Bone mineral density in children with myelomeningocele

SUSAN D APKON MD[1] | LAURA FENTON MD[2] | JOSEPH R COLL PHD[3]

1 Department of Physical Medicine and Rehabilitation, University of Colorado School of Medicine and The Children's Hospital, Aurora CO, USA. **2** Department of Radiology, The Children's Hospital, Aurora CO, USA. **3** Department of Preventive Medicine and Biometrics, University of Colorado School of Medicine, Aurora CO, USA.

Correspondence to Dr Susan D Apkon at Department of Rehabilitation Medicine, The Children's Hospital, 13123 East 16th Avenue, B285, Aurora, CO 80045, USA. E-mail: apkon.susan@tchden.org

PUBLICATION DATA
Accepted for publication 9th June 2008.
Published online September 22 2008.

LIST OF ABBREVIATIONS
BMD Bone mineral density
DEXA Dual energy X-ray absorptiometry

ACKNOWLEDGMENTS
This work was supported in part from grant number H133B980022, National Institute on Disability and Rehabilitation Research (NIDRR), and grant number RR00069, General Clinical Research Centers Program, National Center for Research Resources, National Institutes of Health.

The aim of the present study was to document bone mineral density (BMD) in children with myelomeningocele and to identify variables that contribute to reduced BMD. The study included 24 children with myelomeningocele (nine males, 15 females; age range 4–18y), who had varied levels of neurological impairment (thoracic/high-lumbar, *n*=6; mid-lumbar, *n*=9; sacral, *n*=9) and ambulatory status (non-ambulators, *n*=12; part-time ambulators *n*=2; full-time ambulators, *n*=10). BMD measurements of the femoral neck and whole body using dual energy X-ray absorptiometry assessments of dietary calcium intake, and serum markers of bone metabolism were obtained. BMD is presented as standardized scores (z-scores) which are age- and sex-matched to normally developing children. The mean femoral-neck z-score was –2.41. Femoral-neck z-scores differed significantly according to ambulatory status, with lower z-scores in children who were wheelchair-dependent (p=0.03). The mean z-score at the femoral neck demonstrated a trend toward lower z-scores in children with higher levels of lesions. Almost all children met their recommended daily intake of calcium. Markers of bone metabolism were normal in all patients. This study demonstrates that reduced BMD is a major complication in children with myelomeningocele. There is a significant relationship with low BMD in children who are wheelchair-dependent, a trend in those with higher neurological levels, and no relationship between fractures and reduced BMD.

Spina bifida is the second most common disability in childhood after cerebral palsy.[1] It represents a variety of congenital neural-tube defects, including myelomeningocele. Children with spina bifida have variable degrees of sensory and motor loss, typically in the lower extremities, and ambulation is impaired in many children as a result of these losses. The level of neurological injury assists in predicting the child's ability to ambulate within the home and community.[2] Children with spina bifida have a higher incidence of fractures than normally developing children. The incidence of fractures in this population has been reported to range from 11.5 to 30%.[3–6] This high rate is thought to be secondary to osteoporosis, related to immobility and muscle weakness, and infrequently related to significant trauma.[6] Documentation of osteoporosis in this population is limited.

The primary aim of the present study was to determine the prevalence of osteoporosis in children with myelomeningocele. A secondary aim was to identify other variables that may contribute to the presence of osteoporosis, such as nutritional status, neurological level, and ambulatory status. We hypothesized that children who were wheelchair-dependent would have lower bone mineral density (BMD) than children who were ambulatory.

METHOD

Participants

A cross-sectional observational study was performed with 24 children and adolescents from the Spinal Defects clinic at the Children's Hospital, Aurora, Colorado, USA. All children had the diagnosis of myelomeningocele. Children and adolescents aged 4 to 21 years were eligible to

participate in the study regardless of their neurological level or ambulatory status, but were excluded if they had treatment with bisphosphonate medication, a history of a spine fusion or other procedure resulting in the presence of orthopedic hardware, or a recent history (<3mo) of casting of one or more extremity. Children were also excluded if they had a hip flexion contracture greater than 30° in both lower extremities or a recent proximal femur fracture, as this prevented an accurate measurement at the femoral neck.

A total of 24 children (nine males, 15 females) were enrolled in this study. The mean age was 9 years 8 months (range 4y 5m–18y). Neurological levels of the children were classified into three groups, with six children having a thoracic or high-lumbar level, nine children having a mid-lumbar level (knee extension but no movement at the foot or ankle), and nine children having a sacral level. Twelve children were non-ambulatory, requiring a wheelchair full-time, two children were part-time ambulators, and 10 children were full-time ambulators. Ten children had histories of at least one fracture: all fractures were in the lower extremities and occurred with minimal trauma, three children had multiple fractures, and in one child the fracture occurred after the lower extremity was casted.

Informed consent was obtained from all parents, and children over 7 years old signed an assent form. This study was approved by the Colorado Multiple Institutional Review Board.

Bone density measurements

BMD of the femoral neck and whole body was measured using dual energy X-ray absorptiometry (DEXA; Lunar Corporation, Model DP3, Madison, WI, USA). The lumbar spine was not evaluated because of known vertebral arch abnormalities in children with spina bifida. To adjust for the normal increases seen with aging, BMD is presented as standardized scores (z-scores), which are age- and sex-matched to normally developing children. Normative data were provided by the Lunar Corporation software package. In this study, an SD of 2.5 or more below the mean for age- and sex-matched normally developing children represented osteoporosis, and an SD of between 1 and 2.5 below the mean for age- and sex-matched normally developing children represented osteopenia.

Calcium intake

Calcium intake was assessed using the Rockett Youth/Adolescent food frequency questionnaire, which reviews the diet over the past year. Daily calcium needs were based on the recommended daily allowances of the US Food and Nutrition Board.[7]

Serum analyses

Peripheral venous blood samples were obtained to assess levels of calcium, phosphorus, alkaline phosphatase, and urine calcium and creatinine. They were analyzed by the Children's Hospital Laboratory, Denver, CO, USA.

Statistical analyses

The BMD z-scores were used to classify the existence of osteoporosis and osteopenia in children with spina bifida. Exact 95% confidence intervals [CI] were calculated for the prevalence of osteoporosis and osteopenia based on the binomial distribution. Two-sided one-sample *t*-tests were used to test whether the age- and sex-matched BMDs were significantly different from zero. Comparisons of whole-body and femoral-neck z-scores for children with and without a history of fractures were evaluated using a two-sided two-sample *t*-test. Differences in BMD by neurological impairment and ambulatory status were evaluated using a one-way analysis of variance (ANOVA) to compare the groups. The small sample did not allow a two-way ANOVA comparing neurological impairment and ambulatory status simultaneously. Multiple linear regression analysis was used to evaluate the association of fracture history and age with the femoral-neck z-score. Distribution of residuals appeared to follow a normal distribution, indicating that the assumptions of the multiple linear regression were not violated. Pearson's correlation coefficients were calculated to measure the association between BMD and laboratory assessments. The 95% confidence limits of the correlation coefficients were constructed using Fisher's z transformation. Missing data were not imputed. Data were analyzed using SAS (version 9.1).

RESULTS

Bone mineral density

Whole-body DEXA was obtained from 23 of the 24 children, with a mean z-score of 0.15, indicating no difference between the study group and age- and sex-matched comparison groups (Table I). No child had values in the osteoporosis range, and only two had evidence of osteopenia. A DEXA at the femoral neck was obtained from 21 of the 24 children. Scans of the first two children were not obtained because the radiology staff were not used to obtaining this scan on a regular clinical basis, and were unobtainable for a third child because of difficulty positioning on the table. The mean femoral-neck z-score for the remaining 21 children was −2.41, indicating a statistically significant decrease in BMD. Significant osteoporosis was diagnosed in nine of the 21 children (42.9%; exact 95% confidence limits 21.8%, 65.0%), and osteopenia was diagnosed in seven children (33.3%; exact 95% confidence limits 14.6%, 57.0%).

The mean femoral-neck z-score for children with a history of fractures was −2.66. Children without a history of fractures had a mean z-score of −1.89. The univariate relationship between a history of fractures and the femoral-neck z-score was not significant (p=0.39). However, multiple regression analysis of the femoral-neck z-score by fracture history controlling for age showed a significant interaction of age and fracture history ($F_{1,16}$=7.46; p=0.01; Fig. 1). When stratifying the analysis by fracture history, there is a strong negative correlation between age and femoral-neck z-score for those with a history of a fracture (r=−0.82; 95% confidence limits −0.96, −0.30; p=0.004), indicating that increasing age is associated with lower z-scores. There does not appear to be a relationship between age and femoral-neck z-score for children without a history of fractures (r=0.02; 95% confidence limits −0.59, 0.61; p=0.96).

Neurological impairment and ambulatory status

Whole-body z-scores did not differ significantly among the neurological impairment groups ($F_{2,20}$=0.30; p=0.75). The mean z-score at the femoral neck demonstrated a clear trend toward lower z-scores in the children with higher levels of lesions, but the difference was not statistically significant among the three groups ($F_{2,18}$=1.80; p=0.19).

Comparison of whole-body z-scores by ambulatory status demonstrated no significant difference among children who were wheelchair-dependent, partial ambulators, or fully ambulatory ($F_{2,20}$=0.56; p=0.58). There was a statistically significant difference in femoral-neck z-scores among the ambulatory status groups, with lower z-scores in children who were wheelchair dependent ($F_{2,18}$=4.14; p=0.03).

Dietary calcium intake

According to a food frequency questionnaire, 18 of 19 children who completed the survey met the recommended daily intake of calcium based on their age requirements. None of the children took supplemental calcium or vitamin D on a daily basis.

Biochemical markers of bone metabolism

Serum levels of calcium, phosphorus, and alkaline phosphatase were normal in all children. The ratio of urine calcium to creatinine was normal in all 18 children from whom urine was obtained.

Table I: Whole-body and femoral-neck z-scores by fracture history, neurological injury level, and ambulatory status

	n	Mean z-score	SD	95% CL	Min	Max	t	*p*
Whole body	23	0.15	0.89	(−0.23, 0.54)	−1.30	1.70	0.81	0.42
Fractures								
No history	12	−0.08	0.85	(−0.62, 0.46)	−1.10	1.30	−0.34	0.74
History	9	0.33	0.92	(−0.37, 1.03)	−1.30	1.70	1.08	0.31
Neurological impairment level								
Thoracic/high lumbar	5	−0.04	1.02	(−0.95, 0.88)	−1.30	0.60	−0.11	0.92
Mid lumbar	9	0.33	1.02	(−0.46, 1.11)	−1.10	1.70	0.96	0.37
Sacral	9	0.08	0.89	(−0.60, 0.76)	−1.00	1.40	0.26	0.80
Ambulatory status								
Wheelchair-dependent	11	0.32	0.93	(−0.30, 0.95)	−1.30	1.70	1.15	0.28
Partial ambulators	2	−0.35	1.06	(−9.88, 9.18)	−1.10	0.40	−0.47	0.72
Fully ambulatory	10	0.06	0.86	(−0.55, 0.67)	−1.00	1.40	0.22	0.83
Femoral neck	21	−2.41	2.05	(−3.34, −1.47)	−6.61	0.71	−5.37	<0.001
Fractures								
No history	11	−1.89	1.43	(−2.85, −0.92)	−4.11	0.35	−4.36	0.001
History	9	−2.66	2.47	(−4.56, −0.77)	−6.61	0.71	−3.24	0.01
Neurological impairment level								
Thoracic/high lumbar	4	−3.54	2.41	(−7.37, 0.30)	−6.61	−0.98	−2.93	0.06
Mid lumbar	8	−2.86	2.09	(−4.60, −1.11)	−5.79	0.05	−3.87	0.01
Sacral	9	−1.50	1.67	(−2.79, −0.22)	−4.11	0.71	−2.70	0.03
Ambulatory status								
Wheelchair-dependent	9	−3.60	2.27	(−5.35, −1.85)	−6.61	0.05	−4.75	0.001
Partial ambulators	2	−2.82	1.05	(−12.28, 6.65)	−3.56	−2.07	−3.78	0.16
Fully ambulatory	10	−1.25	1.30	(−2.17, −0.32)	−3.08	0.71	−3.03	0.01

CL, confidence limits.

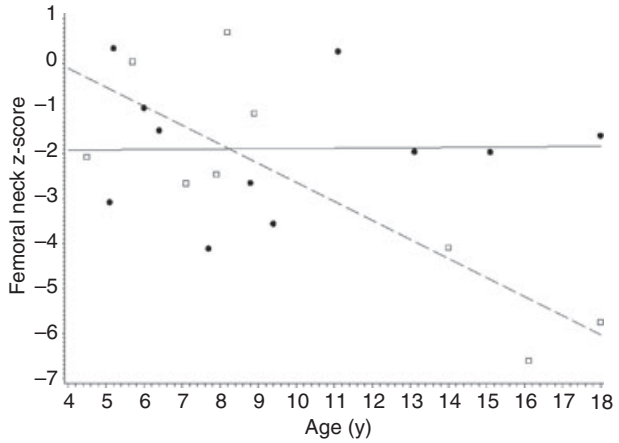

Figure 1: Multiple regression analysis of femoral-neck z-scores by fracture history controlling for age, showing a significant interaction of age and fracture history. Solid data points indicate `no history of fracture' and open squares indicate `history of fracture'.

Correlations of the femoral-neck z-score with the laboratory assessments demonstrated that alkaline phosphatase had a positive correlation with improved BMD (r=0.41; 95% confidence limits −0.03, 0.71; p=0.06). No relationship was seen with the other assessments, including calcium or phosphorus.

DISCUSSION

Our findings support a high prevalence of reduced BMD at the femoral neck in children with spina bifida, regardless of their neurological level or ambulatory status. This study supports the work of Rosenstein and Quan, who both reported reduced BMD in children with spina bifida.[8,9] In children with myelomeningocele, Rosenstein and colleagues found that the neurological level of the spinal cord injury and the child's ambulatory status best predicted their BMD in their upper and lower extremities as measured by ^{125}I photon absorptiometry.[8] Quan and colleagues measured BMD at the distal radius in children with spina bifida,[9] using similar outdated technology to Rosenstein. BMD at the distal radius was approximately 1 to 2 SDs below the mean of a normal population. Ambulatory status did not affect BMD in their study. Valtonen et al. studied the presence of osteoporosis in adults with spina bifida:[10] one-third of participants had osteoporosis in at least one of the measured sites, which included the proximal femur and distal radius. This is the only known published study addressing bone health in adults with spina bifida.

Mingin et al. investigated the bone growth and metabolic consequences of bladder augmentation on children with myelomeningocele.[11] The authors found no difference in BMD of the forearm between those who were augmented and those who were not. Koch et al. similarly investigated metabolic changes with urinary diversion procedures.[12] Their results did demonstrate reduced BMD in those with ileal conduits, but there was no difference between patients with conduits and the comparison children.

A strength of the present study was the comparison of the study group with age- and sex-matched peers, the standard method when using DEXA, as BMD accrues as children get older and peaks early in the second decade. This was something not done in the study by Rosenstein et al.[8] In comparison to our study, Quan et al.[9] reported DEXA results of the distal radius, a site that is less frequently fractured in children with spina bifida. The selection in the present study of the femoral neck to measure BMD was based on the higher incidence of fractures of the femur. However, six children had to be excluded from our study because of significant hip flexion contractures. Measurement of the lateral distal femur has been described by Henderson et al. and can be used whenever prominent hip flexion contractures exist.[13] In the future, use of this technique is likely to replace the measurement at the femoral neck in children with disabilities.

As expected, our study documented that ambulatory status affected BMD at the proximal hip. Children who were full-time ambulators had significantly better BMD at the femoral neck than children who were dependent on wheelchairs for mobility or who ambulated only part-time. These findings are likely to be a result of the benefits of active weight-bearing on BMD. Weight-bearing during ambulation should not be confused with passive weight-bearing in a device such as a standing frame. There is a dearth of evidence that passive weight-bearing in children with spina bifida improves BMD.

The strong trend toward improved BMD in children with lower neurological levels was expected. A small sample size did not provide the necessary power to detect a statistical significance between groups. The presence of low BMD in children with sacral-level myelomeningocele with minimal gait impairments was unexpected, as all but one of the children in the sacral-level group was fully ambulatory. The explanation for this finding may be related to the presence of generalized weakness around the hip due to poor innervation of the sacral-level gluteal muscles. Larson and Henderson reported development of early osteoporosis in young males with Duchenne muscular dystrophy and proximal muscle weakness while they were ambulatory with minimal gait abnormalities.[14] Inclusion of children who were ambulatory and had lower neurological levels allows a greater understanding of all children with spina bifida rather than just those who are wheelchair-dependent.

Although fractures were present in 45% of our children, no relationship between a history of fractures and low BMD was seen. This may be due to the mean age of the children (9y 8mo). If an older population had been studied, the relationship might have existed, as the results suggest that older children with a history of fractures have lower femoral-neck z-scores than older children without a history of fractures. The lack of an association is an important clinical point, in that treatment of the low BMD may not improve the incidence of fractures for younger children with spina bifida.

The present study contributes to the growing body of evidence that osteoporosis exists in children with disabilities. Future research needs to establish a clearer relationship between low BMD and risk of fractures, as this study could not confirm these findings. Children with spina bifida who sustain a fracture may lose time from school and can develop pressure sores related to placement of a poorly padded cast, and wheelchair positioning may be difficult because of the cast or splint.

Despite evidence of osteoporosis in children with spina bifida, this center and many centers like ours have not adopted a universal treatment regimen to prevent or treat osteoporosis. There is no current evidence that supplemental calcium or vitamin D alone will improve BMD in children with spina bifida. Use of bisphosphonate medications such as oral alendronate and intravenous pamidronate have demonstrated improvements in BMD in children with a variety of disabilities but are not currently standard care or approved by the US Food and Drug Administration (FDA) to be used in children.[15–18] The FDA has approved teriparatide, a portion of human parathyroid hormone, for the treatment of osteoporosis in postmenopausal women who are at high risk of a fracture, but again this is not approved for use in children.

CONCLUSION

The present study demonstrates that osteoporosis and osteopenia are a major complication in children with spina bifida. It establishes the significant relationship with low BMD in children who are wheelchair-dependent compared with ambulatory children. There was a strong trend toward lower BMD in children who have higher neurological levels. Children with a history of fractures did not appear to have reduced BMD.

REFERENCES

1. Molnar GE, Murphy KP. Spina bifida. In: Molnar GE, Alexander MA, editors. Pediatric Rehabilitation. Philadelphia: Hanley & Belfus, 1999; 219–44.
2. Agre JC, Findley TW, McNally MC, et al. Physical activity capacity in children with myelomeningocele. *Arch Phys Med Rehabil* 1987; **68:** 372–77.
3. Drummond DS, Moreau M, Cruess RL. Post-operative neuropathic fractures in patients with myelomeningocele. *Dev Med Child Neurol* 1981; **23:** 147–50.
4. James CC. Fractures of the lower limbs in spina bifida cystica: a survey of 44 fractures in 122 children. *Dev Med Child Neurol* 1970; **22:** (Suppl 22) 88–9.
5. Korhonen BJ. Fractures in myelodysplasia. *Clin Orthop* 1971; **79:** 145–55.
6. Lock TR, Aronson DD. Fractures in patients who have myelomeningocele. *J Bone Joint Surg* 1989; **71:** 1153–57.
7. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. DRI Dietary Reference Intakes For Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington DC: National Academy Press, 1999.
8. Rosenstein BD, Greene WB, Herrington RT, Blum AS. Bone density in myelomeningocele: the effects of ambulatory status and other factors. *Dev Med Child Neurol* 1987; **29:** 486–94.
9. Quan A, Adams R, Ekmark E, Baum M. Bone mineral density in children with myelomeningocele. *Pediatrics* 1998; **102:** E34.
10. Valtonen KM, Goksor LA, Jonsson O, Mellstrom D, Alaranta HT, Viikari-Juntura ER. Osteoporosis in adults with meningomyelocele: an unrecognized problem at rehabilitation clinics. *Arch Phys Med Rehabil* 2006; **87:** 376–82.
11. Mingin GC, Nguyen HT, Mathias RS, Shepherd JA, Glidden D, Baskin LS. Growth and metabolic consequences of bladder augmentation in children with myelomeningocele and bladder exstrophy. *Pediatrics* 2002; **110:** 1193–98.
12. Koch MO, McDougal WS, Hall MC, Hill DE, Braren HV, Donofrio MN. Long-term metabolic effects of urinary diversion: a comparison of myelomeningocele patients managed by clean intermittent catheterization and urinary diversion. *J Urol* 1992; **147:** 1343–47.
13. Henderson RC, Lark RK, Newman JE, et al. Pediatric reference data for dual x-ray absorptiometric measures of normal bone density in the distal femur. *Am J Roentgenol* 2002; **178:** 439–43.
14. Larson CM, Henderson RC. Bone mineral density and fractures in boys with Duchenne muscular dystrophy. *J Pediatr Orthop* 2000; **20:** 71–74.
15. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *N Engl J Med* 1998; **339:** 947–52.
16. Steelman J, Zeitler P. Treatment of symptomatic pediatric osteoporosis with cyclic single-day intravenous pamidronate infusions. *J Pediatr* 2003; **142:** 417–23.
17. Plotkin H, Rauch F, Bishop NJ, et al. Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. *J Clin Endocrinol Metab* 2000; **85:** 1846–50.
18. Henderson RC, Lark RK, Kecskemethy HH, Miller F, Harcke HT, Bachrach SJ. Bisphosphonates to treat osteopenia in children with quadriplegic cerebral palsy: a randomized, placebo-controlled clinical trial. *J Pediatr* 2002; **141:** 644–51.