

Analysis of the Musculoskeletal System in Children and Adolescents Receiving Anticonvulsant Monotherapy With Valproic Acid or Carbamazepine

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ABSTRACT. *Objective.* To examine bone development in children and adolescents who have uncomplicated idiopathic epilepsy and had received monotherapy with carbamazepine or valproic acid for at least 1 year.

Methods. Thirty-nine patients from 6 to 19 years of age (18 girls) were studied. Total bone mineral content (BMC) and trabecular volumetric bone mineral density were measured at the distal radius using peripheral quantitative computed tomography. Maximum isometric grip force was determined with a standard dynamometer. Alkaline phosphatase activity and deoxypyridinoline (a marker of bone resorption) were assessed in serum and urine, respectively.

Results. Trabecular volumetric bone mineral density was significantly decreased in the entire group (z score mean \pm standard deviation: -0.62 ± 1.04) and in the subgroup using valproic acid (-0.75 ± 1.18). In the carbamazepine subgroup, there was a similar but nonsignificant trend (-0.50 ± 0.90). Total BMC and isometric maximum grip force were normal in the entire study population (0.10 ± 1.22) and in the 2 subgroups. The relationship between BMC and grip force was similar between patients and healthy participants. Urinary levels of deoxypyridinoline were significantly elevated above normal in the whole study population (1.35 ± 2.00) and in both the valproic acid and the carbamazepine subgroups.

Conclusion. Bone turnover can be increased, but bone mass is adequate in children and adolescents who have uncomplicated idiopathic epilepsy and who receive monotherapy with carbamazepine or valproic acid. *Pediatrics* 2001;108(6). URL: <http://www.pediatrics.org/cgi/content/full/108/6/e107>; *anticonvulsant, bone density, bone mass, bone metabolism, muscle.*

ABBREVIATIONS. CBZ, carbamazepine; VPA, valproic acid; BMD, bone mineral density; vBMD, volumetric bone mineral density; pQCT, peripheral quantitative computed tomography; BMC, bone mineral content; SD, standard deviation.

The effect of chronic anticonvulsant drug therapy on bone development has been a subject of debate for more than 3 decades. Early investigators were mainly concerned about the potential of these drugs (mostly phenytoin and phenobarbital) to

induce rickets and osteomalacia.¹⁻³ However, histologic studies in adults did not provide convincing evidence that anticonvulsant therapy as such causes osteomalacia in patients who had epilepsy without comorbidity and who were adequately exposed to sunlight.^{4,5}

In recent years, the focus has shifted to the question of whether the "newer" anticonvulsant drugs—carbamazepine (CBZ) and valproic acid (VPA)—might increase the risk of fracture in later life by interfering with bone mass accumulation. A study on adolescents with uncomplicated idiopathic epilepsy found a low areal bone mineral density (BMD) in patients who received monotherapy with VPA but not in patients receiving CBZ.⁶ However, other authors reported that areal BMD was normal in such patients⁷ or that areal BMD was decreased in girls but not in boys.⁸

These studies were limited to the analysis of areal BMD (g/cm^2), a measure integrating both bone size and 3-dimensional ("volumetric") BMD (vBMD).⁹ The size dependence of areal BMD often makes results difficult to interpret in the pediatric setting, because short children will have a lower areal BMD than their peers, even if their (smaller) bones are absolutely normal.¹⁰ This problem can be overcome by using peripheral quantitative computed tomography (pQCT). Cross-sectional images of long bones are analyzed,¹⁰ and bone size and vBMD are determined independent of each other. It is possible not only to determine the total mineral mass of an entire bone cross-section but also to evaluate trabecular bone without interference from cortical bone.

Whatever densitometric technique is used, it is often difficult for the pediatric user of bone densitometry to decide whether a given amount of bone is adequate for a given child or not. The usual approach to this problem is to compare a measure of bone mass to a gender- and age-dependent reference range. However, from a more functional perspective, the important question is not whether the bones of a patient are as heavy as the bones of a healthy child but rather whether the bones of a patient are normally adapted to the physiologic loads to which they are exposed.^{11,12} The largest physiologic loads on the skeleton are created by the contraction of muscles.^{13,14} It therefore could be useful not only to compare bone mass results to an age-specific reference range but also to test whether bone strength (as

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reflected by bone mass) is adequately adapted to muscle force.^{10,15} In the present cross-sectional study, we tested the hypothesis that anticonvulsant monotherapy with VPA or CBZ interfered with the adaptation of the skeletal system to the mechanical requirements during growth and development.

PARTICIPANTS AND METHODS

Patients

The original study population comprised ambulatory outpatients of the Department of Neurology at the University Children's Hospital of Cologne, Germany. Patients were eligible for the present study if they were 6 years or older (because younger children usually do not cooperate sufficiently to perform the tests described here), had received anticonvulsant monotherapy with either VPA or CBZ with serum levels in the therapeutic range for at least 1 year, had not received other anticonvulsant therapy before, and had a normal neurologic status. Patients with seizure disorders secondary to structural brain defects or other diseases were excluded. Thirty-nine children and adolescents (age 6–19 years; 18 girls, 21 boys) met these criteria and were evaluated once for the purpose of the present study. None of the participants of this study was on other drugs known to affect bone metabolism, and none was on a specialized diet. Nutrition and physical activity were appropriate for age. Weight was measured to the nearest 0.1 kg using digital electronic scales with the patients clothed in underwear. Forearm length was measured to the nearest millimeter as the distance between the ulnar styloid process and the olecranon using a caliper. Pubertal stage was obtained by self-assessment. Informed consent was obtained from the children's parents or from the patients aged 18 years or older. The study protocol was approved by the Ethics Committee of the University of Cologne.

Results for grip force, pQCT analyses, and anthropometric parameters were compared with the findings in a well-characterized reference population of healthy children and adolescents, which has been described before.¹⁶ This cohort comprised 371 healthy children and adolescents aged 6 to 23 years (185 male, 186 female), who were participants in the Dortmund Nutritional and Anthropometric Longitudinally Designed Study. This is an ongoing observational study investigating the interrelations of nutrition, growth, and metabolism in healthy children, which is performed at the Research Institute for Child Nutrition in Dortmund, Germany. On an annual basis, all participants of this study undergo a full medical history and examination starting in infancy.

Grip Force

Maximum isometric grip force of the nondominant hand was determined with a standard Jamar dynamometer (Preston, Jackson, MI). The handle was adjusted so that the line of the patient's proximal interphalangeal joints rested exactly on top of the handle. Setting 1 of the dynamometer was used for the younger children, and setting 2 was used for most of the older children and adolescents; setting 3 was used for some of the adolescents, and settings 4 and 5 were never used.

The patients were seated with their shoulder adducted and neutrally rotated. The dynamometer was held freely without support. The elbow was flexed at 90°, and care was taken that it did not touch the trunk. The forearm was in a neutral position, and the wrist was held at between 0° and 30° dorsiflexion and between 0° and 15° ulnar deviation. The patients were told to put maximum force on the dynamometer. The maximum value of 2 trials was noted. The scale of the dynamometer indicates the result in kilograms, which is incorrect, because this is the unit of mass, not force. Grip force (Newtons) was calculated by multiplying the dynamometer reading by a factor of 9.81.

pQCT

pQCT analysis (XCT-900; Stratec, Pforzheim, Germany) was performed at the nondominant forearm. The scanner was positioned on the distal forearm, and a scout view was conducted to position the scanner at the site on the radius whose distance to the radial articular cartilage corresponded to 4% of ulnar length. At that site, a tomographic slice of 2.5 mm trans-sectional thickness

was measured at a voxel size of 0.59 × 0.59 × 2.5 mm. The effective radiation is approximately 0.1 μSv and thus is less than for most other densitometric techniques, such as dual-energy radiograph absorptiometry of the lumbar spine.¹⁰

Image processing and the calculation of numerical values was done using the manufacturer's software package (version 5.10; Stratec, Pforzheim, Germany). The outer bone contour was detected at a threshold of 280 mg/cm³. Trabecular vBMD was determined as the mean mineral density of the 45% central area of the bone cross-section. Bone mineral content (BMC) represents the mass of mineral per millimeter slice thickness of the entire bone's cross-section.

Biochemistry

Intact parathyroid hormone serum levels were measured by 2-site immunoradiometric assay (Nichols Allegro PTH kit; Nichols Institute Diagnostics, San Juan, CA). Serum concentrations of 25-OH vitamin D were quantified by radioimmunoassay (Nichols Institute Diagnostics). The urinary concentration of deoxypyridinoline was analyzed by enzyme immunoassay (Pyrilinks-D; Metra Biosystems, Mountain View, CA). Alkaline phosphatase activity was measured by the optimized standard method (Monotest-a; Boehringer Mannheim Diagnostica; Mannheim, Germany) according to the "Recommendations of the German Society for Clinical Chemistry."¹⁷ Serum and urinary calcium as well as serum phosphate levels were measured by standard procedures in the routine laboratory. Urinary creatinine was measured using a Beckman creatinine analyzer (Beckman Instruments, Fullerton, CA). Z scores were calculated for serum alkaline phosphatase and the urinary deoxypyridinoline/creatinine ratio using reference data established in our laboratory.^{18,19}

Statistical Analyses

Z scores were calculated for various parameters using the following formula: z score = [(test result for a patient) – (age- and gender-specific mean in reference population)] / (age- and gender-specific standard deviation in reference population). To evaluate whether a parameter was significantly increased, we assessed the difference of the mean z score to 0 by the rank-sum test. T tests were used for comparisons between 2 groups. Multiple regression analysis in the inclusive mode was used to test the influence of duration of therapy on the relationship between grip force and BMC. This analysis was performed for girls and boys separately. Throughout, *P* < .05 was considered significant. All statistical analyses were performed using the SPSS software package (version 6.0 for Windows; SPSS Inc, Chicago, IL).

RESULTS

The mean duration of anticonvulsant drug therapy was approximately 3.5 years (Table 1). Height, body weight, and body mass index were normal in the patients, and none of these individuals had pubertal delay. Individual results of musculoskeletal analyses are shown in Fig 1. These results were converted into age- and gender-specific z scores (Table 1). Trabecular vBMD was significantly decreased in the entire group and in the subgroup that was receiving VPA. In the carbamazepine subgroup, there was a similar but nonsignificant trend (-0.50 ± 0.90 ; *P* = .06). In contrast to trabecular vBMD, BMC and isometric maximum grip force were normal in the entire study population and in the 2 subgroups. The relationship between BMC and grip force was similar between patients and healthy participants (Fig 2). A multiple regression analysis was performed and included grip force and duration of therapy as independent variables to explain the variation in BMC. This revealed that grip force (*P* < .001 for both genders) was a significant predictor of BMC, whereas duration of therapy did not have a significant influence (*P* = .13 in boys; *P* = .42 in girls).

TABLE 1. Clinical Characteristics of the Entire Study Population and in Subgroups Treated With VPA or CBZ

	All	VPA	CBZ	Reference Range
<i>n</i> (m/f)	39	19 (9/10)	20 (13/7)	—
<i>n</i> (pubertal stage 1–5)	15/8/5/3/8	7/3/4/1/4	8/5/1/2/4	—
Age	12.7 ± 3.4	12.5 ± 3.7	13.0 ± 3.3	—
Duration of therapy	3.6 ± 2.1	3.7 ± 2.5	3.6 ± 1.6	—
Height (z)	0.0 ± 1.2	0.2 ± 1.2	−0.2 ± 1.1	−2–+2
Weight (z)	0.1 ± 1.3	0.3 ± 1.5	0.0 ± 1.1	−2–+2
BMC (z)	0.1 ± 1.2	0.4 ± 1.4	−0.2 ± 0.9	−2–+2
Trabecular vBMD (z)	−0.6 ± 1.0‡	−0.8 ± 1.2‡	−0.5 ± 0.9	−2–+2
Grip force (z)	0.2 ± 1.0	0.1 ± 1.1	0.2 ± 0.9	−2–+2
Calcium (mmol/L)	2.38 ± 0.10	2.39 ± 0.09	2.36 ± 0.10	2.10–2.65
Phosphorus (mg/dL)	4.32 ± 0.62	4.25 ± 0.60	4.39 ± 0.65	—
25-OH vitamin D (ng/mL)	22 ± 12	25 ± 14	18 ± 7	9–45
Parathyroid hormone (pg/mL)	33 ± 21	24 ± 9	42 ± 26	10–65
Alkaline phosphatase (z)	0.5 ± 1.3	0.4 ± 1.4	0.5 ± 1.3	−2–+2
Deoxy pyridinoline/creatinine (z)	1.4 ± 2.0‡	0.9 ± 1.5*	1.7 ± 2.3‡	−2–+2

* Values are mean ± SD. The significance for the difference of the mean z score from 0 (rank sum test) is indicated in superscript: * *P* < .05; † *P* < .01; ‡ *P* < .001.

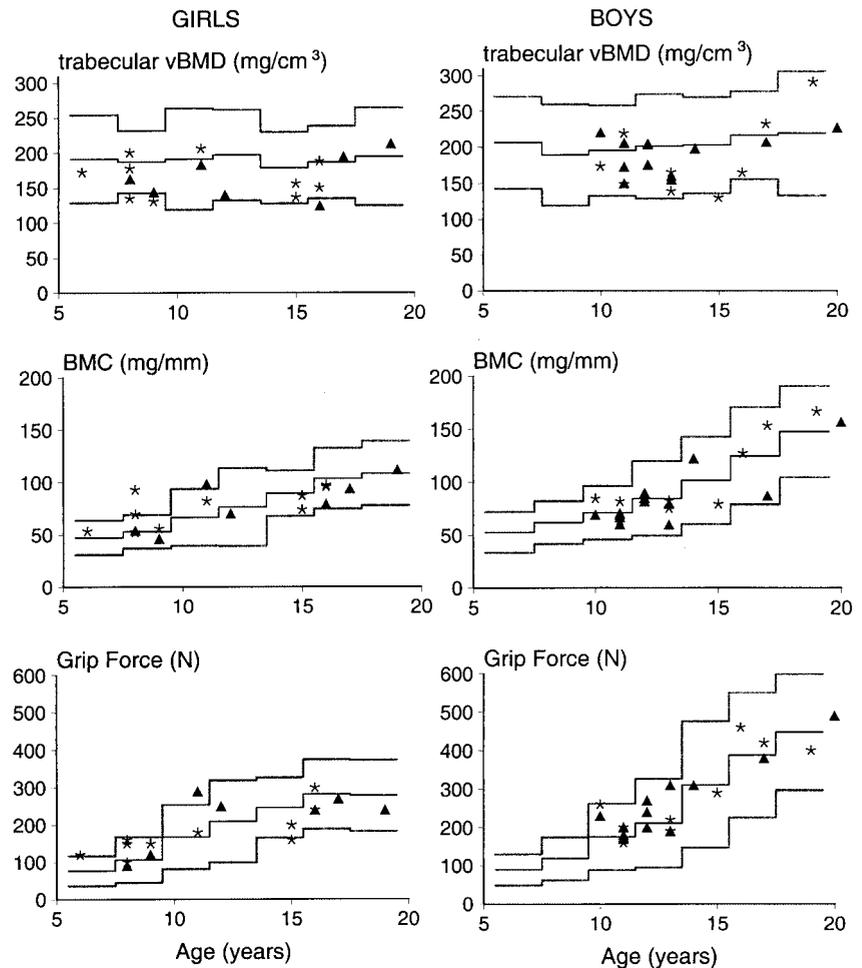


Fig 1. Results of musculoskeletal analyses in 39 children and adolescents who were receiving monotherapy with CBZ (Δ) or VPA (*). The upper and lower lines indicate mean +2 SD and mean −2 SD in the reference population, respectively. The middle line represents the mean in the reference population.

Serum total calcium and phosphorus values were within the reference range for all individuals (Table 1). Serum levels of 25-OH vitamin D levels were similar to the values found in a control population of children and adolescents, in whom the samples had been obtained during the same time of the year (21.9 ± 11.6 vs 21.1 ± 10.9 ng/mL; *P* = .77). The parathyroid hormone serum concentration was normal in the group as a whole. However, 2 patients who were receiving CBZ had low vitamin D levels

(4.5 ng/mL and 5.2 ng/mL) and elevated parathyroid hormone levels (123 pg/mL and 83 pg/mL), respectively. In 1 of these patients, levels normalized spontaneously within 2 months; in the other (a 12-year-old girl), high parathyroid hormone persisted despite vitamin D supplementation.

The group means for serum alkaline phosphatase activity were not significantly elevated (Table 1). However, 6 patients (15% of the entire group; 3 patients receiving VPA and CBZ each) had levels more

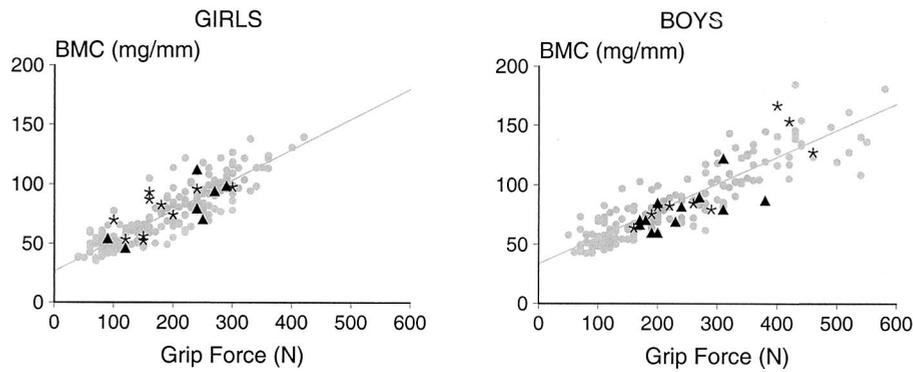


Fig 2. Relationship between grip force and BMC. Data and the regression line for healthy participants are shown in gray. Δ , CBZ-treated patients; *, VPA-treated patients.

than 2 standard deviations (SD) above the mean. These patients were similar to the remainder of the study population regarding age, duration of treatment, mineral metabolism, BMC, and grip force but had significantly lower trabecular vBMD (mean \pm SD of z score: -1.5 ± 1.1 vs -0.5 ± 1.0 ; $P = .02$).

Urinary levels of deoxypyridinoline, a marker of bone resorption, were significantly elevated above normal in the whole study population and in both the VPA and the CBZ subgroups (Table 1). However, the 7 patients (5 receiving CBZ, 2 receiving VPA) who had a deoxypyridinoline excretion more than 2 SD above the reference mean did not differ from the other patients in any of the measured parameters. Gender differences were not significant for any of the studied parameters.

DISCUSSION

In this study, we found that trabecular vBMD at the distal radius was decreased in children and adolescents who were receiving monotherapy with VPZ or CBZ. In contrast, the mass of the entire radial cross-section (ie, BMC) was normal for age and also was normally adapted to local muscle force. Bone turnover, as assessed by the most bone-specific marker, deoxypyridinoline, was increased, but there was no evidence of a disturbed calcium or vitamin D metabolism. What can we make of this array of findings?

Trabecular vBMD reflects the mineral mass per unit volume of the trabecular bone compartment.⁹ As such, it represents the product of trabecular thickness, trabecular number, and material density of the trabeculae. A low trabecular vBMD means that 1 or several of these composites are decreased, but in the absence of histomorphometric evidence, it is impossible to decide which of these alternatives is correct. Nevertheless, low trabecular vBMD does not come as a surprise when bone turnover is increased, as a result of the so-called "remodeling transient."²⁰ During a remodeling cycle, osteoclasts temporarily remove a certain amount of bone that is later put back by a team of osteoblasts. Thus, when bone remodeling activity is high, there is an increased number of sites where bone is temporarily missing. This leads to lower trabecular vBMD, even if the net effect of the remodeling cycle on bone mass is 0.

High bone remodeling activity is a common finding in studies on the bone effects of anticonvulsant drug treatment.^{3,5,21–23} In the older literature, this was often interpreted as a sign of osteomalacia and a link to decreased vitamin D levels was suspected.^{3,21} However, markers of bone metabolism remain elevated when vitamin D supplementation is given to CBZ-treated patients,²⁴ and later studies did not find a correlation between bone turnover and vitamin D levels.²³ This is in accordance with the present study, in which bone turnover was increased in the presence of normal vitamin D levels. The elevated remodeling activity could be attributable to a direct drug effect on bone cells.²⁵

BMC was normal despite low trabecular vBMD. This suggests that the decrease in the amount of bone in the trabecular compartment was compensated by a concomitant increase in the amount of cortical bone. The resolution of the pQCT system that was used in the present study is not sufficient to examine directly the thin cortex at the distal radius.¹⁶ Nevertheless, there was no evidence that overall bone mass was decreased in our patients, related either to age or to local muscle force.

CONCLUSION

This study suggests that in children and adolescents who are treated with either CBZ or VPA, trabecular vBMD is slightly decreased, possibly as a result of increased bone turnover. There seems to be a compensatory mechanism that ensures that the mineral mass of the entire bone cross-section is adequately adapted to mechanical loads. These data do not provide arguments for repeated densitometric examinations in such patients. It is important to note that these observations were made in ambulatory children and adolescents with uncomplicated idiopathic epilepsy. The conclusions, therefore, cannot be generalized to adults or to patients with additional neurologic manifestations.

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