

Assessment of bone density in children with cerebral palsy by areal bone mineral density measurement

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SUMMARY: Esen İ, Demirel F, Güven A, Değerliyurt A, Köse G. Assessment of bone density in children with cerebral palsy by areal bone mineral density measurement. *Turk J Pediatr* 2011; 53: 638-644.

The aim of this cross-sectional study was to investigate the frequency of decreased areal bone mineral density (aBMD) among patients with cerebral palsy (CP), as estimated by using various aBMD Z-score adjustment methods. In addition, this study examined factors related to decreased aBMD scores. One hundred and two children between the ages of 3.2 and 17.8 years were examined. In patients with severe CP, the incidences of decreased aBMD according to various adjusting methods based on decimal age, bone age, height age, and height-for-age Z-score (HAZ) were 79.5%, 69.5%, 51.9%, and 38.3%, respectively. Abnormal levels of calcium, phosphorus, alkaline phosphatase, parathyroid hormone, or anticonvulsant were not predictive for a decreased aBMD. Mean aBMD Z-scores were significantly lower in all aBMD Z-score adjustment methods in patients with severe CP compared to patients with mild-to-moderate CP, except for the adjustment method based on HAZ.

Key words: cerebral palsy, bone mineral density, anticonvulsant medications, vitamin D, pediatrics.

Cerebral palsy (CP) is the most common form of chronic motor disability in children. The prevalence of CP has been reported to be as high as 3.6 cases per 1,000 children^{1, 2}. Decreased bone mineral density (BMD) is common in these cases, and spontaneous fractures attributed to low BMD have been observed³. Prolonged immobilization is one of the major factors contributing to impairment of bone accretion. In addition, nutritional factors, pubertal status and chronic use of anticonvulsants may interfere with normal skeletal maturation in children with CP^{4,5}. Despite its limitations, dual X-ray absorptiometry (DXA) remains the gold standard technique for the assessment of BMD in the pediatric population. Pediatric software algorithms should be used for the acquisition of data, and this data should be compared with normative pediatric datasets specific for age, sex, body size, and ethnicity of the patient⁶.

In clinical practice, short children might be inappropriately diagnosed as having a decreased areal BMD (aBMD), which may result in adoption of inappropriate lifestyle

changes and administration of potentially inappropriate treatments in an attempt to improve low bone density⁷. The objective of this study was to investigate the frequency of decreased aBMD in patients with CP based on various adjustment methods used for the calculation of Z-scores. In addition, we intended to evaluate the association of related factors, such as nutritional status, chronic use of anticonvulsants, and 25-hydroxy vitamin D (25-OH-D) status, with decreased aBMD in patients with severe CP.

Material and Methods

Subjects

One hundred and two children with CP (3.2 - 17.8 years of age, median age: 9.75 years; 68 males, 34 females) admitted to our hospital between 1 September and 31 December 2009 were enrolled in this study.

Study Design

Medical charts and collected demographic, auxological and laboratory data, as well as

bone density measurements of the patients, were reviewed. Auxological data consisted of body weight, height and body mass index (BMI). Laboratory data included serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), parathyroid hormone (PTH), and 25-OH-D values. Serum analyses were performed using the same methods. The X-rays of both hands and wrists were used to determine the bone age of each patient by the same the researcher (I. E.) according to Greulich and Pyle. The BMD values of lumbar vertebrae (L1-L4) were determined by DXA. Bone density measurements were performed using the Hologic QDR-4500A S/N 45130 device (Hologic Inc., Bedford, MA, USA). Mobility capacities of patients were classified by functional levels of 1 to 5 based on the Gross Motor Functional Classification System (GMFCS)⁸. Severe CP was defined by a functional level of 4 or 5 on the GMFCS scale.

For the analyses, standard deviation scores (SDS) of weight, height, BMI, and height age were calculated by using standards for Turkish children^{9,10}. BMD values were used to calculate aBMD Z-scores according to decimal age, bone age and height age. Previously published data of Turkish children's BMD sets specific for age and sex were used as normative data¹¹. In this reference study, the children who had a bone age between -1 and +1 SD from their chronologic age were enrolled. In our study, the same model device as mentioned in the reference study was used for measurement of BMD.

In addition, to obtain height-for-age Z-score (HAZ), the predicted aBMD Z-score model proposed by Zemel and colleagues¹² was used to adjust aBMD for HAZ.

BMD Z-score for HAZ = aBMD Z-score_{according to decimal age} - Correction value

Using this approach, if a subject's bone Z-score is appropriate for his/her height status, then the correction value is zero. If the bone Z-score is greater than expected given the height status, the HAZ-adjusted correction value is positive, and if the bone Z-score is less than expected given the height status, the correction value is negative. The prediction equation of correction value for BMD Z-scores based on HAZ for non-black males is as $[(-0.016 \times \text{Age}) + (0.228 \times \text{HAZ}) + (0.024 \times \text{Age} \times$

$\text{HAZ}) + 0.148]$ and for non-black females is as $[(-0.032 \times \text{Age}) + (0.325 \times \text{HAZ}) + (0.017 \times \text{Age} \times \text{HAZ}) + 0.322]$ ¹².

To determine the impact of prolonged immobilization on BMD, subjects were divided into two groups according to severity of CP, and aBMD values and adjusted aBMD Z-scores were compared. The frequency of decreased aBMD score (Z-score < -2.0) was investigated with different adjustment methods in patients with severe CP. The effects of nutritional status, use of anticonvulsants and vitamin D status on aBMD were also investigated. For the analyses related to the nutritional status, patients with a BMI SDS below -2.0 were categorized as undernourished¹³. Assessment of vitamin D status was made according to 25-OH-D levels. Vitamin D deficiency was defined as a 25-OH-D level ≤ 15 ng/ml, and vitamin D insufficiency was defined as a 25-OH-D level of 15-20 ng/ml. A serum 25-OH-D level >20 ng/ml was indicative of sufficient vitamin D levels¹⁴. Analysis of contributing factors was done in a homogeneous subgroup that included patients with severe CP to exclude the impact of immobilization on BMD.

Statistics

Descriptive statistics were used, and results are shown as mean \pm SD or median (25-75 percentiles) for the data that had skew distribution. *T*-test was used to examine the differences between groups with regard to mean adjusted aBMD Z-scores. Mann-Whitney U test was used for the comparison of nonparametric data. Nominal variables were compared using chi-square test. Univariate regression analyses were performed with adjusted aBMD Z-scores as the dependent variable and serum Ca, P, ALP, PTH, and 25-OH-D levels as independent variables. Statistical analyses were performed using SPSS 16.0 (SPSS Inc, Chicago, IL, USA). The *P*-value for significance was set at 0.05.

Results

Eighty-one patients (median age: 9.7 years, range: 3.2 to 17.8 years; 52 males and 29 females) had severe CP. Twenty-one patients (median age: 10.5 years, range: 4.4 to 17.8 years; 16 males and 5 females) had mild-to-moderate CP. aBMD Z-scores, according to various adjustment methods (based on decimal

age, bone age, height age, and HAZ) were 79.5%, 69.5%, 51.9%, and 38.3%, respectively, in patients with severe CP (Fig. 1). Mean scores based on all adjustments, except for mean HAZ-adjusted scores, were significantly lower in patients with severe CP than in patients with mild-to-moderate CP. However, mean HAZ-adjusted Z-score was significantly lower in the latter patient group (Table I).

Abnormal levels of Ca, P, ALP, and PTH were not predictive of a decreased aBMD in patients with severe CP ($p>0.05$). Nine patients had low Ca levels, all having vitamin D deficiency. Mean aBMD Z-scores based on the various adjustment methods were not significantly lower in children with abnormal Ca, P, ALP, or PTH levels than in children with normal values for these parameters ($p>0.05$).

In the group of patients with severe CP, 48 patients (59.3%) exhibited malnutrition, and 43 (53.0%) had vitamin D deficiency or insufficiency. The mean aBMD Z-scores based on decimal age were lower in patients with malnutrition. Sixty (74.1%) patients with severe CP had taken a minimum of one antiepileptic drug for at least six months. Patients receiving anticonvulsant drugs had lower serum Ca levels compared to patients not receiving anticonvulsants. In addition, patients with a vitamin D deficiency/insufficiency had higher levels of PTH compared to those without this condition. There were no other differences, as shown in Table II.

Mean HAZ-adjusted aBMD Z-scores were lower in patients with vitamin D deficiency or insufficiency. Serum 25-OH-D levels were not correlated with aBMD Z-scores. However, when patients with 25-OH-D levels <10 ng/ml were compared to the others, they showed significantly lower mean aBMD Z-scores based

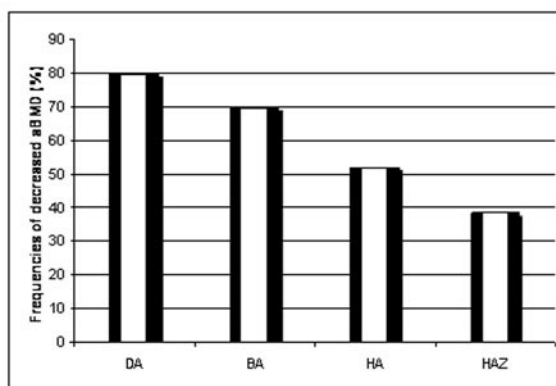


Figure 1. Frequencies of decreased aBMD Z-scores according to different adjustment methods in patients with severe cerebral palsy. DA: Adjusted for decimal age. BA: Adjusted for bone age. HA: Adjusted for height age. HAZ: Adjusted for height-for-age.

on decimal age (data not shown). On the other hand, groups did not differ with regard to mean aBMD Z-scores adjusted for other parameters (Table III).

Discussion

Children with CP may have decreased BMD stemming from various etiologies. Therefore, they are at risk for fractures. Loss of the ability to walk, feeding problems and associated undernutrition, use of anticonvulsants, low vitamin D levels, and pubertal delay are potential etiological factors responsible for decreased BMD in children with CP¹⁵⁻¹⁷. A systematic review and meta-analysis of the association between bone density and fractures in otherwise healthy children suggests that bone mass may contribute to fracture risk during childhood¹⁸. Fractures are frequently reported in patients with CP¹⁹⁻²². Prolonged immobilization is the major etiological factor for decreased BMD in non-ambulant patients^{4,23,24}. This study confirms previous findings that show

Table I. Bone Mineral Density and Adjusted aBMD Z-scores of Patients According to GMFCS

	N	BMD (mg/cm ²)	Z-score DA	Z-score BA	Z-score HA	Z-score HAZ
All patients	102	441±117	-2.89±1.48	-2.60±1.41	-1.76±1.43	-1.83±1.45
GMFC score						
Level 1-3	21	522±125*	-2.00±1.10*	-1.95±1.22*	-1.21±1.41*	-2.65±0.68#
Level 4-5	81	420±106*	-3.12±1.49*	-2.82±1.41*	-1.91±1.41*	-1.62±1.52#

DA: Adjusted for decimal age. BA: Adjusted for bone age. HA: Adjusted for height age. HAZ: Adjusted for height-for-age. BMD: Bone mineral density. GMFCS: Gross Motor Functions Classification System.

* $p<0.05$ # $p<0.01$

Table II. Concentrations of Calcium, Phosphorus, Alkaline Phosphatase (ALP), Parathyroid Hormone (PTH), and 25-Hydroxy Vitamin D (25-OH-D) in Patients with Severe CP

	n	Calcium (mg/dl)	Phosphorus (mg/dl)	ALP (U/L)	PTH (pg/ml)	25-OH-D (ng/ml)
All patients	81	9.2±0.9	4.5±0.8	445 (317-646)	47.6 (24.4-72.5)	17.6 (8.9-30.5)
Receiving anticonvulsants						
Yes	60	9.0±1.0 [#]	4.5±0.8	436 (291-697)	47.9 (27.0-73.0)	16.7 (9.3-31.5)
No	21	9.5±0.6 [#]	4.6±0.8	457 (368-511)	42.6 (21.4-70.9)	21.5 (8.2-26.7)
Malnutrition						
Yes	48	9.1±1.1	4.4±0.8	401 (286-620)	51.0 (30.7-81.0)	16.1 (9.5-31.5)
No	33	9.3±0.6	4.6±0.8	486 (386-727)	38.7 (21.4-62.2)	24.3 (8.2-28.7)
Vitamin D						
Deficient or insufficient	43	9.2±0.7	4.5±0.8	490 (325-687)	58.4 (36.5-84.8)*	9.4 (6.8-13.2) [#]
Normal	38	9.3±0.6	4.5±0.6	428 (324-658)	40.5 (22.3-54.6)*	31.5 (25.2-55.3) [#]

* p<0.05 # p<0.01

decreases in mean BMD Z-scores in patients with severe CP.

The administration of anticonvulsants remains another factor contributing to the impairment in pediatric BMD. Some studies on the impact of antiepileptic drugs remain contradictory²⁵. By inducing the CYP450 system, anticonvulsant drugs can alter the liver metabolism of 25-OH-D²⁶. However, non-enzyme-inducing antiepileptic drugs may also exert adverse effects on bone mineralization²⁷. Henderson et al.²³ reported that the use of anticonvulsant medications independently contributes to lower aBMD Z-scores in the distal femur in children with CP. However, they found that there was no influence of anticonvulsant medications in aBMD Z-scores in the lumbar spine. Conversely, this study showed that patients receiving anticonvulsant drugs have similar aBMD Z-scores for the lumbar spine as non-epileptic patients. Since anticonvulsant drugs do not all have the same potential impact on bone metabolism, there is a limitation to interpreting this data. Furthermore, this study showed that mean Ca concentration was significantly less in children receiving anticonvulsant medications. Several studies have reported hypocalcemia associated with anticonvulsant medications²⁸⁻³¹. The findings of this study do not support the suggestion that children with low levels of Ca concentration receiving anticonvulsant medications may have long-term adverse effects on bone, since mean

Ca concentrations were within normal limits in this study in both patients receiving and not receiving anticonvulsant medications. Despite increasing evidence suggesting that epilepsy and its treatment can affect bone mineralization and Ca metabolism, the mechanism of this important side effect remains unclear³².

Optimizing vitamin D and Ca intake is a commonly accepted approach for the prevention and treatment of osteoporosis in patients with CP^{33,34}. In this study, abnormal Ca, P, ALP, and PTH levels were not associated with decreased BMD in children with severe CP. Similar results were reported by Henderson et al.^{23,35} in two different studies. Vitamin D is essential for maintaining serum Ca levels and optimizing skeletal mineralization. Most natural sources of vitamin D are not commonly consumed by children; as a result, adequate sun exposure becomes important in providing normal vitamin D concentrations. Outdoor activities are significantly diminished among children with severe CP, which could be the cause of low serum 25-OH-D concentrations in these patients. In non-institutionalized children with CP, the prevalence of low levels of calcidiol has been reported as significant and dependent on the season of the year in which the level was measured³⁶. This study showed that decreases in 25-OH-D concentrations were more common in patients with severe CP, but no differences were observed in adjusted aBMD Z-scores in the lumbar spine between patients

Table III. Bone Mineral Density and Adjusted BMD Z-Scores of Patients with Severe CP

	n	Z-score DA	Z-score BA	Z-score HA	Z-score HAZ
All patients	81	-3.12±1.49	-2.28±1.15	-1.91±1.41	-1.62±1.53
Receiving anticonvulsants					
Yes	60	-3.10±1.47	-2.83±1.44	-2.01±1.48	-1.57±1.51
No	21	-3.19±1.57	-2.81±1.39	-1.62±1.19	-1.77±1.60
Malnutrition					
Yes	48	-3.47±1.24*	-3.06±1.33	-2.05±1.22	-1.51±1.55
No	33	-2.62±1.68*	-2.42±1.48	-1.71±1.65	-1.77±1.49
Vitamin D status					
Deficient or insufficient	43	-3.02±1.63	-2.87±1.55	-2.04±1.33	-1.79±1.59#
Normal	38	-3.10±1.56	-2.83±1.38	-1.71±1.61	-0.85±1.00#

DA: Adjusted for decimal age. BA: Adjusted for bone age. HA: Adjusted for height age. HAZ: Adjusted for height-for-age. BMD: Bone mineral density.

* p<0.05 # p<0.01

with low (<20 ng/ml) and normal 25-OH-D concentrations. There is significant evidence from previous studies on the association between circulating 25-OH-D concentrations and established BMD³⁷. Although vitamin D is a significant factor for bone mineralization, it is not the only determinant of bone health in children with CP. Reduced mobility and anticonvulsant medications, in addition to comorbidities of CP, are important factors affecting complex bone metabolism in these children. However, this study showed that 25-OH-D levels <10 ng/ml are associated with decreased BMD in children with severe CP. The authors believe that severe vitamin D deficiency may lead to a decrease in BMD.

Children with CP usually have poor growth and malnutrition stemming from multifarious factors. Malnutrition has a wide range of adverse effects on physiology, motor function and neurological and psychological function³⁸. It probably has an unfavorable impact on bone metabolism. In this study, malnutrition was associated with decreased aBMD in children with severe CP. Henderson et al.^{16, 23, 39} examined the impact of growth on bone density in several observational studies and showed that factors affecting bone density were weight and nutritional status. Poor nutritional status (as measured by skinfolds) and oral-motor dysfunction (difficulty in feeding) were shown to be independent contributors to changes in bone density²³. Despite increasing evidence on the negative impacts of malnutrition on BMD, Stevenson et al.²² reported higher body fat and

gastrostomy use as risk factors for fractures in children with CP.

The most popular technique for the evaluation of skeletal health is the clinical tool dual X-ray absorptiometry. Despite its limitations, DXA remains the gold standard technique for the assessment of BMD in the pediatric population. Since DXA is a projectional technique, the data obtained are two-dimensional areal measurements of three-dimensional objects, including bone⁶. Areal BMD is a size-dependent measure; as a result, smaller bones appear to have a lower aBMD than larger bones⁴⁰. There is consensus for using aBMD Z-score values adjusted for age, sex and body size⁴¹. Gafni et al.⁷ reported that inattention to short stature is a frequent error in the interpretation of children's DXA scan results. Children with CP frequently have short stature resulting from multiple factors, including poor nutritional status, reduced physical activity and recurrent convulsions. As a result, it is important to correct for height when interpreting aBMD in this population³³. There is to date no consensus on how to adjust aBMD measurements for short or tall stature patients. Recently, Zemel et al.¹² proposed an adjustment method based on HAZ in assessing DXA measurements of bone mass and density in children. This study has shown that the frequency of decreased aBMD is quite variable according to the methods used to adjust aBMD Z-scores. Several studies have suggested that pediatric bone mineralization is closely associated with the stage of skeletal (puberty) maturation rather

than chronologic age⁴⁰. Delay of puberty is a common complication of chronic illness and can result in an erroneous reduction in aBMD when comparing results to that of normally developed age-matched controls. This has led some authors to suggest that DXA results should be corrected for bone age³³. In patients with severe CP, mean bone age was found to be 1.4 years retarded compared to mean decimal age. As a result, decreased BMD was less frequent when aBMD Z-scores were adjusted for bone age rather than decimal age. Interestingly, when we used the adjustment method proposed by Zemel et al.¹² in this study, patients with severe CP showed higher aBMD Z-scores than patients with mild-to-moderate CP. Since mean height Z-scores in ambulant and non-ambulant patients were -1.53 and -2.87, respectively, severe growth retardation in non-ambulant patients may account for this unexpected result. In addition, there is a limitation for using Zemel's method of adjusting aBMD for HAZ, as this method was based on equations that used the Centers for Disease Control and Prevention (CDC) growth references of healthy children. Thus, the Zemel prediction model for adjusting aBMD Z-scores may not be feasible in interpreting aBMD values in patients with severe CP.

In conclusion, wide variations in height and, therefore, bone size and skeletal maturation in children complicate the interpretation of aBMD results, especially in children with CP. Decreased BMD is prevalent in children with severe motor dysfunction. There are a number of modalities for the assessment of pediatric skeletal structure. However, each modality comes with distinct advantages and disadvantages. DXA remains the preferred method for clinical evaluation of bone density in children due to its wide availability, reproducibility and quick provision of results, low exposure to ionizing radiation, and the presence of robust pediatric reference data. This study showed that there were significant differences in the frequency of patients diagnosed with decreased BMD according to various aBMD Z-score adjustment methods. It is not clear which approach is more helpful for adjusting aBMD Z-score in children with CP: based on bone age, chronological age, height age, or HAZ. To clarify this issue, further prospective studies able to identify the probability of spontaneous fractures more

precisely are required. Until a consensus on a method that could predict skeletal fragility and fracture risk exists, we think that adjusting aBMD results based on bone age in children with CP will be useful in avoiding overdiagnosis of decreased BMD.

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