 (.8)	8.6 (.8)	NS
2.0 kg	8.8 (.1)	9.0 (.4)	NS
Gain	.7 (.1)	.4 (.1)	.05 (ANCOVA)*
Lean mass (g)			
Entry	12.8 (3.5)	12.5 (2.8)	NS
2.0 kg	18.1 (3.3)	17.4 (2.9)	NS
Gain	5.3 (2.9)	4.9 (3.2)	.04 (ANCOVA)
Fat mass (g)			
Entry	4.7 (2.6)	4.7 (2.4)	NS
2.0 kg	9.3 (3.8)	8.0 (3.0)	NS
Gain	5.0 (2.7)	3.6 (3.6)	NS

NS indicates not significant.
* Significant for feeding—preterm formula > fortified human milk.

Biochemical findings are provided in Table 4. Serum collections were complete at study entry and 2.0 kg for 27 infants (PA = 15; C = 12) and for urine measurements in 23 infants (PA = 11; C = 12). No differences were found for serum or urine values at study entry. At study completion, serum PICP levels had decreased in C infants but remained constant in PA infants. The change in PICP values over time was significant: −94 ng/mL for C infants versus −5 ng/mL in PA infants (Table 5; $P = .03$, ANCOVA). Serum PTH levels were greater in PA infants at 2.0 kg ($P = .03$, *t* test); however, the change from study entry to 2.0 kg for PTH levels did not differ statistically and were within normal range. Urine Pyd levels did not change significantly in either group, suggesting a constant rate of bone resorption. All other serum and urine values were within normal limits for preterm infants at baseline and completion of study.

DISCUSSION

This is the first longitudinal, randomized study to describe the effect of daily PA on bone and body mass using the DEXA technique in preterm, hospitalized infants.

Previous longitudinal studies using single photon absorptiometry (SPA) of the distal radius confirmed the need for higher intakes of dietary calcium, phosphorus, and vitamin D to improve bone mineralization in preterm, hospitalized infants.[23–26] We have also used SPA to assess bone mineralization in preterm infants and found a greater response when a daily physical activity program was provided in addition to an adequate intake of bone nutrients.[16] The

TABLE 4. Serum and Urine Markers of Bone Activity

	PA	C	Normal Range	*P* Value
Serum	$n = 15$	$n = 12$		
Alkaline phosphatase (U/L)				
Entry	69.7 (26.2)	81.6 (23.4)	50–120[20]	NS
2.0 kg	61.8 (19.6)	57.5 (22.5)		NS
1,25-$(OH)_2$ vitamin D (pg/mL)				
Entry	19.8 (1.5)	18.8 (2.0)	16–65[20]	NS
2.0 kg	19.4 (2.5)	20.5 (3.3)		NS
PTH (pg/mL)				
Entry	24.6 (15.5)	24.5 (25.6)	10–50[20]	NS
2.0 kg	28.3 (17.3)	16.4 (11.8)		.03 (*t* test) NS (ANCOVA)
PICP (ng/dL)				
Entry	998 (122)	895 (270)	1041–1354[21]	NS
2.0 kg	1002 (161)	861 (273)		.03 (ANCOVA)
Urine	$n = 11$	$n = 12$		
Calcium:creatinine (mg/dL:mM)				
Baseline	.29 (.26)	.32 (.19)	≥.20[22]	NS
2.0 kg	.32 (.22)	.43 (.30)		NS
Phosphorus:creatinine (mg/dL:mM)				
Baseline	.41 (.25)	.37 (.21)	≥.30[22]	NS
2.0 kg	.60 (.51)	.41 (.33)		NS
Pyd (nM/mM creatinine)				
Baseline	491 (253)	517 (238)	430–1033[23]	NS
2.0 kg	517 (238)	605 (397)		NS

Mean (SD).
NS indicates not significant.

use of pDEXA in this study allowed the bedside evaluation of a daily PA program on site-specific bone mineralization in preterm infants.

The results support our previous findings[16] that daily PA enhances bone growth and development in preterm VLBW infants. Although all bone mass indices increased for both groups, PA infants had much greater gains in forearm length, BA, BMC, and fat-free mass. Bone growth and development is a dynamic process initiated by an increase in bone surface area or matrix and completed by the binding of calcium salts into hydroxyapatite, which fill in or mineralize the bone matrix. Once the bone matrix is formed, an additional 10 days is required for mineralization.[27] Therefore, one would expect to see an increase in BA before an increase in BMC or BMD during periods of rapid growth. We suggest that PA maintains bone growth and development, while routine care, which limits movement, slows the rate of bone formation in preterm VLBW infants. The rise in PTH activity in PA infants may have contributed to bone growth and mineralization because PTH levels increase after PA in adults[28] and PTH administration has been noted to stimulate bone formation.[29] Our data support the positive effect of a daily PA program on forearm bone growth and mineralization.

Infants in this study were fed an energy and nutrient intake at recommended levels[3] and similar to our previous work.[16] As in the previous study, a greater rate of weight gain during the study, despite similar energy and nutrient intakes between groups, was an unexpected finding. Initial weight loss after birth and the rate of weight gain from birth to study entry and from study entry to 1.8 kg did not differ between groups. The similar growth rate between PA and C infants from study entry to 1.8 kg decreases the likelihood that outside factors, ie, catch-up growth, were influencing weight gain. Weight gain was accelerated in PA infants from 1.8 to 2.0 kg, although energy and nutrient intakes did not diminish or differ between groups. Further work that examines the interaction of PA and growth hormones and mediators and their effect on growth in preterm infants may provide answers to this unexpected outcome.

The American Academy of Pediatrics[19] has stated that the nutritional goal for preterm infants is to provide optimal nutrition to support growth equivalent to in utero gain during the third trimester. Nutritional intervention, while promoting adequate weight gain, has variable effect on postnatal bone mineralization in preterm infants. Multiple factors influence bone growth and development including diet and PA. Although we have shown the positive effects of PA on bone mineralization in preterm infants, a PA program may not be appropriate for infants with poor nutrient intake. Recently, Specker et al[30] reported on the effects of a 1-year PA program on BMC in older infants and found that BMC is related to calcium intake. Infants randomized to activity or control with moderately high calcium intakes had similar BMC, but low calcium intakes in infants in the activity program resulted in lower BMC. The authors speculate that participation in a PA program during rapid bone growth may lead to reduced bone accretion in the presence of a low calcium intake. Thus, caution should be used before starting a PA program in infants with a limited nutrient intake, ie, preterm infants fed unfortified breast milk or standard infant formula or infants with chronic illness or medication use that interferes with delivery of advised bone nutrients.

We have successfully shown in 2 studies, 1 using SPA[16] and the present work using pDEXA, that a daily PA program increases bone mass indices when preterm infants receive daily PA in addition to recommended levels of energy and nutrients. Although the pDEXA technique allows convenient bedside as-

sessment of forearm bone mass, further study to decide whether the pDEXA technique can reliably predict total body bone mass in preterm infants needs to be peformed. We conclude that a daily activity program for healthy preterm infants promotes increased forearm length and BA.

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BASIC HISTORY TEST STUMPS MANY COLLEGIANS

Nearly 80% of seniors at 55 top colleges and universities, including Harvard and Princeton, received a D or an F on a 34-question high school level test on American history.

More than a third of the students did not know that the Constitution established the division of power in American government, said the Center for Survey Research and Analysis at the University of Connecticut, which administered the test as part of a study to measure the teaching of American history.

Students were much more knowledgeable about popular culture—99% of the seniors tested identified "Beavis and Butthead" as "television cartoon characters."

New York Times. June 27, 2000