Reduced Bone Density Among Children With Severe Hemophilia

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ABSTRACT. *Objective.* **Children with severe hemophilia are at risk for reduced bone mineral density (BMD) because of reduced weight-bearing exercise and hepatitis C infection. Reduced bone density in childhood is a risk factor for osteoporosis in later life.**

Study Design. **We performed a cross-sectional survey of bone density among 19 children with severe hemophilia, at the Royal Children's Hospital. Results were correlated with findings of blinded objective evaluations of the joints of the lower limb and with hepatitis C status.**

Results. **The mean lumbar bone mineral apparent density for patients was reduced (0.102 g/cm³), compared with that for control subjects (0.113 g/cm³). The mean areal BMD *z* score was −0.92, which was significantly reduced, compared with that for control subjects. The difference in bone density was independent of body size. There was a statistically significant relationship between the lumbar BMD *z* scores and the maximal single joint evaluation scores, but there was no difference based on hepatitis C status.**

Conclusions. **Our results suggest that children with severe hemophilia have reduced BMD. Patients at risk are those with signs of hemophilic arthropathy. Because osteoporosis may complicate the future treatment of patients with hemophilia, screening of young patients for reduced bone density is recommended.** *Pediatrics* **2004; 114:e177–e181. URL: http://www.pediatrics.org/cgi/content/full/114/2/e177; *hemophilia, bone density.***

ABBREVIATIONS. BMD, bone mineral density; BMC, bone mineral content; BMAD, bone mineral apparent density; BMI, body mass index.

Osteoporosis is common, occurs throughout the world, and has become a major public health concern.[1,2] Adequate bone mass accumulation in early life is important in preventing osteoporosis.[1,3] Lifetime plots of bone density and age show that late childhood and adolescence are important periods of bone mineral acquisition.[2,3] Persons with the greatest bone mass at the end of adolescence have the greatest protection against the gradual decline in bone mass that occurs with aging.[1]

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Weight-bearing exercise is critical to ensure adequate bone mass accrual in childhood and may be even more important than dietary calcium intake.[4,5] The exact mechanism by which weight loading increases bone mass is not known but is likely related to dynamic strains in bone tissue regulating bone formation and resorption.[6] Unusually high strains and high strain rates are particularly osteogenic.[6] The skeleton is particularly responsive to the effects of weight-bearing exercise during childhood, specifically during the prepubertal years.[7] Immobilization is significant in the development of reduced bone density among children with cerebral palsy.[8,9]

Patients with severe hemophilia may be at risk for developing reduced bone density in childhood and adolescence, for a number of reasons. Until recently, only a few sports, such as golf and swimming, were recommended for patients with severe hemophilia.[10] Despite liberalization of these recommendations, children with severe hemophilia may be less likely to participate in weight-bearing, high-impact exercise. Patients with established changes of hemophilic arthropathy, characterized by pain, swelling, and joint instability, are even less likely to participate in sporting activities and may be at particular risk for reduced bone density. Finally, patients with hemophilia who have been exposed to hepatitis C through infusion of contaminated clotting factor concentrates may develop liver impairment and abnormalities in vitamin D metabolism and may be at risk of low bone density.[11,12] Patients with hemophilia and reduced bone mineral density (BMD) may be at increased risk of fractures and osteoporosis in later life.

There are no available data on the bone density of children with severe hemophilia. The aims of this study were to perform a cross-sectional survey of BMD among children with severe hemophilia and to correlate bone density with findings regarding the presence of joint disease and hepatitis C status.

METHODS

Patient Identification

Patients with severe hemophilia were identified from records maintained by the Henry Ekert Hemophilia Treatment Centre at the Royal Children's Hospital, the major tertiary pediatric institution in Melbourne, Australia. An information letter was sent to patients and parents, inviting them to participate in the study. Information regarding current treatment regimens and hepatitis C status was collected from the patients' records.

Joint Evaluation

Lower limb joints (knee and ankle) were evaluated by a study author (BE), according to published guidelines for joint evaluation among patients with hemophilia.[13] Evaluations included assessment and grading of swelling, muscle atrophy, joint deformity, presence of crepitus, range of motion, presence of flexure contracture, strength, and pain at rest and during activity. Each joint was ascribed a score. Normal joints were scored as 0, and the highest score possible for the knee or ankle was 25. The total joint evaluation scores (sum of scores for both ankles and both knees) and the maximal single joint evaluation scores were used in the analysis. The joint evaluator was blinded with respect to the bone density results.

Bone Densitometry

The BMD of the lumbar spine was assessed by using a Hologic QDR 4500 Elite densitometer (Hologic, Bedford, MA). BMD results are traditionally reported as areal BMD, which is calculated by dividing the bone mineral content (BMC) by the area measured. Areal BMD calculations have been shown to underestimate the bone density of short children, however, and to not reflect changes in bone geometry that occur during puberty.[14] The bone mineral apparent density (BMAD) is an approximation of the volumetric density of bone, calculated from the BMC and the projected volume of bone, and is a more accurate measure of bone density among children.[15] Interpretation of bone density results for children of different ages is standardized by reporting results as a SD or *z* score. A *z* score is defined as the number of SDs above or below the mean, determined using age- and gender-matched reference data, and is calculated as $(x - \text{mean})/\text{SD}$, where x is the patient value and the mean and SD are derived from control data. The expected mean *z* score for a normal population is 0.

Anthropometric Data

Height, without shoes, was measured to the nearest 1.0 cm by using a standard, Harpenden, wall-mounted stadiometer. Weight, with light indoor clothing but without shoes, was measured to the nearest 1.0 kg by using standard electronic scales. Body mass index (BMI) was calculated with the standard formula. To facilitate interpretation of patient and control anthropometric data, the values for weight, height, and BMI were converted to *z* scores by using United States revised growth charts.[16]

Control Subjects

Control patients were identified as described by Ma and Jones.[17] Briefly, control subjects were selected from schools in southern Tasmania, as part of a population-based, case-control study investigating the association between reduced bone density and upper limb fractures among children 9 to 16 years of age. All control subjects were male.

The BMD for control subjects was measured by using a Hologic QDR 2000 densitometer. Results are directly comparable between Hologic densitometers.[18]

Statistical Analyses

Results are expressed as means with 95% confidence limits or SDs. *P* values of $<.05$ were considered significant. Nonparametric tests were used to compare means between groups. Spearman rank correlation was used to compare joint evaluation and bone density results. Multivariate analysis was used to determine the effects of age, height, and weight on bone density among patients with hemophilia. Univariate and multivariate analyses were performed with SPSS software, version 8.0 for Windows (SPSS Inc, Chicago, IL). All other analyses were performed with Stata software, version 8.0 (Stata Corp, College Station, TX).

Ethics Committee Approval

The Royal Children's Hospital ethics committee and the Radiation Safety Committee of the Department of Human Services, State Government of Victoria, approved the study.

RESULTS

Demographic Findings

Thirty-nine patients with severe hemophilia A were invited to participate in this study. Twenty-one patients (53%) responded, with ages ranging from 5.73 to 18.5 years. Two patients were excluded, ie, 1 patient with morbid obesity, which affected the measurement of BMD, and 1 patient with cerebral palsy, who was wheelchair-bound. There was no difference between responders and nonresponders with respect to severity of hemophilia (for all patients, factor VIII levels were <1%) or mean age (mean age for responders: 12.2 years; mean age for nonresponders: 12.0 years; $P = .89$).

Of the 19 patients involved in the study, 15 patients (79%) were receiving thrice-weekly prophylactic factor VIII replacement. The remaining 4 patients had been treated previously with prophylactic factor VIII, but 2 patients were currently receiving on-demand factor VIII and 2 patients had developed inhibitors to factor VIII and were being treated with on-demand recombinant factor VIIa. Eight patients (38.1%) exhibited hepatitis C-specific antibody positivity. None of those patients was being treated actively for the hepatitis C infection.

Two hundred fifteen male control subjects were recruited as previously described. There was no difference between the mean age of the patients and that of the control subjects (Table 1).

Joint Evaluation

The mean maximal single joint evaluation score was 5.3 of a possible 25 (range: 1–10 of 25). The mean total joint evaluation score was 9.9 of a possible 100 (range: 2–24 of 100).

Anthropometric Data

Anthropometric data for patients and control subjects are presented in Table 1. There was no significant difference in height or weight between patients and control subjects. There was also no difference in weight, height, or BMI *z* scores between patients and control subjects.

Bone Density

The mean BMC, areal BMD, and BMAD results are reported in Table 1. The difference in BMAD between patients and control subjects was significant (Mann-Whitney test, $P = .0047$). The areal BMD *z* scores for patients were reduced (−0.92; 95% confidence interval, −1.40 to −0.45), compared with those for control subjects (Fig 1).

TABLE 1. Age and Anthropometric Data for Patients With Hemophilia and Control Subjects

	Mean (SD)		*P* Value*
	Hemophilia ($N = 19$)	Control ($N = 215$)	
Age, y	12.2 (3.5)	12.8 (2.1)	.40
Weight, kg	46 (15)	52 (18)	.23
Height, cm	151 (20)	157 (17)	.13
Weight *z* score	0.25 (1.1)	0.46 (0.91)	.37
Height *z* score	0.66 (0.84)	0.33 (1.0)	.31
BMI *z* score	0.19 (1.3)	0.38 (0.87)	.37
Spine BMC, g	38 (19)	39 (16)	.38
Spine BMD, g/cm^2	0.72 (0.19)	0.79 (0.19)	.07
Spine BMAD, g/cm^3	0.102 (0.02)	0.113 (0.01)	.005

* Mann-Whitney test.

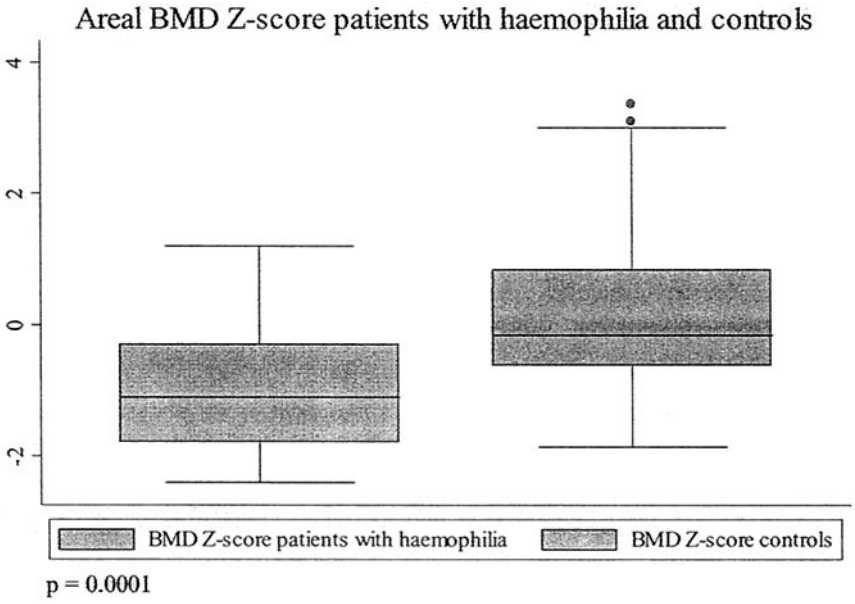


Fig 1. Areal BMD *z* scores for patients with severe hemophilia.

Univariate and multivariate regression analyses demonstrated the difference in bone density to be independent of height and weight (Table 2). Spearman regression analysis showed a statistically significant relationship between the BMD *z* scores and the maximal single joint evaluation scores (Spearman $\rho = -0.49$; $P = .03$). The correlation between BMD *z* scores and maximal total joint evaluation scores approached statistical significance (Spearman $\rho = -0.44$; $P = .06$) (Fig 2). There was no statistical difference in the mean lumbar BMD *z* scores for patients with hepatitis C exposure versus those without hepatitis C exposure ($P = .65$).

DISCUSSION

The long-term survival of children with hemophilia has improved dramatically, with respect to both life expectancy and quality of life.[19,20] This is partly attributable to primary prophylaxis and improved treatment regimens.[19] Skeletal integrity is crucial for a good quality of life. In this study, we demonstrated that children with severe hemophilia could have moderately reduced bone density, compared with gender- and age-matched control subjects. This reduction in bone density was independent of differences in age and body size. There was a statistically significant association between areal BMD *z* scores and objective lower limb joint evaluation results. Patients with more established changes resulting from hemophilic joint disease exhibited the lowest BMD. There was no difference in bone density according to hepatitis C exposure. These results support reduced physical activity as the most likely explanation for reduced bone density among children with severe hemophilia.

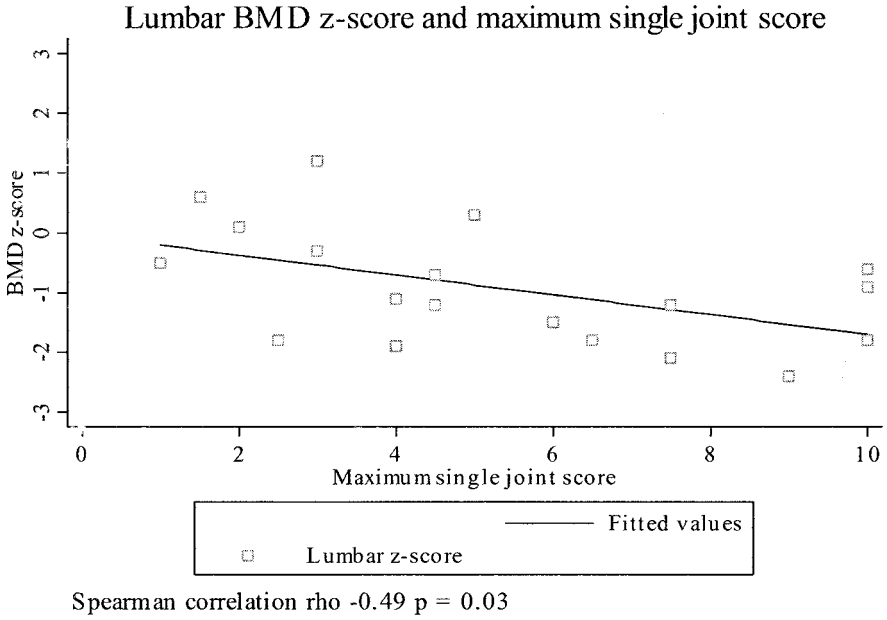
One study previously investigated the incidence of reduced bone density among patients with hemophilia.[11] Gallacher et al[11] reported a reduction in bone density among 19 adult patients with severe hemophilia (age range: 18–69 years). There was no difference in markers of bone resorption between patients and control subjects, suggesting that the reduced bone density was not secondary to increased bone turnover. Minor abnormalities in liver function tests and testosterone metabolism among the patients with hemophilia were suggested to be secondary to hepatitis C-associated liver disease and the likely cause of the reduced BMD. Liver disease may be associated with hypogonadism, abnormalities in vitamin D metabolism, and hyperbilirubinemia, leading to reduced bone formation and increased bone resorption.[12,21] Eight patients in our study had been exposed to hepatitis C, and there was no significant difference in bone density between those patients and the patients who had not been exposed to hepatitis C. None of the hepatitis C-positive patients was receiving treatment for liver disease. If the hepatitis C-associated liver disease progressed, however, then it might have significant effects on bone density among those patients.

There was a significant correlation between reduced bone density and joint evaluation scores in our study. The use of joint evaluation tools is designed to detect hemophilic arthropathy changes.[13] Although prophylactic clotting factor therapy and modern hemophilia treatment regimens have dra-

TABLE 2. Univariate and Multivariate Analyses of Hemophilia and Bone Mass

	Univariate β (95% CI)	Multivariate* β (95% CI)
BMC (g)	−1.7 (−9.3, +6.0) ($P = 67$)	+3.8 (−0.2, +7.7) ($P = .06$)
BMD (g/cm^2)	−0.06 (−0.14, +0.01) ($P = .09$)	−0.02 (−0.06, +0.03) ($P = .50$)
BMAD (g/cm^3)	−0.011 (−0.018, −0.003) ($P = .001$)	−0.009 (−0.014, −0.003) ($P = .002$)

* Adjusted for age, height, and weight.



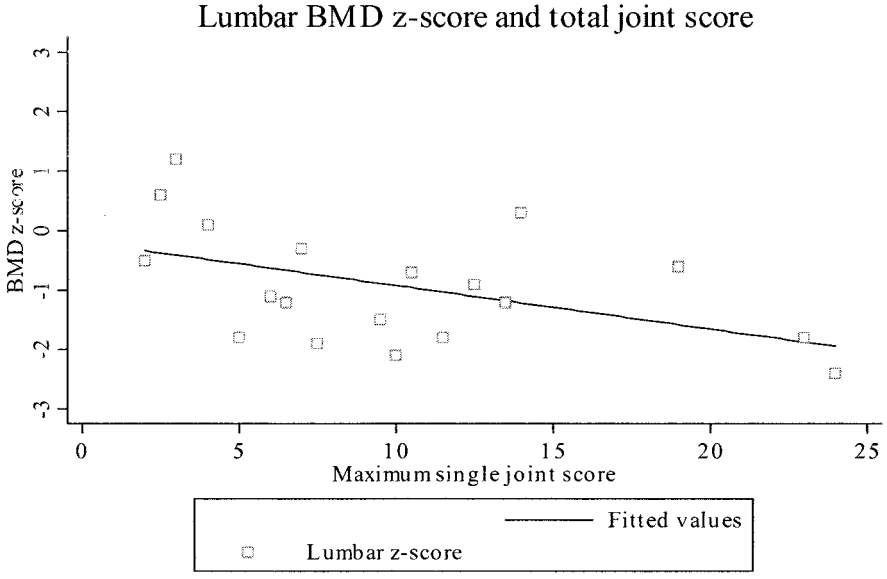


Fig 2. Regression analysis of z scores and joint evaluation scores.

matically reduced the incidence of hemophilic arthropathy,[19] some patients continue to experience episodes of repeated bleeding into "target joints," with synovial membrane thickening, reduced range of movement, and muscle wasting.[22] Treatment of these patients may be difficult and may require prolonged periods of immobilization and joint splinting. The significant correlation between BMD and joint changes in our study provides support for the role of weight-bearing activity in maintaining adequate bone density among children with hemophilia.

A number of therapies exist for children with reduced bone density.[1,23] Calcium and vitamin D supplementation can be used to increase spinal BMD.[1] Exercise intervention trials have demonstrated durable beneficial effects of high-impact exercise on bone density among children.[24,25] Developing exercise programs to treat low bone density among patients with severe hemophilia may be difficult, particularly for patients with established hemophilic arthropathy changes. However, supervised exercise training performed at times of maximal clotting factor prophylaxis could reduce the risks of additional joint bleeding. Bisphosphonate therapy has been effective for treatment of children with metabolic bone disease and osteoporosis, but a number of issues (including the optimal dose and duration of therapy among children) need to be resolved.[23]

A strength of this study was the fact that we used randomly selected, population-based, control subjects; this provided a representative sample for comparison and facilitated evaluation of the important question of whether the deficit in bone mass was attributable to smaller body size or was an accurate indication of bone density. Currently, there is no acceptable reference database for children in our geo-

graphic location; therefore, locally recruited control subjects were preferred. The control subjects were not from the same source population as the patients, however. This might lead to bias if there are regional differences in bone density and its determinants. Although southern Tasmania and Victoria have similar latitudes and remarkably similar total fracture rates among adults,[26] there are no comparative data on bone densities among children in the 2 regions. However, recent work demonstrated only very small differences in bone density between control populations in Hobart, Sydney, and New Zealand (M. Henry, unpublished data), and any potential differences attributable to location bias are very unlikely to explain the difference we observed between patients and control subjects in this study.

Given the importance of adequate bone mineralization in childhood for the prevention of osteoporosis in later life, we recommend assessment of bone density for children with severe hemophilia, particularly children with objective changes of hemophilic arthropathy. Management of reduced bone density among those patients is then possible.

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