

# Bone Density and Metabolism in Children and Adolescents With Moderate to Severe Cerebral Palsy

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**ABSTRACT.** *Objectives.* Diminished bone density and a propensity to fracture with minimal trauma are common in children and adolescents with moderate to severe cerebral palsy (CP). The purpose of this study was to provide a detailed evaluation of bone mineral density (BMD) and metabolism in this population and to assess the relationship of these measures to multiple other clinical, growth, and nutrition variables.

*Methods.* The study group consisted of 117 subjects ages 2 to 19 years (mean: 9.7 years) with moderate to severe CP as defined by the Gross Motor Functional Classification scale. Population-based sampling was used to recruit 62 of the participants, which allows for estimations of prevalence. The remaining 55 subjects were a convenience sampling from both hospital- and school-based sources. The evaluation included measures of BMD, a detailed anthropometric assessment of growth and nutritional status, medical and surgical history, the Child Health Status Questionnaire, and multiple serum analyses. BMD was measured in the distal femur, a site specifically developed for use in this contracted population, and the lumbar spine. BMD measures were converted to age and gender normalized z scores based on our own previously published control series ( $n > 250$ ).

*Results.* Osteopenia (BMD z score  $< -2.0$ ) was found in the femur of 77% of the population-based cohort and in 97% of all study participants who were unable to stand and were older than 9 years. BMD was not as low in the lumbar spine (population-based cohort mean  $\pm$  standard error z score:  $-1.8 \pm 0.1$ ) as in the distal femur (mean z score:  $-3.1 \pm 0.2$ ). Fractures had occurred in 26% of the children who were older than 10 years. Multiple clinical and nutritional variables correlated with BMD z scores, but interpretation of these findings is complicated by covariance among variables. In stepwise regression analyses, it was found that severity of neurologic impairment as graded by Gross Motor Functional Classification level, increasing difficulty feeding the child, use of anticonvulsants, and lower triceps skinfold z scores (in decreasing order of importance) all independently contribute to lower BMD z scores in the femur.

*Conclusions.* Low BMD is prevalent in children with moderate to severe CP and is associated with significant fracture risk. The underlying pathophysiology is complex, with multiple factors contributing to the problem and significant variation between different regions of the skeleton. *Pediatrics* 2002;110(1). URL: <http://www.pediatrics.org/cgi/content/full/110/1/e5>; cerebral palsy, bone mineral density, osteoporosis, pediatrics, bone metabolism, growth, nutrition, osteopenia.

ABBREVIATIONS. CP, cerebral palsy; 25-OHD, 25-hydroxy vitamin D; NAGCePP, North American Growth in Cerebral Palsy Project; GMFC, Gross Motor Functional Classification scale; UNC, University of North Carolina; CHOP, Children's Hospital of Philadelphia; DXA, dual-energy x-ray absorptiometry; BMD, bone mineral density; SE, standard error.

Fractures are common in individuals with moderate to severe cerebral palsy (CP), and many of those who sustain a fracture will sustain repeated fractures.<sup>1-3</sup> Low bone density, stiff joints, poor balance leading to falls, and violent seizures are factors that can contribute to fractures in this population. The most common site of fracture is the femur. In reported series of nonambulatory children and young adults, nearly 20% had sustained a femur fracture at some time in their life.<sup>4,5</sup> Usually these fractures are treated nonoperatively, but hospitalization may be required<sup>6</sup> and malunion of the fracture is common.<sup>7</sup> Repeated fractures diminish the quality of life for these children and add to their care requirements. It has been reported that the single most costly medical problem in a residential school for severely involved children is treatment of fractures.<sup>8</sup>

Multiple factors may adversely affect bone density and metabolism in individuals with CP. Clearly, limited weight-bearing ambulation during skeletal growth is 1 such factor. Another mechanical factor is the temporary immobilization that follows the orthopedic surgical procedures often performed on a child with CP. Hip spica casting of children with CP has been associated with increased risk of subsequent fracture,<sup>1,4,9</sup> and even normal children who had an uncomplicated fracture of the lower limb that was treated with  $>4$  weeks of casting have a small, persistent deficit in bone density.<sup>10</sup>

Oral-motor dysfunction increases feeding difficulty for many individuals with CP.<sup>11,12</sup> Poor nutrition and low calcium intake are common in this population<sup>13,14</sup> and may contribute to poor mineral-

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ization. Many children with CP take or have taken anticonvulsant medications, which some authors suggest may adversely affect bone mineralization.<sup>15,16</sup> CP is often associated with premature birth, which in turn may be associated with metabolic bone disease, the “rickets of prematurity.”<sup>17</sup> It has been found that low birth weight premature infants have lower than normal bone mineral content when evaluated as older children.<sup>18</sup> Outdoor activities may be significantly diminished in physically impaired individuals, which could be of consequence to bone metabolism given that seasonal sunlight exposure is an important determinate of serum 25-hydroxy vitamin D (25-OHD) levels in children with CP.<sup>19</sup> Understanding the pathophysiology of skeletal mineralization in CP is difficult given the heterogeneity of the condition and the multitude of potentially important factors.

The purpose of this study was to further our understanding of bone density and metabolism in children and adolescents with CP. The most “at risk” subset of the population has been previously identified as children with little or no ability to ambulate.<sup>14</sup> This study focuses on this group, including a population-based cohort necessary to determine true prevalences. Bone density is assessed in the clinically relevant distal femurs, and bone metabolism is evaluated with various serum markers. The multiple factors such as malnutrition, inadequate vitamin D levels, and use of anticonvulsants that may potentially have an impact on bone density and metabolism in these children closely covary. This study provides greater statistical power than previous studies to discern the relative importance of these factors.

## METHODS

The North American Growth in Cerebral Palsy Project (NAGCePP) is a multicenter (6 sites), cross-sectional, observational study of growth and nutrition in population-based samples of children and adolescents with CP. The project is described in detail elsewhere.<sup>20</sup> Briefly, an intense effort was made to identify and evaluate all children with moderate to severe CP within defined geographic regions. Hospital records, newspaper notices, pediatric physical therapists, handicap equipment vendors, special education teachers in the local school systems, and regional United Cerebral Palsy newsletters are examples of the means by which potentially eligible children were identified.

Inclusion criteria were age 2.0 to 18.9 years and moderate to severe CP as defined by functional levels 3, 4, or 5 on the Gross Motor Functional Classification (GMFC) scale.<sup>21</sup> Simply summarized, GMFC level 3 children achieve independent sitting and by 4 years of age are ambulatory with assistive mobility devices and/or aid from an adult. GMFC level 4 children are minimally ambulatory, even with assistance, and have some difficulty with sitting trunk control. GMFC level 5 children lack independent motor function even for basic antigravity postural control.

Excluded were children with recognized chromosomal abnormalities and children who were normal until a specific event or injury that occurred after 12 months of age resulted in their impairment. The core data collected at all NAGCePP study sites included a detailed anthropometric assessment, developmental assessment, GMFC assessment, complete medical and surgical history, and the Children’s Health Status Questionnaire.<sup>22</sup> The Children’s Health Status Questionnaire is an established tool for the assessment of health-related quality of life, including the child’s physical health, parental perception of the child’s overall health, and the impact of the child’s health on the family.

Given the close proximity, investigators at the University of North Carolina (UNC; Chapel Hill) and Duke University

(Durham) collaborated as a single site in the NAGCePP, with all of the evaluations completed at UNC. At the UNC/Duke site and the Children’s Hospital of Philadelphia (CHOP) site, the NAGCePP evaluation was expanded to include an assessment of bone density and metabolism. The results of this additional evaluation are the focus of this article.

## Population-Based Study Participants

Sixty-five eligible children and adolescents were identified and contacted by telephone in the 3-county area of the UNC/Duke site, from a total population of 219 000 who were younger than 18 years. Forty-three (66%) of these 65 children and adolescents consented to the core evaluation of the NAGCePP. Thirty-nine of the 43 NAGCePP participants agreed to the additional dual-energy x-ray absorptiometry (DXA) evaluation described below and had at least 1 reliable measure of bone density. Similarly, 47 eligible children and adolescents were identified from a population of 688 000 who were younger than 18 years within the defined geographic region used by the CHOP site. Thirty-seven (79%) of these 47 potential subjects participated in the NAGCePP, including 23 who agreed to the additional DXA evaluation and had a reliable assessment of bone density.

## Convenience Sampling Participants

At the UNC/Duke site, an additional 55 children and adolescents underwent the entire NAGCePP evaluation, including the additional DXA evaluation. This was a convenience sampling of otherwise eligible children who lived outside the defined geographic region. These children were located and recruited from multiple sources, including the pediatric orthopaedic clinics ( $n = 27$ ), nonorthopedic tertiary care clinics ( $n = 12$ ), and special education centers ( $n = 16$ ). Therefore, the study group reported herein consists of 117 children and adolescents with moderate to severe CP, including 62 population-based participants (39 at the UNC/Duke site, 23 at the CHOP site) plus 55 additional subjects from a convenience sampling. The median age was 9.4 years (range: 2.0–19.0 years). There were 71 boys, 76 whites, 37 blacks, and 4 of mixed or other ethnic backgrounds. Informed consent approved by the institutional review board at each site was obtained for all study participants.

## Bone Density Measurements

Bone mineral density (BMD) in the lumbar spine, proximal femurs, and distal femurs was measured with DXA. Standard scanning procedures were used for the lumbar spine and proximal femurs. Motion artifact, previous hip or scoliosis surgery, or contractures usually precluded reliable assessment of BMD in the proximal femurs and occasionally in the lumbar spine. BMD was reliably measured in 1 or both proximal femurs of just 16 (14%) of the 117 study participants and in the lumbar spine of 98 participants (84%).

The technique for assessing BMD of the distal femur projected in the lateral plane has been previously described in detail.<sup>23,24</sup> This technique was developed specifically to deal with the significant hip and knee contractures that are common in this population and interfere with measurements in the standard proximal femur site. Three separate regions within the distal femur are examined independently. Region 1 is located within the metaphysis just proximal to the growth plate. Region 3 is the distal portion of the femoral diaphysis, and region 2 is the region of transition between the broad metaphysis (region 1) and narrow femoral shaft (region 3). These regions were defined such that region 1 is predominately cancellous bone and region 3 is predominately cortical bone. As with scans of the lumbar spine and proximal femurs and despite repeated attempts, motion artifact secondary to limited cooperation or involuntary muscle spasms made it impossible to obtain acceptable quality scans of the distal femur on all subjects. BMD was successfully measured in at least 1 distal femur for 78 (67%) of the 117 study participants.

A Hologic (Waltham, MA) model 1000W scanner was used at the UNC/Duke site, and model 2000 was used in the pencil-beam mode at the CHOP site. Exchange of each site’s calibration spine phantom confirmed the reliability of pooling results from the 2 scanners. BMD measurements ( $\text{g}/\text{cm}^2$ ) were converted to age- and gender-normalized standard deviation scores ( $z$  scores) using our own series of normal pediatric controls ( $n = 365$  for lumbar spine

and proximal femur,  $n = 256$  for distal femur<sup>23,25</sup>). BMD measures in the lumbar spine were also normalized for race, but it is important to note that the distal femur normal series did not include sufficient numbers of black children to control for race. The mean BMD of paired right- and left-sided measurements was used when converting to z scores.

### Anthropometric Assessment

An anthropometrist who was trained and tested for reliability as part of the broader NAGCePP completed this portion of the evaluation, which focuses on growth and nutritional status of the children and is described in greater detail elsewhere.<sup>20</sup> Weight in light clothing was measured on a digital scale. Contractures, scoliosis, and inability to stand erect make it impossible to obtain a reliable measure of standing height in these children. Alternative measures of linear growth were obtained, including upper arm length, tibial length, and sitting knee height. For the analyses, knee height was converted to an estimate of standing height,<sup>26,27</sup> which in turn was expressed as an age- and gender-normalized height z score.<sup>28</sup> Body fat was assessed with measures of calf, triceps, and subscapular skinfolds on the child's right side. For the analyses, nutritional status defined as adequacy of caloric intake was assessed based on age- and gender-normalized z scores for triceps skinfold measures.<sup>29</sup> Upper arm, calf, and head circumferences were measured, and Tanner stage was determined.

### Anticonvulsant Medication

Use of anticonvulsant medications was graded as never ( $n = 32$ ), only in the past ( $n = 31$ ), or ongoing ( $n = 54$ ). Children who were categorized as having taken anticonvulsants only in the past received the medication for at least 6 months but none for at least 1 year before the evaluation. It is likely that the various anticonvulsant medications all do not have the same potential impact on bone metabolism.<sup>30</sup> Nonetheless, statistical power was not sufficient to categorize this variable more elaborately.

### Temporary Immobilization

Periods of immobilization, usually for orthopedic surgical procedures, were categorized as none ( $n = 58$ ), brief ( $n = 17$ ), or prolonged ( $n = 42$ ). Children in the "none" group had not had on the lower limbs surgical procedures requiring postoperative casting but may have had brief periods of inhibitory casting to improve motion that did not diminish the child's usual weightbearing activities. Brief immobilization was considered as casting above or below the knee for a maximum of 6 weeks postoperatively. Prolonged immobilization was a cumulative total of >6 weeks of casting or any time in a hip-spica cast (a cast that includes the torso and lower limbs).

### Feeding Difficulty

The care provider reported difficulty feeding the child as a result of oral-motor dysfunction on a categorical scale developed for this population<sup>31</sup> as none ( $n = 48$ ), mild ( $n = 17$ ), moderate ( $n = 11$ ), or severe ( $n = 41$ ). The scale is based on whether the child has no problems with a regular diet (none category); has slight difficulty swallowing or feeding and requires some modification of foods (mild category); has moderate feeding difficulties, some difficulty swallowing liquids and requires moistened, mashed, or chopped foods (moderate category); or has a diet limited to well-moistened solid foods, thickened fluids, and/or tube feedings (severe category).

### Calcium Intake

Dietary calcium intake was readily determined in children who received some ( $n = 10$ ) or all ( $n = 23$ ) of their caloric intake through feeding tubes, because the volumes and calcium content of prepared formulas and supplements are known. Calcium intake from normal foods was estimated using a calcium-focused food frequency questionnaire.<sup>32</sup> Determination of dietary calcium intake also included specific calcium supplements if regularly given to the child ( $n = 9$ ). Total calcium intake from all sources was categorized as <500  $\mu\text{g}/\text{d}$  ( $n = 7$ ), 500 to 1000  $\mu\text{g}/\text{d}$  ( $n = 46$ ), and >1000  $\mu\text{g}/\text{d}$  ( $n = 64$ ).

### Serum Analyses

A peripheral nonfasting venous blood sample was obtained for analysis of multiple factors relating to nutrition or bone metabolism. The hospital laboratory at the respective institutions determined serum levels of calcium, phosphate, alkaline phosphatase, total protein, albumin, and transthyretin (prealbumin). Serum 25-OHD was measured in the Research Laboratories at the UNC Department of Orthopaedics using an equilibrium radioimmunoassay (DiaSorin, Stillwater, MN).

Even in skeletally mature individuals, bone is continuously in a state of flux, with both bone formation and bone resorption occurring simultaneously. Osteocalcin and bone-specific alkaline phosphatase, synthesized by osteoblasts during the process of bone formation, are released into the blood. Serum levels of these proteins can serve as useful markers of bone formation.<sup>33,34</sup> Similarly, N-terminal telopeptides are breakdown products of collagen resulting from osteoclast-mediated resorption of the extracellular matrix of bone, and are a marker of bone resorption.<sup>35</sup> These markers of bone formation and resorption were measured in the UNC Orthopaedic Research Laboratories. Bone-specific alkaline phosphatase was measured using the Alkphase B immunoassay (Metra Biosystems Inc, Mountain View, CA). Osteocalcin was measured with an immunoradiometric assay (Elsa-Osteo; CIS-US Inc, Bedford, MA). Serum N-telopeptides were measured with the Osteomark serum NTx immunoassay (Ostex Inc, Seattle, WA).

A blood sample was obtained from 80 (68%) of the 117 study participants, with the remainder declining or unattainable. The quantity of serum available in 13 of the 80 samples was inadequate for the full series of analyses.

### Statistical Analyses

The population-based and convenience sampling cohorts significantly differ in several ways (Table 1). The convenience sample includes a higher proportion of more severely involved children as judged by multiple factors, including GMFC level, nutritional status (triceps skinfold z score), and feeding difficulty. Therefore, only the population-based cohort is used for determinations of prevalence.

For the assessment of the relationship between the analysis variables and BMD z scores, it is valid to include all children. In the first phase of these analyses, each of the key variables is independently examined for a relationship with BMD z scores at each of the 3 distal femur sites and the lumbar spine (Table 2). The proximal femur site was not included in the analyses because of the very limited number of children ( $n = 16$ ) for whom data were obtainable.

It is expected that many of the key variables will closely covary, and this may have a significant impact on the apparent relationship between BMD z scores and the variable in question. For example, use of anticonvulsant medications is likely to be more prevalent in children with greater motor impairment (GMFC level 5) than in children with less severe CP (GMFC level 3). Covariance is important to consider when assessing the potential direct impact of these factors on BMD. Therefore, in the second phase of the analyses, multifactorial stepwise regression is used to assess the relationship between BMD z scores and the multiple clinical and nutritional factors that may adversely affect BMD.

## RESULTS

BMD was severely diminished in the distal femur (mean  $\pm$  standard error [SE] lowest of the 3 regions BMD z score:  $-3.5 \pm 0.2$ ) and to a lesser extent in the lumbar spine (mean BMD z score:  $-2.0 \pm 0.1$ ). Consistent with low BMD, fractures were common. Despite the young age of the study group (mean age: 9.7 years), 18 of the children (15%) had already sustained a fracture, and 7 of these children had had more than 1 fracture. In the subset of nonambulatory children (GMFC levels 4 and 5) who were older than 10 years, fractures were even more common (11 [28%] of 40). A total of 28 fractures were reported, with the femur (13 fractures) and tibia (4 fractures)

**TABLE 1.** Comparison of Population-Based and Convenience Cohorts

	Population Based	Convenience Sample	<i>P</i> Value*
Demographic variables			
Age (y)			
Mean ± SE	9.7 + 0.6	9.6 + 0.6	≥.2
Range	2.0–19.0	2.1–18.2	
Gender (male:female)			
<i>n</i>	36:26	35:20	≥.2
%	58%:42%	64%:36%	
Race (white:black:other)			
<i>n</i>	41:21:0	35:16:4	≥.2
%	66%:34%:0%	64%:29%:7%	
Clinical variables			
GMFC level (levels 3:4:5)			
<i>n</i>	16:17:29	2:10:43	.0005
%	26%:27%:47%	4%:18%:78%	
Anticonvulsants (never:past only:current)			
<i>n</i>	20:17:25	12:14:29	≥.2
%	32%:27%:40%	22%:25%:53%	
Fracture (no:yes)			
<i>n</i>	55:7	44:11	≥.2
%	89%:11%	80%:20%	
Lower limb or scoliosis surgery (no:yes)			
<i>n</i>	29:33	28:27	≥.2
%	47%:53%	51%:49%	
CHQ z score (mean ± SE)	−0.9 + 0.2	−0.8 + 0.2	≥.2
Nutrition variables			
Feeding difficulty (no:mild:mod:severe)			
<i>n</i>	33:8:5:16	15:9:6:25	.04
%	53%:13%:8%:26%	27%:16%:11%:45%	
Triceps skinfold z score (mean ± SE)	−0.4 + 0.1	−0.9 + 0.2	.04
Tube feedings ever (no:yes)			
<i>n</i>	29:33	25:30	≥.2
%	47%:53%	45%:55%	
Serum transthyretin level (mean ± SE)	22.6 + 0.9	21.3 + 0.8	≥.2
Growth variables			
Height z score (mean ± SE)	−2.5 + 0.2	−3.3 + 0.3	.01
Weight z score (mean ± SE)	−1.8 + 0.3	−3.5 + 0.4	.002
Bone density variables			
Distal femur z scores			
Region 1 (mean ± SE)	−2.6 + 0.2	−3.6 + 0.2	.001
Region 2 (mean ± SE)	−2.8 + 0.2	−3.8 + 0.2	.003
Region 3 (mean ± SE)	−2.6 + 0.2	−3.7 + 0.3	.001
Lumbar spine z score (mean ± SE)	−1.8 + 0.1	−2.3 + 0.1	.006

\* Statistical comparison between the population-based and convenience cohorts.

being the most common sites of injury. There were no known spinal compression fractures.

Multiple factors were examined in univariate analyses for a relationship to BMD z scores at each of the measurement sites. The findings are summarized below and in Table 2. BMD z scores in the 3 regions of the distal femur correlated highly with each other ( $r = 0.84$ – $0.94$ ) and showed very similar relationships to the other analysis variables. (Table 2 reports the findings for region 2 of the distal femur.) Lumbar spine BMD z scores correlated only weakly with BMD z scores in the 3 regions of the distal femur ( $r = 0.51$ – $0.55$ ). As shown in Table 2, differences were also observed between distal femur and lumbar spine BMD z scores in their relationships with the other analysis variables.

### General Demographics

There was a relationship between advancing age and declining BMD z scores at all 3 distal femur sites, but not the lumbar spine (Table 2, Fig 1). In the population-based cohort the prevalence of osteopenia ( $z$  score:  $< -2.0$ ) in the distal femur was 86% in

children older than 9 years (19 of 22 children). Two of the 3 exceptions were children who were capable of assisted ambulation (GMFC level 3).

Distal femur BMD z scores, which were normalized for age and gender but not for race were higher in the black children than in the white children (Table 2). With lumbar spine BMD measures, however, it was possible to normalize for race as well as age and gender, and no racial difference was observed (Table 2).

### Neurologic Impairment and Other Clinical Factors

BMD z scores at all sites correlated strongly with the GMFC level (Table 2, Fig 2). Forty-five (96%) of 47 GMFC level 5 children had osteopenia ( $z$  score  $< -2.0$ ) in the distal femur, as compared with 6 (43%) of 14 GMFC level 3 children. Other clinical variables, including use of anticonvulsants and whether the child had ever had a fracture, correlated with BMD z scores in the distal femur, but none of the other clinical variables besides GMFC level correlated with lumbar spine BMD z scores (Table 2).

**TABLE 2.** Bone Density z Scores: Univariate Analyses

	N	Mean BMD z Score $\pm$ SE	
		Distal Femur Region 2	Lumbar Spine
Demographic variables			
Age			
2.0–5.9 y	31	$-2.9 \pm 0.4$	$-2.5 \pm 0.2$
6.0–11.9 y	50	$-3.0 \pm 0.2$	$-1.8 \pm 0.1$
12.0–19.0 y	36	$-3.7 \pm 0.3$	$-2.0 \pm 0.2$
		$P = .01$	$P \geq .2$
Gender			
Boys	71	$-3.1 \pm 0.2$	$-2.1 \pm 0.1$
Girls	46	$-3.6 \pm 0.3$	$-1.9 \pm 0.2$
		$P = .1$	$P \geq .2$
Race			
White/other	80	$-3.5 \pm 0.2$	$-2.0 \pm 0.1$
Black	37	$-2.7 \pm 0.2$	$-2.1 \pm 0.2$
		$P = .01$	$P \geq 0.2$
Clinical variables			
GMFC level			
Level 3	18	$-1.8 \pm 0.3$	$-1.5 \pm 0.2$
Level 4	27	$-3.1 \pm 0.3$	$-1.9 \pm 0.2$
Level 5	72	$-3.8 \pm 0.2$	$-2.2 \pm 0.1$
		$P < .0001$	$P = .03$
Anticonvulsants			
Never	32	$-2.5 \pm 0.3$	$-2.1 \pm 0.2$
Past only	31	$-3.0 \pm 0.3$	$-1.8 \pm 0.1$
Current	54	$-3.8 \pm 0.2$	$-2.2 \pm 0.2$
		$P < .003$	$P \geq .2$
Fracture			
No	99	$-3.1 \pm 0.2$	$-2.0 \pm 0.1$
Yes	18	$-3.9 \pm 0.4$	$-2.2 \pm 0.4$
		$P = .06$	$P \geq .2$
Temporary immobilization			
Never	58	$-3.1 \pm 0.3$	$-2.2 \pm 0.1$
Brief	17	$-3.8 \pm 0.4$	$-1.7 \pm 0.4$
Prolonged	42	$-3.2 \pm 0.2$	$-2.0 \pm 0.2$
		$P \geq .2$	$P \geq .2$
Children's Health Status Questionnaire z score			
$> -1.0$	54	$-2.9 \pm 0.2$	$-1.9 \pm 0.1$
$-1.0$ to $-2.0$	24	$-3.1 \pm 0.4$	$-2.4 \pm 0.2$
$< -2.0$	31	$-3.7 \pm 0.3$	$-2.1 \pm 0.3$
		$P \geq .2$	$P = .09$
Nutrition variables			
Triceps skinfold z score			
$> 0$	31	$-3.0 \pm 0.3$	$-1.6 \pm 0.2$
0 to $-1.0$	32	$-3.4 \pm 0.3$	$-2.1 \pm 0.2$
$-1.0$ to $-2.0$	46	$-3.3 \pm 0.3$	$-2.3 \pm 0.2$
$< -2.0$	8	$-3.5 \pm 0.5$	$-1.9 \pm 0.3$
		$P \geq .2$	$P = .003$
Feeding problems			
None	48	$-2.6 \pm 0.3$	$-1.7 \pm 0.1$
Mild	17	$-2.9 \pm 0.3$	$-2.2 \pm 0.3$
Moderate	11	$-4.4 \pm 0.8$	$-2.3 \pm 0.3$
Severe	41	$-3.9 \pm 0.2$	$-2.3 \pm 0.2$
		$P = .0003$	$P = .02$
Currently tube fed			
No	84	$-2.9 \pm 0.2$	$-2.0 \pm 0.1$
Yes	33	$-4.0 \pm 0.3$	$-2.3 \pm 0.2$
		$P = .001$	$P \geq .2$
Calcium intake			
Adequate ( $>1000$ )	64	$-3.2 \pm 0.2$	$-1.9 \pm 0.1$
Marginal (500–1000)	46	$-3.3 \pm 0.3$	$-2.1 \pm 0.2$
Low ( $<500$ mg/d)	7	$-3.4 \pm 0.5$	$-2.7 \pm 0.4$
		$P \geq .2$	$P \geq .2$
Serum transthyretin			
Normal ( $>18$ mg/dL)	51	$-3.4 \pm 0.3$	$-2.0 \pm 0.1$
Marginal (16–18 mg/dL)	7	$-3.6 \pm 0.6$	$-2.9 \pm 0.3$
Low ( $<16$ mg/dL)	5	$-3.4 \pm 0.5$	$-2.9 \pm 0.7$
		$P \geq .2$	$P = .02$

TABLE 2. Continued

	N	Mean BMD z Score $\pm$ SE	
		Distal Femur Region 2	Lumbar Spine
Growth variables			
Height z score (based on sitting knee height)			
> -1.0	15	-2.5 $\pm$ 0.3	-1.9 $\pm$ 0.4
-1.0 to -2.0	25	-2.8 $\pm$ 0.4	-1.8 $\pm$ 0.2
< -2.0	77	-3.6 $\pm$ 0.2	-2.2 $\pm$ 0.1
		$P = .0003$	$P \geq .2$
Weight z score			
> -1.0	31	-2.5 $\pm$ 0.3	-1.4 $\pm$ 0.2
-1.0 to -2.0	27	-3.0 $\pm$ 0.2	-2.2 $\pm$ 0.2
< -2.0	59	-3.9 $\pm$ 0.2	-2.3 $\pm$ 0.1
		$P < .0001$	$P = .0001$
Arm circumference z score			
> 0	36	-2.6 $\pm$ 0.3	-1.3 $\pm$ 0.1
0 to -1.0	22	-3.0 $\pm$ 0.4	-2.2 $\pm$ 0.3
-1.0 to -2.0	28	-3.2 $\pm$ 0.3	-2.2 $\pm$ 0.2
< -2.0	31	-4.4 $\pm$ 0.3	-2.6 $\pm$ 0.1
		$P < .0001$	$P < .0001$
Other serum variables			
25 OHD			
Adequate (>20 ng/mL)	36	-3.5 $\pm$ 0.3	-2.2 $\pm$ 0.2
Marginal (15–20 ng/mL)	27	-3.4 $\pm$ 0.3	-2.2 $\pm$ 0.2
Low (<15 ng/mL)	13	-3.2 $\pm$ 0.4	-2.2 $\pm$ 0.3
		$P \geq .2$	$P \geq .2$
N-telopeptides (bone resorption marker)			
Low tertile (<41 nm/L)	24	-3.5 $\pm$ 0.4	-1.8 $\pm$ 0.2
Mid tertile (41–57 nm/L)	23	-3.3 $\pm$ 0.4	-2.2 $\pm$ 0.2
High tertile (>57 nm/L)	24	-3.1 $\pm$ 0.3	-2.2 $\pm$ 0.3
		$P \geq .2$	$P \geq .2$
Osteocalcin (bone formation marker)			
Low tertile (<38 ng/mL)	25	-3.9 $\pm$ 0.5	-2.4 $\pm$ 0.2
Mid tertile (38–59 ng/mL)	25	-3.3 $\pm$ 0.3	-2.2 $\pm$ 0.2
High tertile (>59 ng/mL)	26	-3.3 $\pm$ 0.3	-1.9 $\pm$ 0.3
		$P \geq .2$	$P \geq .2$
Abnormal phosphorous, calcium, or alkaline phosphatase			
No	62	-3.3 $\pm$ 0.2	-2.2 $\pm$ 0.1
Yes	13	-4.0 $\pm$ 0.6	-2.2 $\pm$ 0.3
		$P \geq .2$	$P \geq .2$

### Nutritional Status and Related Variables

Poor nutritional status defined as triceps skinfold z scores < -1.0 is prevalent in children with moderate to severe CP, involving 23 (37%) of 62 children in the population-based cohort and 58% of the children in the convenience sample. Both triceps skinfold z scores and serum transthyretin level correlated with BMD z scores in the lumbar spine but not with BMD z scores in the distal femur (Table 2, Fig 3). A particularly strong predictor of BMD z scores in both the distal femur and the lumbar spine was difficulty feeding the child as reported by the caregivers (Table 2, Fig 4). Use of a feeding tube was associated with lower BMD z scores in the distal femur but not in the lumbar spine. The remaining feeding- and nutrition-related variables, including previous use of a feeding tube and calcium intake, did not correlate with BMD z scores (Table 2).

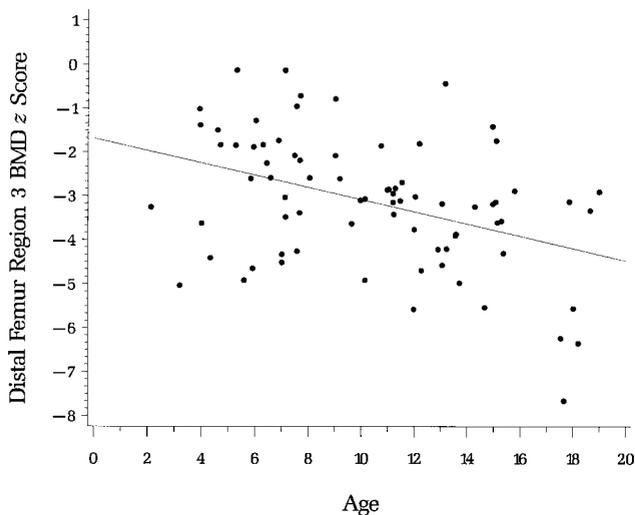
### Growth

Measures of growth including height, weight, and mid-arm circumference were significantly dimin-

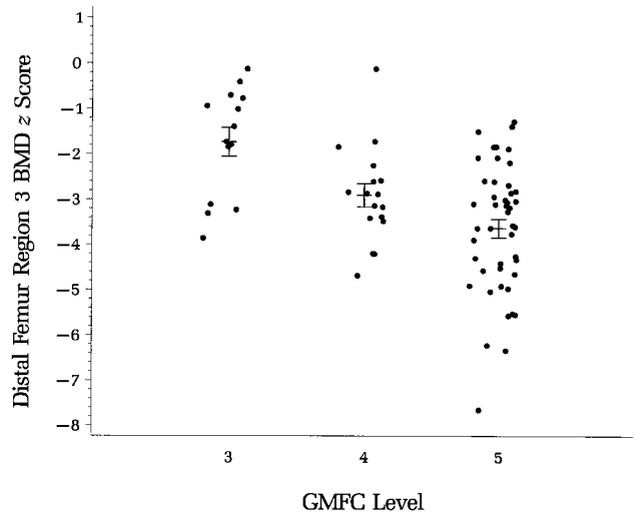
ished relative to age- and gender-matched normal children, with mean ( $\pm$ SE) z scores of  $-2.9 \pm 0.2$ ,  $-2.6 \pm 0.3$ , and  $-0.9 \pm 0.1$ , respectively. These measures of growth correlated strongly with BMD z scores, with the exception of height and lumbar spine BMD z scores (Table 2).

### Serum Vitamin D and Bone Metabolism Markers

In normal children, both dietary intake and sunlight exposure are important sources of 25-OHD, which is the precursor for the more tightly regulated, metabolically active 1,25-dihydroxy metabolite of vitamin D. Many of the children were found to have serum 25-OHD levels <17 ng/mL (25 [33%] of 75). The mean ( $\pm$ SE) 25-OHD level in samples obtained during the colder months of November to February ( $19.3 \pm 1.1$  ng/mL) was not lower than that found in children who were evaluated in June through September ( $20.3 \pm 0.8$  ng/mL). The finding of low levels of 25-OHD throughout the year suggests limited sunlight exposure in these physically impaired chil-



**Fig 1.** BMD z scores in region 3 of the distal femur as a function of age (years). Best fit linear regression line shown.



**Fig 2.** BMD z scores in region 3 of the distal femur as a function of severity of CP as defined by the GMFC scale. Mean  $\pm$  SE bars shown.

dren. However, serum 25-OHD levels were not found to correlate with BMD z scores (Table 2).

Serum markers of bone formation (osteocalcin and bone-specific alkaline phosphatase) and bone resorption (N-telopeptides) ranged widely and correlated with each other ( $r = 0.3\text{--}0.6$ ; Fig 5). This suggests considerable variation in rates of bone turnover. However, there was not a significant correlation between any of these markers and BMD z scores (Table 2).

#### Routine Serum Analyses

Routine hospital laboratory tests were not of value in identifying children with low BMD. Serum calcium level was low ( $<8.8 \mu\text{g/dL}$ ) in only 4 (5%) of 75 children, and 3 of those had serum albumin levels  $<3.5 \mu\text{g/dL}$ . Alkaline phosphatase level was elevated in 4 children. Thirteen children (17%) had an abnormal serum calcium, phosphorus, or alkaline phosphatase; only 1 child had 2 of these outside the normal range. Mean BMD z scores were not significantly lower in these 13 children than in the children with normal values for these routine laboratory tests (Table 2).

#### Multifactorial Analyses

All of the clinical and nutritional variables listed in Table 2 were examined for their relationship to BMD z scores in age- and race-adjusted multifactorial stepwise regression analyses. This approach examines the relationship between each variable and BMD z scores while accounting for covariance with the other variables in the analyses. Severity of neurologic impairment (GMFC level), increasing difficulty feeding the child, use of anticonvulsant medications, and lower triceps skinfold z scores (in decreasing order of importance) all independently contribute to lower BMD z scores in the distal femur. Results were very similar in all 3 regions of the distal femur but differed somewhat with lumbar spine BMD z scores in which just GMFC level and triceps skinfold z scores

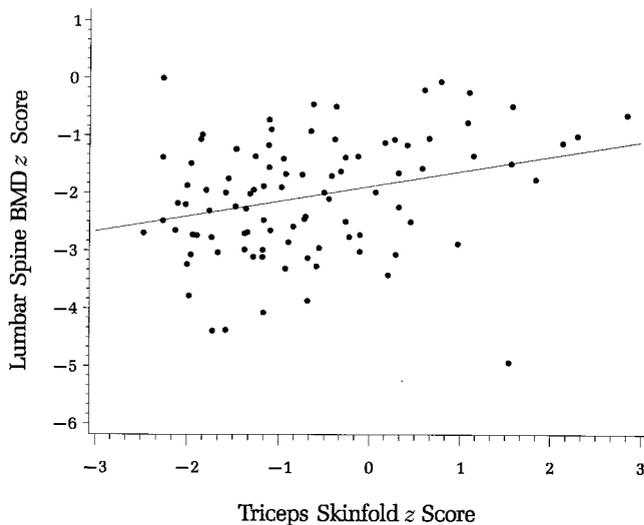
were found to contribute independently to lower BMD z scores.

#### DISCUSSION

Several studies have examined bone density in CP.<sup>36–39</sup> The largest reported series included 139 children and adolescents with CP of wide ranging severity and used DXA to measure bone density.<sup>14</sup> It was found that the quadriplegic subset ( $n = 37$ ), those with diminished mobility and often poor nutritional status, were at greatest risk of having low BMD. It is important to note that BMD assessment in this subset of subjects was usually limited to just the lumbar spine because hip flexion contractures and/or previous hip surgery prevented reliable measures of BMD in the proximal femurs. As discussed in the following paragraph, this proves to be an important limitation of that study.

Whether measures of BMD in the lumbar spine are predictive of fracture risk has been assessed prospectively in a cohort of 43 children with spastic quadriplegic CP.<sup>1</sup> Nine fractures occurred over an observation period that averaged 4 years, and 60% of these injuries involved the femur. Ten (23%) of the 43 children had sustained a fracture at some time in their life. A history of hip spica casting or a previous fracture was found to be predictive of subsequent fracture risk, but BMD of the lumbar spine was not predictive. This seems counterintuitive but is likely explained by the finding in our current study that BMD is much lower in the distal femur (mean z score:  $-3.5 \pm 0.2$ ) than in the lumbar spine (mean z score:  $-2.0 \pm 0.1$ ), and the correlation between BMD in the 2 areas is weak.

In children with quadriplegic CP, a problem exists because BMD usually cannot be measured reliably in the proximal femurs, yet it is the femur that most commonly fractures, and measurement of BMD in the lumbar spine is an unreliable indicator of bone status in the femurs. For addressing this problem, a technique was developed using DXA to obtain measures of BMD in the distal femur projected in the

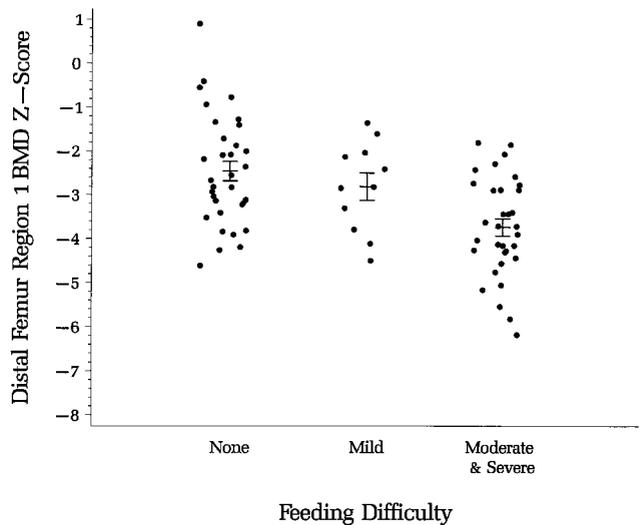


**Fig 3.** BMD z scores in the lumbar spine as a function of nutritional status as defined by triceps skinfold z score. Best fit linear regression line shown.

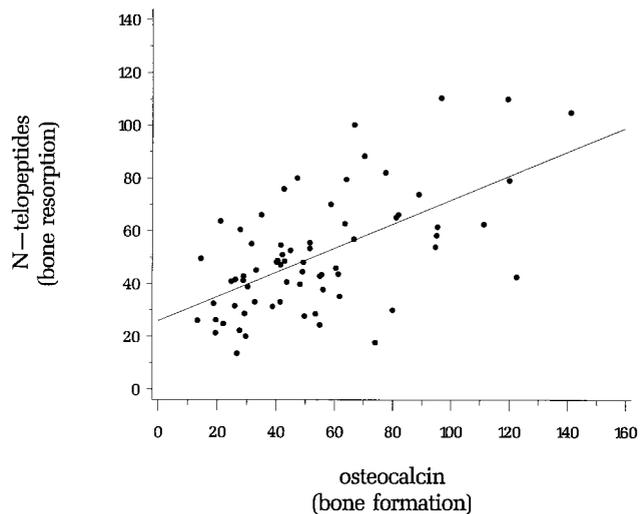
lateral plane.<sup>23,24</sup> This approach to the assessment of bone density is a critical feature of the current study. Unfortunately, it was not possible to obtain an acceptable quality DXA scan of the distal femur because of motion in one third of the study group. Subsequent to this study, however, we found that acceptable quality scans of the distal femur can be obtained without sedation in roughly 90% of these children using the newer model fan-beam DXA scanners that have shorter scan times.

It is important to note that BMD as measured with DXA is an areal density ( $\text{gm}/\text{cm}^2$ ) and not a true volumetric density ( $\text{gm}/\text{cm}^3$ ). Areal bone density may be diminished relative to age-matched normal subjects because of a true decrease in volumetric density or because of differences in the 3-dimensional structure of the bone.<sup>40,41</sup> A diminished outer diameter and thinning of the cortex both will result in diminished areal BMD as measured with DXA, regardless of whether true volumetric density is diminished. The diameter of a cylindrical bone and the thickness of the cortex, however, are important mechanical parameters that have a significant impact on the ability of a bone to withstand loads without fracture. Radiographs of children with quadriplegic CP typically do show the bone to be smaller than normal and the cortex to be thin. Clearly, the diminished bone “density” measured in this study involves more than just a decrease in true volumetric density. However, these other factors that affect areal density also directly relate to mechanical strength and fracture risk, which is the clinically relevant reason for assessing bone “density.”

An observational study such as this identifies only those factors associated with low BMD, not necessarily the causes of low BMD. It is clear that BMD in the femur, like other measures of various growth parameters such as height, weight, and arm circumference, falls further from normal standards as the child with CP ages.<sup>42,43</sup> Diminished growth in CP is a complex issue, with both nutritional and nonnutritional fac-



**Fig 4.** BMD z scores in the distal femur (region 1) as a function of the caregiver’s reported difficulty feeding the child. Mean  $\pm$  SE bars shown.



**Fig 5.** Serum markers of bone resorption (N-telopeptides in nmoles bone collagen equivalents/L) versus bone formation (osteocalcin in  $\text{ng}/\text{mL}$ ). Best fit linear regression line shown.

tors likely contributing.<sup>44–46</sup> Difficulty feeding the child, skinfold measures of body fat, and use of anticonvulsant medications were some of the factors identified in multifactorial regression analyses as likely to be directly related to low BMD.

Another important correlate of low BMD in children with CP is their GMFC level of motor impairment. It is widely thought that absence of weight-bearing is an important direct cause of low BMD in physically impaired children. However, evidence is accumulating that the cause is much more complex. In this study, it was found that BMD z scores were significantly lower in GMFC level 5 children than in level 4 children, yet both groups are nonambulatory. Furthermore, it has been found in boys with Duchenne muscular dystrophy that BMD in the femurs is already very dramatically diminished years before the boys become nonambulatory.<sup>47</sup> It seems that multiple factors intrinsic to the conditions of CP,

muscular dystrophy, and perhaps other conditions contribute to low BMD at least as much as simple inability to bear weight.

It is interesting to note in both CP and muscular dystrophy that BMD is diminished much more in the femurs than in the spine. Consistent with this, fractures in children with these conditions usually involve the limbs, particularly the femur, and virtually never occur in the spine.<sup>2,3,47</sup> In this study, it was found that BMD z scores in the lumbar spine and distal femur were not identically related to the other factors. For example, use of anticonvulsants did correlate with BMD z scores in the distal femur but not in the lumbar spine. Clearly, the pathophysiology of low BMD varies in different regions of the immature skeleton.

Identifying a clinical problem always raises the issue of treatment, and effective interventions may be available to address low BMD in this population. On the basis of small series of children with CP, it has been suggested that physical therapy<sup>38</sup> and calcium/vitamin D supplementation<sup>36</sup> may be beneficial for BMD. It has been shown that nutritional interventions can improve other aspects of growth in children with CP.<sup>48</sup> Perhaps the most promising intervention is with the bisphosphonate medications, which are widely used to treat osteoporosis in the elderly. Lumbar spine BMD increased a mean of 42% per year in an uncontrolled study of 30 children with osteogenesis imperfecta treated with bisphosphonates.<sup>49</sup> In a randomized, placebo-controlled trial, BMD in the distal femur increased a mean of 89% over 18 months in 6 children with quadriplegic CP treated with intravenous pamidronate, as compared with a 9% increase in the placebo group.<sup>50</sup>

### CONCLUSION

Osteopenia defined as BMD z scores  $< -2.0$  is found in the femur of most nonambulatory children with CP by 10 years of age. Fractures had occurred in more than one fourth of the severely involved children who were older than 10 years at the time of their evaluation. The clinical and nutritional factors that most directly correlated with low BMD were severity of impairment as graded by GMFC level, increasing difficulty feeding the child, use of anticonvulsants, and lower triceps skinfold z scores (in decreasing order of importance). The causes of and treatments for low BMD in children with disabilities certainly require additional investigation.

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