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Bone mineral density in children with cirrhosis

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Background. Despite the clinical importance of osteoporosis in individuals with cirrhosis, little is known about it, especially in children. We evaluated the bone mineral density (BMD) and bone mineral content (BMC) of children with cirrhosis. ***Methods.*** Forty children with cirrhosis (mean age, 10.4 ± 3.9 years) were involved. BMD and BMC were measured by dual energy X-ray absorptiometry at lumbar vertebrae 1–4, and the results were compared with those of 62 healthy age- and sex-matched children. ***Results.*** The mean lumbar spine BMD of patients with cirrhosis was 0.482 ± 0.107 g/cm^2 and that of the controls was 0.687 ± 0.172 g/cm^2 ($P < 0.0001$). The mean lumbar spine BMC of patients with cirrhosis was 20.008 ± 8.409 g and that of controls was 32.859 ± 14.665 g ($P < 0.0001$). After the confounding variables (weight, height, and pubertal stage) were controlled for, the difference in BMD and BMC values between patients with cirrhosis and healthy controls was significant (0.535 ± 0.061 g/cm^2 vs 0.653 ± 0.048 g/cm^2, and 24.515 ± 5.052 g vs 29.952 ± 3.971 g, respectively). ***Conclusions.*** Because of the significant difference in BMD and BMC values between our patients with cirrhosis and healthy controls, patients with cirrhosis should be evaluated for osteopenia.

Key words: cirrhosis, children, bone mineral density

Introduction

Osteoporosis is defined as a progressive systemic skeletal disease characterized by remarkable reduction of bone mineral density (BMD) and microarchitectural deterioration of bone tissue.[1] The World Health Organization has defined osteopenia as a bone mineral density between 1 and 2.5 standard deviations (SD) below the mean for healthy young adults, and a BMD SD score below –2.5 defines osteoporosis.[2] In children and adolescents, there are no densitometric criteria for diagnosing osteoporosis. The Z-score (based on pediatric databases of age- and sex-matched controls) can be used for children.

The recommended method to determine the presence and severity of bone disease is to determine BMD.[3] The dual energy X-ray absorptiometry (DEXA) technique, which is noninvasive, sensitive, and specific, has become the most commonly used method for the assessment of bone mineral content (BMC) worldwide.[4]

An association between osteoporosis and various types of liver disease has been described before. Osteoporosis is the most common form of bone disease in individuals with chronic liver disease.[3,5–7] It is associated with pathologic fractures, decreased quality of life, and increased mortality in patients with chronic liver disease.[3] The clinical course of osteoporosis has been best characterized for the chronic cholestatic liver diseases.[8,9] It has also been described in other chronic liver diseases of diverse etiologies, such as chronic viral hepatitis, autoimmune hepatitis, and alcoholic liver disease.[6,10,11] The pathogenesis of osteoporosis in those patients with chronic liver disease is not well understood. Although genetic factors are important in determining bone mass, chronic liver diseases present many potential exogenous insults to the skeleton: chronic cholestasis, poor nutrition, deficiencies in calcium and vitamin D, poor muscle mass and low body mass index, immobility, hypogonadism and other hormonal abnormalities, medications including corticosteroids, and perhaps cirrhotic-stage liver disease itself.[11] The effect of liver transplantation on bone disease is controversial, but improvement of BMD in children with chronic liver disease has been reported after liver transplantation.[12]

The first step toward prevention of this morbidity and mortality is to identify those patients who have

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osteoporosis. However, the exact prevalence of osteoporosis in patients with liver disease is unknown, especially in children. We thought that children with cirrhosis might have low BMD values compared with healthy controls, but we did not know the effect of weight, height, or pubertal stage on BMD and BMC. In this study, we investigated BMD measurements and biochemical parameters of bone metabolism in children with cirrhosis of different etiologies and compared the results with those for healthy children.

Materials and methods

From November 2002 to October 2003, we studied 40 patients with cirrhosis (23 boys, 57.5%) whose mean age was 10.4 ± 3.9 years (range, 3–17 years). The diagnosis of cirrhosis was based on liver biopsy (28 patients, 70%). For the remaining patients, the diagnosis was confirmed with biochemical, clinical, or imaging evidence. The patients were followed up for a mean period of 62.7 ± 34.9 months (median, 61.0 ± 34.9 months; range, 6–170 months). After informed consent was obtained, the Z-score, BMC (g), and BMD (g/cm^2) of lumbar vertebrae 1–4 were measured by DEXA (Hologic QDR 4500 with fan X-ray beam; Hologic, USA). The coefficient of variation, obtained by daily measurements of a standard phantom on the instrument, was 1%. The results for the patients were compared with those for 62 healthy age- and sex-matched children (34 boys, 54.8%), whose mean age was 10.8 ± 3.5 years (range, 3–16.5 years). Patients were categorized into three groups (class A, B, or C) according to Child-Pugh criteria at the beginning of the study.[13]

Serum calcium, phosphate, and alkaline phosphatase (ALP) levels were determined with standard methods for all patients with cirrhosis. 25-Hydoxy vitamin D (25-OH-D_3), intact parathormone (iPTH), and osteocalcin levels were determined by a fully automated chemiluminescence method (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) for 28, 37, and 39 patients with cirrhosis, respectively. Bone-specific alkaline phosphatase (BALP) levels were determined by enzyme-linked immunosorbent assay (Metro EIA Kit; Quidel, San Diego, CA, USA) for 38 patients with cirrhosis. These parameters were not evaluated in the control group.

Data are expressed as means ± SD. Statistical analysis was done by SPSS for Windows, release 10.0. Descriptive statistics are reported for the variables. Analyses of covariance (ANCOVA) were used to evaluate the differences in BMD and BMC between patients with cirrhosis and healthy control subjects after controlling for confounding variables (weight, height, and pubertal stage). A two-tailed P value of <0.05 was accepted as significant.

Results

Forty children with cirrhosis were enrolled in the study: nine with Wilson's disease, five with extrahepatic biliary atresia, three with progressive intrahepatic cholestasis (PFIC), two each with autoimmune hepatitis, cystic fibrosis, celiac disease, and one each with tyrosinemia and Budd-Chiari syndrome. The etiology was obscure in 15 patients and accepted as cryptogenic. The characteristics of the patients and the control group are shown in Table 1. Growth retardation (height below the third percentile) was observed in 32.5% (13 patients) of children with cirrhosis. In addition to the appropriate treatments, patients with biliary atresia and PFIC regularly received supplements of multivitamins containing vitamins D and E.

The mean Z-score of patients with cirrhosis was –2.47 ± 0.89 (range, –4.46 to +0.66) and that of controls was –0.83 ± 1.03 (range, –3.46 to +1.66). Osteoporosis (Z-score <–2) and osteopenia (Z-score between –1 and –2) were observed in 82.5% (33 patients) and 12.5% (5 patients) of children with cirrhosis, respec-

Table 1. Demographic and clinical features of patients with cirrhosis and control subjects

	Patients with cirrhosis *n* (%)	Control *n* (%)	*P*
Sex			
Male	23 (57.5)	34 (54.8)	0.565
Female	17 (42.5)	28 (45.2)	
Age, years[a] (range)	10.4 ± 3.9 (3–17)	10.8 ± 3.5 (3–16.5)	0.712
Weight, kg[a] (range)	29.1 ± 13.2 (12–62)	42.9 ± 8.9 (25.8–56.2)	0.067
Height, cm[a] (range)	122.7 ± 22.6 (89–177)	136.4 ± 19.2 (91–165)	0.388

[a] Mean ± SD

Table 2. Mean BMD and BMC values of patients with cirrhosis and healthy controls

	Patients with cirrhosis $n = 40$ mean ± SD	Controls $n = 62$ mean ± SD	P
Z-score	–2.47 ± 0.89	–0.83 ± 1.03	<0.0001
BMD (g/cm^2)	0.482 ± 0.107	0.687 ± 0.172	<0.0001
BMC (g)	20.008 ± 8.409	32.859 ± 14.665	<0.0001
After controlling for confounding variables (weight, height, and pubertal stage)			
BMD	0.535 ± 0.061	0.653 ± 0.048	<0.0001
BMC	24.515 ± 5.052	29.952 ± 3.971	0.002

BMD, bone mineral density; BMC, bone mineral content

Table 3. Mean serum levels of bone mineral metabolism parameters of patients with cirrhosis

Parameters	Number of patients tested	Patients with cirrhosis mean ± SD (range)
Ca (mg/dl) (N, 8.5–10.5)	40	8.9 ± 0.9 (7.0–10.9)
P (mg/dl) (N, 2.3–4.7)	40	4.3 ± 1.1 (2–8)
ALP (IU/l) (N, 250–1000)	40	823.5 ± 750.8 (55–4617)
25-OH-D_3 (ng/ml) (N, 10–68)	28	35.6 ± 9.6 (7.4–77.9)
iPTH (pmol/l) (N, 10–65)	37	45.3 ± 47.8 (10.8–264)
Osteocalcin (ng/ml) (N, 1.1–13.7)	39	20.6 ± 18.7 (2–100)
BALP (U/l) (N, 15–40)	38	114.2 ± 39.1 (35.2–190)

Ca, calcium; P, phosphate; ALP, alkaline phosphatase; 25-OH-D_3, 25 hydroxy vitamin D; iPTH, intact parathormone; BALP, bone-specific alkaline phosphatase; N, normal range

tively. The mean lumbar spine BMD of patients with cirrhosis and control subjects was 0.482 ± 0.107 and 0.687 ± 0.172 g/cm^2, respectively, while the mean lumbar spine BMC of patients with cirrhosis and control subjects was 20.008 ± 8.409 and 32.859 ± 14.665 g, respectively. The differences in the mean lumbar spine Z-score and BMD and BMC values between patients with cirrhosis and controls were statistically significant (Table 2). After the confounding variables (weight, height, and pubertal stage) were controlled for, the differences in BMD (0.535 ± 0.061 vs 0.653 ± 0.048 g/cm^2) and BMC (24.515 ± 5.052 vs 29.952 ± 3.971 g) between patients with cirrhosis and controls were also significant (Table 2). The patients with cholestatic diseases (five with biliary atresia and three with PFIC) had a lower mean Z-score (–2.53 ± 1.09), BMD (0.452 ± 0.093 g/cm^2), and BMC (19.027 ± 8.424 g) than the mean values of those patients with cirrhosis but without cholestasis (–2.46 ± 0.85, 0.490 ± 0.110 g/cm^2, and 20.254 ± 8.522 g, respectively). As the number of cholestatic patients was small, statistical analysis could not be performed.

Twenty-six (65%) patients were Child-Pugh class A, 11 (27.5%) were class B, and 3 (7.5%) were class C. The mean BMD was 0.495 ± 0.102 g/cm^2 in class A, 0.432 ± 0.104 g/cm^2 in class B, and 0.560 ± 0.121 g/cm^2 in class C patients. The mean BMC was 20.767 ± 77.670 g in class A, 17.134 ± 9.602 g in class B, and 23.967 ± 10.302 g in class C patients. Because of the small number of patients, statistical analysis could not be performed. The diagnosis of patients in class C was Wilson's disease in two patients and cryptogenic in one. There was no difference in BMD or BMC between patients with growth retardation (13 patients) and those without ($P = 0.151$ and $P = 0.345$, respectively).

Hypocalcemia was detected in five (12.5%) patients. High levels of serum ALP were found in 9 (22.5%), phosphate in 11 (27.5%), iPTH in 6 (16.2%), osteocalcin in 24 (61.5%), and BALP in 34 (89.5%) patients. 25-OH-D_3 levels were normal in 25 patients, low in one patient, and high in two patients. The serum osteocalcin level was found to be low in only one patient (Table 3).

Discussion

In recent years, bone mineralization has been examined across a broad spectrum of pediatric disorders, including cystic fibrosis, diabetes mellitus, leukemia, inflammatory bowel disease, and celiac disease.[14] Patients with celiac disease have lower BMD values than normal sub-

jects, regardless of the clinical presentation.[15] In this study, we evaluated the BMD of children with cirrhosis and found that the differences in BMD and BMC between our patients with cirrhosis and the healthy controls were significant after the weight, height, and pubertal stage were controlled for.

Bone mass increases mostly during growth, and the amount of bone acquired during this period of life is an important determinant of future resistance to fracture.[16] The maximum amount of whole-body bone mineral content (peak bone mass), which is thought to be achieved by the early 20s, is determined by several factors. The most important are genetic factors, and also sex and ethnic factors. The others are physical activity, nutrition, hormonal status, drug use, and the presence of chronic diseases.[16,17] The study of bone mass and bone metabolism has been also applied to younger populations since the development of DEXA, a noninvasive, sensitive, and specific method for measuring BMC.[4] However, pediatric reference data are inadequate, limiting our ability to identify children at risk for osteoporosis. Also no reference data on bone mineralization have been scaled for puberty, skeletal maturation, and body size, and data on the normal values of BMD according to ethnicity are insufficient. Only one study has reported the normal values of BMD for healthy Turkish children, and this study also found a positive correlation of BMD with age, pubertal stage, height, and weight.[18] Because of these facts, we preferred to compare BMC and BMD values after controlling for weight, height, and pubertal stage between patients with cirrhosis and controls.

Although an association of osteopenia with cirrhosis was recognized several years ago, its pathogenesis has not been well understood. Some adult studies suggest that there is decreased bone synthesis in such patients, whereas others have shown increased bone resorption in patients with cirrhosis.[5,9,10] It has been shown that, regardless of etiology, cirrhosis causes bone loss and the severity of osteopathy both worsens as liver function does,[10,19] and correlates with the extent and duration of liver disease.[5] There are many adult studies on BMD among patients with cirrhosis. Sokhi et al.[20] reported the overall prevalence of osteopenia and osteoporosis as 34.6% and 11.5%, respectively, for patients with cirrhosis awaiting liver transplantation. Bonkovsky et al.[3] studied 133 chronic liver disease patients and reported a prevalence of osteopenia ranging from 13% to 39%. They reported that the etiology of the liver disease did not affect the prevalence of osteoporosis. Our patients showed a prevalence of osteoporosis and osteopenia of 82.5% and 12.5%, respectively. Some studies have found a correlation between BMD and the clinical severity of cirrhosis[10] while others have not.[5] There are few reports about bone mineralization in pediatric patients with cirrhosis. Goncalves et al.[7] studied 20 children with chronic liver disease and found that 75% of them had osteopenia, which was particularly severe in children under 2 years of age with hyperbilirubinemia and biliary atresia or PFIC. Similarly, the patients with cholestatic diseases in our study showed lower mean BMD and BMC values than those of patients with cirrhosis. Most of our patients (92.5%) were in Child-Pugh class A or B, and only three were in class C. The relationship between the levels of BMD and BMC and the level of cirrhosis could not be determined for our patients.

Although we could not compare the biochemical results of our patients with those of the controls, we found minor hypocalcemia in five patients (two with Wilson's disease) and increased iPTH concentrations. Also BALP, osteocalcin, and ALP were found to be elevated. Increased iPTH, BALP, osteocalcin, and ALP levels can be a result of bone resorption and formation. The 25-0H-D_3 levels were found to be normal, as Bouillon et al.[21] reported before. The studies that have considered bone metabolism indexes in young patients with cirrhosis are not numerous. Some studies have shown increased bone resorption, whereas most others have shown decreased bone formation.[8–10] In general, serum calcium, phosphate, and ALP have been found to be within the normal range. Some studies have shown decreased levels of calcium and phosphorus and increased levels of iPTH.[21] Biochemical markers of bone resorption and formation have indicated no uniform mechanism of bone loss.

In conclusion, because of the difference found in BMD and BMC values between patients with cirrhosis and the healthy controls after weight, height, and pubertal stage were controlled for, patients with cirrhosis are at risk for decreased BMD and should be evaluated for osteopenia. Further studies are needed to define pediatric reference data on bone mineralization that are scaled for puberty, skeletal maturation, body size, and perhaps ethnic factors.

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