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Spinal Bone Mineral Density, IGF-1 and IGFBP-3 in Children with Cerebral Palsy

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Key Words
Cerebral palsy · Osteopenia · IGF-1 · IGFBP-3 · Bone mineral density

Abstract
Background/Aims: Childhood cerebral palsy (CP) is associated with osteopenia and the GH-IGF axis plays an important role in bone metabolism. We studied the relationship between spinal bone mineral density (BMD) and serum IGF-1 and IGFBP-3 in children with CP. ***Methods:*** Cross-sectional study of 30 children (9 F and 21 M, ages 4.5–15) with CP. Subjects underwent dual-energy x-ray absorptiometry scans (spinal BMD), blood tests (IGF-1, IGFBP-3, Ca, P, PTH, vitamin D, osteocalcin) and urine tests (N-telopeptide). ***Results:*** Spinal BMD was decreased in children with CP (average Z-score –2.14 ± 1.08) compared to age- and gender-matched norms. IGF-1 and IGFBP-3 were also decreased compared to age-matched norms (average IGF-1 Z-score –0.74 ± 1.2, average IGFBP-3 Z-score –0.68 ± 1.2). All other blood and urine tests, including measures of calcium and vitamin D status, were normal. In 25 CP children with osteopenia (Z-score >–1), there was a trend towards correlation between spinal BMD Z-score and serum IGF-1 SDS score ($r = 0.328$, $p = 0.09$). IGFBP-3 Z-scores were available in 24 of these patients and had a statistically significant correlation with spinal BMD Z-score ($r = 0.386$, $p = 0.05$). ***Conclusion:*** Osteopenia is common in children with CP and may be associated with lower IGF-1 and IGFBP-3 levels.

Introduction

Cerebral palsy (CP) is a broad range of static, non-progressive motor disabilities that present from birth or early childhood as a result of injury to neuromotor components of the central nervous system [1]. Affected children commonly have evidence of abnormal bone health, including poor linear growth and frequent fractures, often with minimal trauma [2]. In children with CP, bone mineral density (BMD) has been reported to average nearly 1 standard deviation (SD) below the age-matched normal means for both the proximal parts of the femora (–0.92 SD) and the lumbar spine (–0.80 SD) [3]. In addition, children with CP tend to fall further behind their peers as they get older, because their rate of bone mineral growth is decreased relative to healthy children [4]. Comparable data are not available in children, but in adults each 1 SD decrease in BMD is associated with a 2.4- to 3.0-fold increase in the age-adjusted risk of hip fracture [5]. Childhood osteopenia is also likely to be clinically

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significant because childhood is a critical period for bone mineral accrual and failure to accumulate normal bone mass in this age leads to osteoporosis and increased fracture risk in adult life.

Poor bone mineralization in children with CP may be due to a variety of factors, for example: limited weight-bearing ambulation during skeletal growth, temporary immobilization following orthopedic surgical procedures, poor nutrition, and the use of anticonvulsant drugs that interfere with vitamin D metabolism. There are several lines of evidence that suggest that impairment of the GH-IGF axis may be another factor that contributes to decreased BMD in these children. For example, GH and IGF-1 are key regulators of bone-cell function [6], IGF-1 has potent stimulatory effects of on synthesis of bone-specific proteins and osteoblastic proliferation in cell and organ cultures [7], congenic mice with low IGF-1 levels have decreased BMD [8] circulating IGF-1 and IGFBP-3 have been reported to correlate positively with BMD in humans [9], and, IGF-1 and GH have been considered as putative anabolic agents for the treatment of osteoporosis [10].

While the GH-IGF axis has not been systematically studied in children with CP, there are several reports that these children have an increased incidence of GH deficiency, and IGF-1 and IGFBP-3 levels in these children tend to be lower than those seen in age-matched controls [11, 12]. We hypothesized that the GH-IGF axis is impaired in children and adolescents with CP and the degree of impairment is related to the severity of bone disease. As an initial test of this hypothesis, we examined cross-sectional data collected from a group of children with CP followed at the UCLA Center for Cerebral Palsy.

Methods

Subjects

30 patients (9 females and 21 males) ranging from 4.5 to 15 years of age, with CP of varied severity, underwent dual-energy x-ray absorptiometry scanning and blood tests at the outpatient orthopedic clinic of the UCLA Center for Cerebral Palsy. Informed consent was obtained from all these patients as approved by the IRB.

Measurements

Spinal BMD was measured by dual-energy x-ray absorptiometry using a Hologic QDR 4500A scanner. Age- and gender-matched reference data were used for comparison. For children over the age of 9 years, the age-matched SD score (Z-score) was calculated using the standards developed at Stanford University by Bachrach et al. [13]. For children under the age of 9 years, the standards supplied by the manufacturer were used to calculate Z-scores. Peripheral venous blood was obtained for serum analysis. Calcium, phosphorous, creatinine, PTH, 25-hydroxyvitamin D, alkaline phosphatase and osteocalcin levels in the blood and N-telopeptide levels in the urine were measured in the UCLA medical laboratories by standard techniques. Quantification of IGF-1 and IGFBP-3 was performed by radioimmunoassay at Esoterix Laboratories (Calabasas, Calif., USA). Age-matched SD scores for the IGF and IGFBP-3 values were calculated based on the normative data supplied by Esoterix Laboratories.

Statistical Analysis

Bone density age-matched standard deviation scores (Z-scores) were plotted against the corresponding IGF and IGFBP-3 Z-scores. Correlation coefficients based on linear regression were calculated using Instat statistical software. The same software was then used to calculate significance using Student's t test. The null hypothesis was rejected at $p < 0.05$.

Results

The average spinal BMD in these 30 patients was 2.14 $\pm$ 1.08 SD below the age- and gender-specific mean. Only 1 patient (out of 30) had a positive BMD Z-score and 25 out of 30 had osteopenia (spinal BMD >1 SD below the mean) (fig. 1a).

IGF-1 levels were available for all 30 patients. The average IGF-1 Z-score (SDS score compared to age- and sex-specific norms) was –0.735 $\pm$ 1.18. Six out of 30 patients had positive Z-scores while another 6 were >2 SD below the mean. The remaining 18 patients had IGF-1 levels ranging from 0 to 2 SD below the age-specific means (fig. 1b).

IGFBP-3 levels were available on 29 patients and the average IGFBP-3 Z-score was –0.68 $\pm$ 1.2. Three out of 30 patients had positive Z-scores while 3 patients had IGFBP-3 levels >2 SD below the mean. 23 patients had Z-scores ranging from 0 to 2 SD below the mean (fig. 1c).

When the IGF-1 Z-score was plotted against the lumbar spine BMD Z-score, there was a weak correlation, with $r = 0.046$, which was not statistically significant. But when the correlation was limited to the 25 osteopenic patients, the correlation coefficient was 0.328, which approached statistical significance, with $p = 0.09$ (fig. 2a).

Similarly, when the BMD Z-score was plotted against the IGFBP-3 Z-score, there was a weak correlation between the two with an r value of 0.098 (not statistically significant), but when the correlation was limited to the 24 osteopenic patients, the correlation coefficient increased to 0.386, which is statistically significant with $p = 0.05$ (fig. 2b).

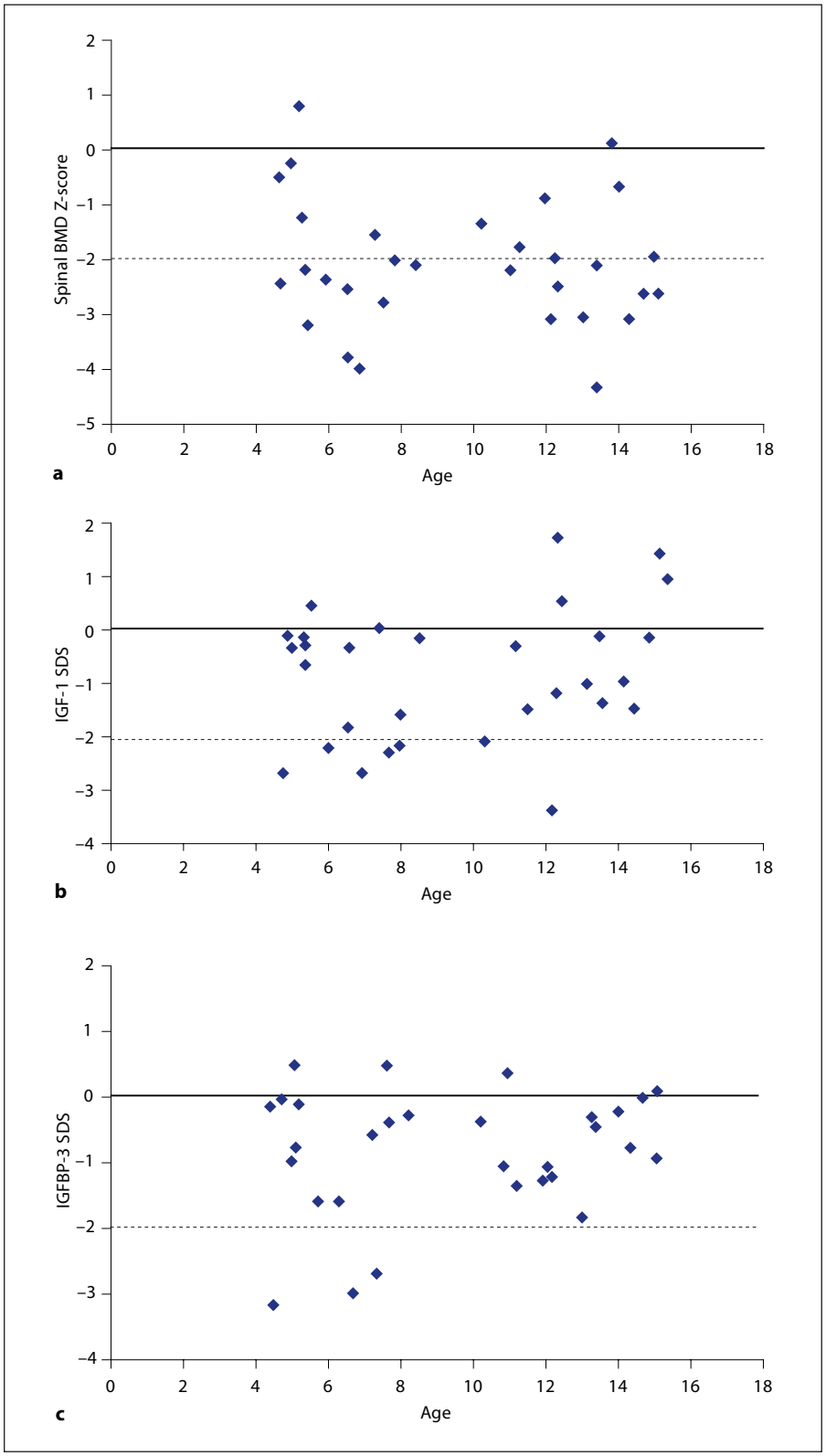

Fig. 1. Graphs showing the distribution of spinal BMD (**a**), IGF-1 (**b**) and IGFBP-3 (**c**) SD scores in relation to age. The solid line represents the mean (0 SDS) for age and the dashed line is –2 SD below the mean.

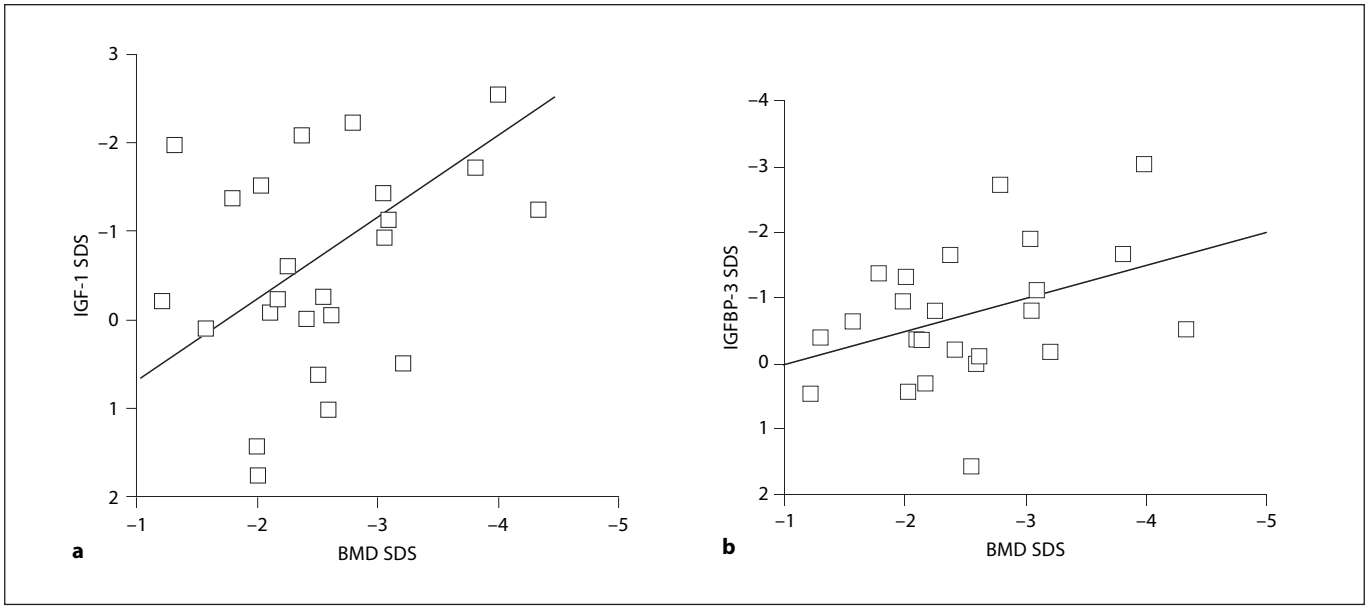

Fig. 2. Graphs showing the relationship between IGF-1 (**a**) and IGFBP-3 (**b**) SD scores versus spinal BMD SD scores. Best fit linear regression line shown.

Table 1. Baseline characteristics of the study population

Age (range 4.5–15 years)	9 ± 3.5
Males/females	21/9
Calcium, mmol/l	2.43 ± 0.08
Phosphorous, mmol/l	1.52 ± 0.24
PTH, ng/l	35.3 ± 18.1
25-OH vitamin D, nmol/l	89.2 ± 34.2
Alkaline phosphatase, U/l	71 ± 25
Osteocalcin, nmol/l	11.5 ± 3.6
Urine N-telopeptide, nmol BCE/mmol Cr	434.6 ± 130

Measures of calcium and vitamin D metabolism (calcium, phosphorous, 25-OH vitamin D, PTH, osteocalcin and urinary N-telopeptide levels) were normal in all patients (table 1).

Discussion

There is abundant evidence that the GH-IGF axis plays an important role in bone growth [14] and previous studies have shown that bone mass is significantly correlated with circulating IGF-1 levels in humans, as well as in a variety of murine models [15, 16]. Our cross-sectional pilot study provides preliminary evidence that a similar relationship may exist in children with CP and osteopenia.

We found that most children with CP have decreased BMD as well as low GH-dependent growth factors (IGF-1 and IGFBP-3). We also found that in the osteopenic patients (though not in the 4 patients who had normal bone density), there was a significant correlation between the IGFBP-3 Z-scores and spinal BMD Z-scores. A similar correlation between IGF-1 and BMD Z-scores fell just short of statistical significance. Again, this was not the case when the 4 patients with normal BMD were included in the analysis. This suggests that deficiencies in the GH-IGF axis may play a role in the decreased bone density seen in children with CP (though this is not the only factor influencing BMD in these patients). The fact that this correlation is stronger with IGFBP-3 than it is with IGF-1 may be due to the fact that IGF-1 levels are influenced by nutritional factors, while IGFBP-3 levels may be more representative of the actual GH status of these patients. The normal Ca, P, vitamin D and alkaline phosphatase levels in these patients indicate that the decreased BMD is not likely to be due to disorders of calcium and vitamin D metabolism.

There are several obvious shortcomings in our study: Firstly, we do not have detailed auxological data on all our patients. Because of this, we were unable to calculate height-based BMD Z-scores on these patients. It is likely

that this cohort of children with CP is shorter than average and height-adjusted BMD SDS will reveal less osteopenia than is seen when SDS is calculated using age-based norms. But if these children are in fact shorter than average (as is likely) then the short stature and decreased BMD may BOTH be related to deficiencies in the GH-IGF axis. Other possible confounding factors include BMI and ambulatory status and it is possible that some of the observed correlation (especially in the case of IGF-1) may be related to decreased BMI. Differences in ambulatory status may correlate with decreased BMD, but they would not explain the observed correlation with IGF and IGFBP-3 levels. The use of two different reference databases for patients above and below 9 years of age is another potential weakness in the study, but was dictated by the absence of published data in children under age 9. Finally, the absence of correlation when we look at all patients, rather than the osteopenic patients alone, weakens the observed association.

Conclusion

This initial pilot study reiterates that BMD is significantly decreased in children with CP when compared to age-matched controls. It provides preliminary evidence that this decrease may be correlated with decreased levels of GH-dependent growth factors (IGF-1 and IGFBP-3) but further studies are needed to clarify this relationship. If proven, this may have implications for the use of GH therapy in children with CP.

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