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Bone density and size in ambulatory children with cerebral palsy

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Abstract

AIM—To examine the relation of axial and appendicular bone properties in ambulatory children with cerebral palsy (CP) to functional (Gross Motor Function Classification System [GMFCS]) level.

METHOD—Quantitative computed tomography measurements were compared among 37 children with CP (12 children in GMFCS level I, five in level II, 18 in level III, two in level IV; five with hemiplegia, 23 with diplegia, two with triplegia, seven with quadriplegia; mean age 9y 4mo, SD 1y 6mo; 18 males, 19 females) and 37 children in a comparison group (same age and sex distributions). Linear regression was used to evaluate differences in volumetric cancellous bone density (vBMD) and geometric properties of the L3 vertebra and tibia, adjusting for height, weight, and sex as covariates.

RESULTS—The comparison group had larger vertebrae than the children with CP (p=0.02) owing to smaller vertebral size in GMFCS levels III and IV, but there was no difference in vertebral vBMD (p=0.49). In the tibia, bone volumetric density (p=0.09) and size (p=0.02) decreased with increasing GMFCS level. GMFCS level had a greater effect on bone size in females than in males (p<0.07).

INTERPRETATION—Children with CP of all levels may have less bone in their tibias, whereas spine deficits differentially affect more involved children. Because even small bone deficits may manifest as osteoporosis later in life, it is important to study bone acquisition in all children with CP.

Children with cerebral palsy (CP) have deficient bone growth and, consequently, an increased propensity for non-traumatic fractures.[1] However, most studies of bone in children with CP have been limited to individuals with moderate to severe involvement (Gross Motor Function Classification System [GMFCS] level III–V). These children have low bone mass in both the lumbar spine[2–4] and the lower extremities,[5,6] with the level of deficiency being related to ambulatory ability and severity of involvement.[4,7] The deficiencies in bone are associated with a high rate of fragility fractures.[2,8] Thus bone acquisition and fractures are clearly a problem for children with moderate to severe CP.

Much less is known about the bone health of higher-functioning children with CP. These children may also be at risk for deficient bone acquisition due to muscle weakness and mobility limitations. In recent years, bone acquisition has become an issue even for children and adolescents without disability owing to the increased awareness that insufficient bone

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accrual during childhood is likely a precursor to the early onset of osteoporosis later in life.[9] As care improves and the lifespan of persons with CP increases, identifying antecedents to adult diseases will become increasingly important.

The aim of this study was to examine axial and appendicular bone properties in ambulatory children with CP to determine the relation between bone properties and functional level. We hypothesized that even highly functional children with CP would have diminished bone size and density, and that the deficits would increase at higher GMFCS levels.

METHOD

This was a secondary analysis of data from previous studies by the investigators.[10–12] Two groups of participants were included: ambulatory children with CP and comparisons without disability. Demographic and anthropometric data were available for both groups, as well as quantitative computed tomography (QCT) measurements of the spine. The group with CP also had QCT measurements of the tibia, which were not available for the controls. Therefore vertebral properties were compared between the CP and comparison groups and among GMFCS levels, whereas properties of the tibia could only be compared among GMFCS levels.

Participants

The group with CP consisted of 37 children who had undergone screening for a clinical trial.[12] The data examined were the baseline data collected before any intervention was started. The participants were children with CP, aged 6 to 12 years, who were at least minimally ambulatory and able to stand for 10 minutes with or without handheld support (such as a walker). The distribution of GMFCS levels was 12 children (32%) in level I, five children (14%) in level II, 18 children (49%) in level III, and two children (5%) in level IV. The distribution of CP was five children with hemiplegia, 23 with diplegia, two with triplegia, and seven with quadriplegia. Exclusion criteria included surgery, casting, or botulinum toxin injection in the previous 12 months, metal rods or plates in the tibia or lumbar spine, scoliosis greater than 20° or bowing of the tibia, concomitant medical conditions affecting bone or muscle, and use of corticosteroids or seizure medication. The participants were recruited by calling current and past patients from the orthopedic clinics at a tertiary pediatric medical center. The clinical trial was approved by the Committee for Clinical Investigations at Childrens Hospital Los Angeles, and written informed assent and consent were obtained from the participants and their parents.

The comparison group consisted of children selected from previous studies on bone acquisition in healthy children.[10,11] The selection was performed by a computer program designed to select the subset of participants best matched to the children with CP in terms of sex and age. The children in the comparison group were healthy and free of any medical conditions that would affect growth or development. Potential participants were excluded if they had scoliosis greater than 20°; kyphosis greater than 40°; previous surgery with metal pins, rods, screws, or staples; non-removable body piercing in the chest or abdomen; medication that might affect growth, appetite, or bone accrual; conditions, such as old fractures, associated with abnormal bone size or shape; a history of recurrent long bone fractures; secondary amenorrhea; or current or previous pregnancy. Children were recruited using flyers distributed in the hospital, mailed to previous research participants, and distributed through schools and males' and females' clubs in the Los Angeles area. The original studies were approved by the Committee for Clinical Investigations at Childrens Hospital Los Angeles, and written informed assent and consent were obtained from the participants and their parents.

QCT measurements

All participants were assessed by QCT using the same scanner (General Electric LightSpeed QX/i, Milwaukee, WI, USA) and the same dipotassium hydrogen phosphate (K_2HPO_4) mineral reference phantom for simultaneous calibration (CT-T bone densitometry package; General Electric). All imaging was performed by the same certified radiology technologist. The time required to complete the QCT scans in individual patients was approximately 10 minutes. In the axial skeleton, identification of the site to be scanned was performed with a lateral scout view. A single 10mm slice was obtained at the midportion of the L3 vertebral body. Volumetric cancellous bone density (vBMD, in milligrams per cubic centimeter) and cross-sectional area (CSA, in square millimeters) were determined at this level. The coefficients of variation for repeated QCT measurements of vertebral density and CSA were 1 to 2%.[13,14]

In the tibia, sites to be scanned were located by physical examination. As it is sometimes difficult to align both limbs in the scanner simultaneously for children with CP, the right side was aligned for children with bilateral involvement and the affected side for children with unilateral involvement. Data from the aligned side were analyzed. Contiguous 1.25mm slices were obtained covering the proximal tibial metaphysis, and an additional 10mm slice at the midshaft of the tibia.[15] Mean vBMD of the entire metaphysis and vBMD in a single slice 1.25mm below the growth plate were determined.[15] CSA and cortical bone area were measured at the midshaft of the tibia. The coefficients of variation for bone measurements in the appendicular skeleton were 0.3 to 2.8%.[5,16]

Statistical analysis

In addition to reviewing summary statistics, the primary method of analysis was linear regression. The main grouping variables were diagnosis (CP or control), GMFCS level (I–II or III–IV), and severity (control, GMFCS I–II, or GMFCS III–IV). The GMFCS levels were grouped as I to II and III to IV owing to the small number of children in GMFCS levels II and IV. First, simple univariable analysis was performed. This was followed by multivariable analysis. Variables considered for entry into the multivariable model included sex, the interaction between sex and dichotomized severity, age, height, weight, body mass index, and their centiles for sex and age calculated using the Center for Disease Control and Prevention norms.[17] The final model was selected to maximize predictive ability (R^2) while maintaining a reasonable level of collinearity (condition number <30).

RESULTS

The children with CP were shorter and had a lower weight centile than the comparison group (Table I). Height, weight, and their respective centiles also decreased with increasing GMFCS level (Table I). Reflecting these differences, the strongest prediction of bone parameters was obtained by including height and weight in the regression model. Height and weight contributed more to the model than using their respective centiles. Sex further improved the model, but age did not (owing to its correlation with height and weight). Therefore the final multivariable regression model included height, weight, sex, and diagnosis, severity, or GMFCS level.

In the simple analysis, vertebral vBMD did not show a significant difference based on diagnosis (95% confidence interval [CI] for coefficient −18 to 3; p=0.15), GMFCS level (CI −22 to 2; p=0.10), or severity (CI −12 to 1; p=0.09; Table II). Vertebral CSA was similar between those in GMFCS level I to II and the comparison group, but lower for GMFCS level III to IV (95% CI for severity coefficient −105 to −40; p<0.001; Table II). All tibia

measures showed a strong decrease with increasing GMFCS level (CIs −56 to −2 and below; $p \leq 0.03$) (Table II).

Similar results were obtained from the multivariable regressions (Table III). There was no difference in vertebral vBMD based on diagnosis (95% CI for coefficient −15 to 7; $p=0.49$), GMFCS level (CI −20 to 19; $p=0.93$), or severity with the GMFCS I to II and comparison groups combined (CI −17 to 10; $p=0.62$). The comparison group had larger vertebrae (CI −81 to −9; $p=0.02$) than the children with CP, primarily because of smaller vertebral size in GMFCS levels III and IV (CI of coefficient for GMFCS III IV vs others −98 to −7; $p=0.02$).

In the tibia, geometric properties of the diaphysis decreased with increasing GMFCS level, even after adjustment for height, weight, and sex (CI −65 to 5 for CSA, $p=0.09$; −45 to −4 for cortical bone area, $p=0.02$). Volumetric density of the metaphysis also tended to decrease with increasing GMFCS level (CI −30 to 1 for entire metaphysis, $p=0.06$; −57 to 5 for slice, $p=0.09$).

For the size variables, a significant interaction was observed between sex and GMFCS level or severity (95% CIs of interaction coefficient −152 to 4 for L3 CSA, −120 to −8 for diaphysis CSA, −66 to 1 for diaphysis cortical bone area; $p<0.07$; Table IV). GMFCS level had a larger effect on bone size in females. No interaction was observed for the volumetric density variables (CIs −22 to 27 for L3 density, −21 to 31 for entire metaphysis, −59 to 48 for metaphysis slice; $p>0.70$).

DISCUSSION

This study is among the first to examine bone volumetric density and size in ambulatory children with CP, including higher-functioning children in GMFCS levels I and II. Deficits in the spine appear to be focused on smaller vertebral size in more involved children (GMFCS level III–IV). However, deficits in the tibia increase with GMFCS level, which suggests that even higher-functioning children may have reduced bone accrual in the lower extremities. Although children in GMFCS level I to II have less severe bone deficits than children in GMFCS level III to IV, research on non-disabled children suggests that even small deficits may manifest many years later as osteoporosis and increased fracture risk.[9] As children with CP live into adulthood and old age, it is increasingly important to identify risk factors for secondary conditions that may arise later in life.

The finding that female children have greater decreases in bone size at higher GMFCS levels may also be clinically important. It is well known that older females have a much higher risk of osteoporotic fractures than older males. Females in GMFCS levels III and IV may therefore develop an extremely high risk of osteoporosis and fractures as they age. Bone size is an important predictor of fracture risk and may, in fact, be a better indicator of fracture risk in children than volumetric bone density.[18] Smaller vertebral CSA results in higher stresses, increasing the likelihood of vertebral compression fractures.

One of the advantages of the current study is its use of QCT, a three-dimensional imaging technique. Most previous studies of bone in children CP have used dual energy X-ray absorptiometry (DXA) measurements. Because DXA is a two-dimensional projection technique, DXA areal bone mineral density is a composite measure reflecting both volumetric density and size, which can be assessed separately using QCT.[1,19] Two previous studies have used three-dimensional techniques to measure bone in children with CP. Using peripheral QCT, Binkley et al.[5] found that children with CP have smaller diaphyses and thinner cortices in the tibia, consistent with our findings. However, Tasdemir et al.,[4] using QCT, found lower volumetric bone mineral density of the lumbar vertebrae in children with CP. This result probably differs from ours because the previous study had more severely

involved patients, with 21% who could only crawl and 62% who were completely non-ambulatory. The QCT results from the current study indicate that the previously observed relation between DXA areal BMD in the spine and GMFCS level is caused by differences in vertebral CSA rather than differences in volumetric density. Therefore, if DXA is used to assess overall skeletal fragility in children with CP, it is inadvisable to apply adjustments aimed at removing the effects of bone size, such as calculations of apparent bone mineral density.

In terms of assessing skeletal fragility in children with CP, QCT may have the most potential at appendicular sites such as the tibia. Because the only difference in the spine was smaller CSA in GMFCS level III to IV, QCT of the lumbar spine does not appear to be particularly useful. Reduced vertebral dimensions can be determined from standard anterior posterior and lateral radiographs as well as DXA. Although we do not have DXA data on this cohort, it can be inferred from the QCT results that children in GMFCS levels III and IV would have lower DXA areal density values than children in GMFCS levels I and II at all of the sites measured. Values of DXA areal BMD in the lumbar spine would be expected to be similar between independent ambulators (GMFCS level I–II) and those in the comparison group.

Two limitations of this study are the small sample size, especially for GMFCS levels II and IV, and the lack of control data for the tibia. This necessitated the grouping of GMFCS level I to II and III to IV. Based on the existing data, we cannot conclusively determine whether differences exist between GMFCS levels I and II and whether bone in the tibia differs between these GMFCS levels and normal development. A larger prospective study is needed to answer these questions. Additional research is also needed to track bone development through young adulthood, when peak bone mass is normally achieved, and later adulthood when osteoporosis becomes common. In addition, because this study uses baseline data from children being screened for a clinical trial, the cohort in this study may not represent the full spectrum of children with CP. In fact, the group studied probably has better bone health than the general population with CP because factors negative to bone like anticonvulsants and recent surgery or casting were excluded.

Having identified deficient bone acquisition as an issue for children with CP, the question of how to address this problem arises. As with non-disabled children, the solution will likely involve a combination of improved nutrition and increased mechanical loading of the skeleton. For more functional children with CP, this may involve increased weight bearing and physical activity. For more involved children, limitations in ambulatory ability, feeding difficulties, and the use of medications detrimental to bone, such as anticonvulsants, may pose additional challenges. Research is needed to develop approaches for maximizing bone acquisition in children with CP. This may first be achieved in more functional children who have the smallest bone deficits and the greatest ability to increase skeletal loading.

What this paper adds

- Even highly functional children with cerebral palsy may have deficient bone acquisition in the tibia.
- Bone deficits in the spine primarily affect more involved children (Gross Motor Function Classification System levels III and IV).
- Females exhibit larger decreases in bone size than males as Gross Motor Function Classification System level increases.

- In children with cerebral palsy, quantitative computed tomography may be most useful for assessing skeletal fragility at appendicular sites such as the tibia.

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ABBREVIATIONS

CSA	Cross-sectional area
DXA	Dual energy X-ray absorptiometry
QCT	Quantitative computed tomography
vBMD	Volumetric cancellous bone density

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Table I

Demographic and anthropometric characteristics of the cerebral palsy and comparison groups, presented as mean (SD)

	Comparison (*n*=37)	GMFCS level I–II (*n*=17)	GMFCS level III–IV (*n*=20)
Age (y:mo)	9:4 (1:6)	9:10 (1:4)	8:11 (1.6)
Height (cm)	132.7 (10.0)	133.9 (9.6)	120.2 (9.7)
Weight (kg)	31.4 (8.2)	33.9 (11.7)	25.5 (6.5)
Body mass index (kg/m^2)	17.6 (2.7)	18.5 (4.6)	17.5 (3.4)
Height centile	39.2 (22.2)	32.2 (29.4)	6.4 (7.7)
Weight centile	49.5 (26.7)	47.6 (33.1)	25.7 (29.6)
Body mass index centile	55.8 (26.7)	56.3 (36.1)	56.6 (32.3)
Sex	19 females, 18 males	7 females, 10 males	12 females, 8 males

GMFCS, Gross Motor Function Classification System.

Table II

Bone measures (raw) by group and Gross Motor Function Classification System level, presented as mean (standard error of the mean); the *p* value is from simple linear regression

	Comparison (*n*=37)	GMFCS level I–II (*n*=17)	GMFCS level III–IV (*n*=20)	*p*
Spine				
L3 vBMD (mg/cm^3)	132 (4)	128 (7)	121 (4)	0.09
L3 CSA (mm^2)	806 (21)	801 (26)	650 (24)	<0.001
Tibia				
Metaphysis vBMD				
Entire metaphysis (mg/cm^3)	–	72 (5)	52 (5)	0.007
Single slice (mg/cm^3)	–	123 (10)	94 (9)	0.03
Midshaft geometry				
CSA (mm^2)	–	286 (19)	185 (14)	<0.001
CBA (mm^2)	–	191 (10)	126 (8)	<0.001

GMFCS, Gross Motor Function Classification System; CSA, cross-sectional area; CBA, cortical bone area.

Table III

Multivariable regression results

Outcome	Predictors	Coefficient	SEM	R^2	*p*
L3 density	GMFCS level III–IV	−3.5	7.0	0.04	0.62
	Height	0.8	0.4	0.07	0.07
	Weight	−0.5	0.5	0.09	0.33
	Male	−1.7	5.3	0.09	0.74
L3 CSA	GMFCS level III–IV	−52.5	22.8	0.26	0.02
	Height	4.6	1.3	0.57	0.001
	Weight	4.8	1.5	0.61	0.002
	Male	86.4	17.3	0.71	<0.001
Tibia density	GMFCS level III–IV	−14.6	7.4	0.19	0.06
	Height	0.6	0.4	0.19	0.22
	Weight	−0.7	0.5	0.25	0.13
	Male	21.3	6.0	0.46	0.001
Tibia CBA	GMFCS III–IV	−24.3	10.0	0.42	0.02
	Height	1.7	0.6	0.73	0.008
	Weight	1.8	0.6	0.78	0.006
	Male	11.9	8.2	0.79	0.16

SEM, standard error of the mean; GMFCS, Gross Motor Function Classification System; CSA, cross-sectional area; CBA, cortical bone area.

Table IV

Interaction between sex and GMFCS level or severity (GMFCS III IV vs others). Values are adjusted for height and weight based on prediction from linear regression and are presented as mean (SEM). The *p* value is from linear regression including height, weight, sex, GMFCS level III to IV grouping, and sex × GMFCS level III to IV interaction

	Female		Male		*p* value for interaction
	GMFCS level III–IV (*n*=12)	Others (*n*=26/7[a])	GMFCS level III–IV (*n*=8)	Others (*n*=28/10)[a]	
L3 CSA (mm^2)	672 (26)	799 (21)	704 (24)	785 (16)	0.064
Tibia CSA (mm^2)	185 (17)	291 (30)	209 (16)	262 (22)	0.025
Tibia CBA (mm^2)	129 (11)	191 (17)	142 (10)	176 (12)	0.054

[a]Larger *n* is for L3 CSA, smaller *n* is for tibia measures. GMFCS, Gross Motor Function Classification System; CSA, cross-sectional area; CBA, cortical bone area.