ABSTRACT. Background. Difficulties with ambulation in patients with myelomeningocele often lead to physical inactivity, osteoporosis, and subsequent development of pathologic fractures.

Objective. The purpose of this study was to examine bone mineral density and biochemical markers of bone metabolism in patients with myelomeningocele.

Design and Methods. A total of 35 patients between 6 and 19 years of age with myelomeningocele (ambulatory and nonambulatory) were randomly chosen at the Texas Scottish Rite Hospital for Children. We measured bone mineral density of the distal radius in these patients using single photon absorptiometry and measured the biochemical markers of bone metabolism including parathyroid hormone, 1,25 vitamin D, osteocalcin, urinary pyridinolines/deoxypyridinolines, and urinary calcium excretion.

Results. Bone mineral density of the distal radius in the patients with myelomeningocele was 1 to 2 standard deviation units below the mean of the normal population. There were no significant differences between ambulators and nonambulators. However, bone mineral density of the 8 patients who suffered multiple fractures (19) was significantly lower than that for those remaining patients without fractures. Elevated urinary pyridinoline levels, which indicate elevated bone reabsorption, were found more frequently in both non- and limited ambulators than in full-time ambulators. Urinary calcium excretion also was greater than twofold higher in nonambulatory patients versus ambulatory patients. There were no other differences in the biochemical markers of bone metabolism (osteocalcin, parathyroid hormone, 1,25 vitamin D, and urinary deoxypyridinolines) between ambulators and nonambulators. Bone mineral density rises in normal growing children 6 to 19 years of age. When the boys and girls were considered separately, bone mineral density rises with age in boys, but not in girls.

Conclusion. Patients with myelomeningocele have decreased bone mineral density and are at risk of suffering pathologic bone fractures. The measurement of bone mineral density may help to identify those patients at greatest risk of suffering multiple fractures. The urinary calcium excretion of nonambulators was higher than that of ambulators and likely contributes to their decreased bone mineral density. Bone mineral density increases with age in boys, but not in girls. Pediatrics 1998;34(102). URL: http://www.pediatics.org/cgi/content/full/34/102/e34; spina bifida, bone densitometry, osteoporosis, pathologic fractures.

ABBREVIATIONS. FTWC, full-time wheelchair patient; LA, limited ambulator; FTA, full-time ambulator; PTH, parathyroid hormone; OSTEO, serum osteocalcin; PYR, urinary pyridinolines; dPYR, urinary deoxypyridinolines.

Lower extremity sensory and motor deficits are found frequently in patients with myelomeningocele. These deficits can impair normal ambulation and lead to variable degrees of physical inactivity, osteoporosis, and development of pathologic fractures.1–6 Such fractures lead to a vicious cycle in which further inactivity continually heightens the risk of repeated fractures. Frequent spine surgeries followed by spica cast immobilization also exacerbate the development of such pathologic fractures.3,4

Despite the high risk of fractures in children with myelomeningocele, little is known about their bone mineral density and its relationship to fractures. Rosenstein et al found that the neurologic level of spinal cord involvement and ambulatory status affected bone mineral density of both the upper and the lower extremities as measured by 125I photon absorptiometry of the distal radius, tibia, and first metatarsal, respectively.7 Specifically, ambulatory patients who had sacral involvement had greater bone mineral density than those who were nonambulatory and had higher level thoracic involvement. However, this study only examined and compared bone mineral density measurements between different subgroups of patients with myelomeningocele. No comparisons of bone mineral density were made with those of normal children and no biochemical markers of bone metabolism were examined.

In this study, we report the results of bone mineral density measurements in patients with myelomeningocele and compare them with results for North American children. Measures of metabolic bone activity also are examined.

METHODS

Patients

Sixty patients with myelomeningocele were randomly chosen from a roster of >700 patients with myelomeningocele followed at the Texas Scottish Rite Hospital in Dallas, TX. Patients with metabolic acidosis, renal insufficiency, or other metabolic bone disease (ie, hyperparathyroidism) were excluded from this study. Of these 60 patients, 43 consented to participate in the study. Because known bone mineral density standards in children are available for the 6- to 19-year-old age group, we limited our study to the 35 patients (18 males and 17 females) in this age range. The remainder were younger than 6 years of age. The average age was 11.1 ± 3.6 years.

The ambulatory status of individuals within this group varied greatly and was categorized into three broad groups, defined as...
Bone Densitometry Measurements

Bone density measurements were obtained with a Norland Digital Model 278 \(^{12}\) absorptiometer (Norland, Fort Atkinson, WI). A highly collimated low-energy \(^{125}\)I photon beam (27.4 keV) and its corresponding scintillation detector are scanned across the forearm on opposite sides of the distal radius (one-third the distance from the ulnar styloid process to the olecranon). Changes in the beam intensity noted after traversing the radius are inversely proportional to bone mineral content and bone width. The absolute bone mineral content also varies according to the size and shape of the proximal radius. \(^9\) –11

Bone mineral density (BMC/BW) in different ambulatory categories; and for FTA patients, 8 had lumbosacral involvement; for LA patients, 10 had lumbar involvement; and for FTA patients, 8 had lumbar involvement and 5 had sacral involvement.

In all study patients, blood and urine samples were collected at the Texas Scottish Rite Hospital for Children and sent for analysis at either the hospital’s clinical laboratory or the Nichols Institute (San Juan Capistrano, CA). In all 35 patients, laboratory evaluation of the blood sample consisted of measurement of serum electrolytes, including BUN and creatinine, venous blood gas, parathyroid hormone (PTH), di-hydroxy 1,25 vitamin D, and serum osteocalcin (OSTEO). PTH and OSTEO levels were measured at the Nichols Institute via a radioimmunoassay and radioimmunoassay, respectively. Osteocalcin is a small peptide released into circulation during bone mineralization and therefore represents bone formation. The di-hydroxy 1,25 vitamin D level was measured at the Nichols Institute via a radioimmunoassay after extraction from serum and chromatography separation. Urine was collected over a 24-hour period and sent for measurement of pyridinoline and deoxypyridinoline levels. Urinary pyridinolines (PYR) and deoxypyridinolines (dPYR) are excreted as a result of the breakdown of collagen in bone and therefore is a marker of bone resorption. PYR and dPYR values are measured at the Nichols Institute via high performance liquid chromatography.

Statistics

\(z\) Scores of bone mineral content and bone mineral density for all patients in each ambulatory category are shown in Fig 1. Bone mineral content and bone mineral density for all patients with myelomeningocele in each of the three ambulatory categories are 1 to 2 SD units below the mean for the normal population. The \(z\) scores of bone mineral content and bone mineral density were nearly identical across all three ambulatory categories.

Eight of our 35 patients (5 FTWC and 3 LA patients) suffered 19 lower extremity fractures. Bones fractured include the femur (11), metatarsal bones (2), patella (4), and lower tibia/fibula (2). The number of fractures per patient ranged from one in 2 patients to four in 2 patients. Bone mineral density \(z\) score of the 8 patients with bone fractures \((-3.13 \pm 1.3 SD)\) were significantly lower than that for the remaining patients \((-1.03 \pm 0.38 SD; P < .05)\) (Fig 2). Bone mineral density \(z\) scores among the 8 patients with multiple fractures ranged from -0.46 to -10.22.

Biochemical Markers of Bone Metabolism

The serum electrolytes and venous blood gas measurements in all patients were within normal limits.

<table>
<thead>
<tr>
<th>FTWC</th>
<th>LA</th>
<th>FTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>-4</td>
<td>-3</td>
<td>-2</td>
</tr>
<tr>
<td>-3</td>
<td>-2</td>
<td>-1</td>
</tr>
<tr>
<td>-2</td>
<td>-1</td>
<td>0</td>
</tr>
</tbody>
</table>

Fig 1. \(z\) Scores of bone mineral content (BMC) and bone mineral density (BMC/BW) in different ambulatory categories of patients with myelomeningocele. Via analysis of variance, there was no significant difference between the \(z\) scores among FTWC, LA, or FTA.
The average values for all biochemical markers of bone metabolism within each ambulatory category are shown in Table 1. Table 2 shows normal values for biochemical markers of bone metabolism. PYR and dPYR are collagen cross-link byproducts of bone breakdown and are excreted during bone reabsorption. In contrast, OSTEO (bone Gla protein) is released into circulation during bone formation.

Within each specific ambulatory group, a few patients were noted to be outside the normal range for age (Table 1). In the FTWC group (12 patients), 3 subjects had elevated pyridinoline and deoxypyridinoline levels, 1 had an elevated PTH level, 4 had elevated vitamin D levels, whereas 1 had decreased osteocalcin and 1 had decreased vitamin D levels. In the LA group (10 patients), 3 subjects had elevated PYR levels, 2 had elevated dPYR levels, 1 had an elevated PTH level, and 1 had elevated urinary calcium excretion. In the FTA group (13 patients), only 1 patient each had an elevated deoxypyridinoline level, a PTH level, and a urinary calcium excretion level, whereas 3 patients had elevated vitamin D levels, and 1 had a decreased pyridinoline level. Using Fisher’s exact test to compare the biochemical parameters of bone metabolism, abnormally elevated PYR levels were found more frequently in both the FTWC and the LA subjects than in the FTA subjects (P = .05). Urinary calcium excretion also was significantly higher in the FTWC subjects when compared with the ambulators (combination of the LA plus the FTA subjects) (P < .05).

**Relationship of Bone Mineral Density With Increasing Age**

Bone mineral density in normal children rises with increasing age until its peak at 19 to 20 years of age. Bone mineral density at any given age usually is higher in boys than in girls, except between the ages 12 and 14 years, when the girls have already undergone pubertal maturation.10 We examined the relationship of bone mineral density with age in the boys and girls with myelomeningocele separately. As shown in Fig 3, bone mineral density in boys with myelomeningocele is below normal, but nevertheless, rises with advancing age until its peak at 19 years of age (r = 0.49; P ≤ .05). In contrast, there is no significant rise in bone mineral density in girls with advancing age (Fig 3) (r = 0.24; P > .55). A comparison of the two regression lines reveals that they are statistically different with two different β coefficients (P = .005).

**DISCUSSION**

Since the 1960s, the falling mortality rate of patients with myelomeningocele has allowed increas-

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**TABLE 1. Biochemical Markers of Bone Metabolism**

<table>
<thead>
<tr>
<th>Ambulatory category</th>
<th>PYR (nmol/mmol creat)</th>
<th>dPYR (nmol/mmol creat)</th>
<th>PTH (pg/mL)</th>
<th>OSTEO (pg/mL)</th>
<th>Vitamin D (pg/mL)</th>
<th>Urine Ca (g/k/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTWC</td>
<td>316 ± 48 (164–637)</td>
<td>73 ± 11 (30–135)</td>
<td>36 ± 6 (19–102)</td>
<td>15 ± 3 (2–39)</td>
<td>49 ± 6 (14–86)</td>
<td>3.9 ± 1.2* (1.2–11.8)</td>
</tr>
<tr>
<td>LA</td>
<td>279 ± 28 (72–459)</td>
<td>74 ± 19 (17–140)</td>
<td>49 ± 4 (32–73)</td>
<td>17 ± 3 (11–33)</td>
<td>48 ± 2 (32–56)</td>
<td>1.6 ± 0.5 (0.3–4.6)</td>
</tr>
<tr>
<td>FTA</td>
<td>215 ± 28 (59–402)</td>
<td>57 ± 9 (15–116)</td>
<td>41 ± 5 (15–82)</td>
<td>13 ± 1 (6–23)</td>
<td>46 ± 4 (23–74)</td>
<td>1.9 ± 0.4 (0.5–4.6)</td>
</tr>
</tbody>
</table>

Numbers in parentheses represent the range of values within that group.

*P < .05, FTWC compared with LA and FTA.
ing numbers to survive into adolescence and early adulthood. Among the many new challenges faced by these patients are osteoporosis and pathologic bone fractures. The frequency and severity of such bone fractures in patients with myelomeningocele has been well documented by a number of orthopedists caring for these children. Quilis reported 55 fractures of the lower extremities occurring in 15 of 130 children, and Drennan and associates reported 58 fractures occurring in 25 of 84 children. Similarly, James reported 44 lower extremity fractures occurring in 22 of 122 patients. All authors felt that disuse of the limbs and overall physical inactivity contributed greatly to the increased risk of bone fractures. Likewise, we found 19 lower extremity fractures occurring in 8 of 35 patients. Despite these reports of frequent bone fractures in patients with myelomeningocele, few quantitative studies of bone mineral content or bone mineral density have been conducted in this patient population. Yet, bone mineral density has been shown to correlate with bone strength and the incidence of fractures. This study is the first to examine and compare bone mineral density (via single photon absorptiometry) of patients with myelomeningocele to that of normal children.

Single photon absorptiometry is a well substantiated technique to measure bone mineral density in children and is more accurate and reproducible than radiographic morphometry. Mazess et al studied 763 North American children and established normative bone density data of the upper extremities as measured by photon absorptiometry for the 6- to 19-year-old age group. He found that bone mineral density (bone mineral content/bone width) increased with age and peaked at 18 to 19 years of age. Using single photon-absorptiometry in the distal radius of our patient population, bone mineral density of all patients was 1 to 2 SD units below the mean of the normal population.

### Table 2: Normal Values for Biochemical Markers of Bone Metabolism

<table>
<thead>
<tr>
<th>Age Range</th>
<th>PYR (nmol/mmol creat)</th>
<th>dPYR (nmol/mmol creat)</th>
<th>OSTEO (pg/mL)</th>
<th>PTH (pg/mL)</th>
<th>Vitamin D (pg/mL)</th>
<th>Urine Ca (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–10 Y</td>
<td>160–440</td>
<td>31–110</td>
<td>2.8–41.0</td>
<td></td>
<td>15–60</td>
<td>&lt;4.0</td>
</tr>
<tr>
<td>2–17 Y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>11–14 Y</td>
<td>105–400</td>
<td>17–100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–17 Y</td>
<td>42–200</td>
<td>&lt;59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>20–61</td>
<td>4–19</td>
<td></td>
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</table>

*Values do not vary by age.*
density were made with that in normal children. These studies, nevertheless, underscore the importance of physical inactivity or “disuse” of a limb in contributing to both the decreased bone mineral density and the greater risk of fractures in our patients. The association of decreased bone mineral density and pathologic fractures is highlighted in Fig 2. Patients with multiple fractures had greatly diminished bone mineral density compared with those without fractures. Bone mineral density measurements may be an important clinical tool to help identify those patients at risk for multiple pathologic bone fractures. The affordability, low maintenance cost, and ease of use of a modern single photon absorptiometer should help to make bone mineral density measurements readily available. Newer single photon absorptiometers do not require handling of radioactive material and require only minimal training for operation. No trained technician is required, and single photon absorptiometers are typically used by office or clinic personnel.

Disuse of a limb, especially of the lower extremities, however, is unlikely to be the sole factor involved in decreased bone mineralization in patients with myelomeningocele. In our study, we found decreased bone mineral density in the radius of the upper extremity, an extremity often used extensively, especially in FTWC subjects. Overall physical inactivity may have a systemic effect on total body bone mineralization and influence the mineralization of bones not affected directly and locally by the neurologic lesions. Such a systemic effect, rather than a direct and localized effect, also is suggested by the large decrease in bone mineral density of the distal radius across all three ambulatory groups of our patient population (Fig 1). Rosenstein and coworkers found that bone mineral density of the distal radius in nonambulatory patients with myelomeningocele was reduced by 31% over those who were ambulatory, again arguing for a systemic effect of physical inactivity on bone mineralization.7 Similar reductions in bone mineral density were seen in the weight-bearing lower extremities (tibia and first metatarsal) between nonambulators and ambulators.7 Thus, both direct and localized factors as well as indirect and systemic factors affect total body bone mineralization. It has been suggested that a direct neuropathic effect of the neurologic lesions might contribute to decreased bone mineralization.13-15 However, the decreased bone mineral density of the distal radius, a normally innervated limb in our patients with myelomeningocele, argues against this possibility.

Only one other study has compared bone mineral density of children with neurologic deficits to that of normal children. Henderson et al examined patients with cerebral palsy and found that bone mineral density of the lumbar spine and the proximal femur of these patients also was 1 SD unit below that for age-matched control subjects.18 These findings are in agreement with results of bone mineral densities obtained in our study.

Disorders of bone metabolism may be associated with abnormal values of OSTEO or PYR.19 We examined these biochemical bone parameters and found that FTWC and LA subjects had elevated PYR levels (and therefore greater bone reabsorption) more frequently compared with FTA subjects. No differences in deoxypyridinoline, PTH, vitamin D, and osteocalcin levels exist among the different ambulatory groups. Henderson et al were unable to find any correlation between serum vitamin D levels and OSTEO with bone mineral density in patients with cerebral palsy.18 In contrast, low OSTEO levels is a useful marker of excessive bone loss in postmenopausal women.16,19

FTWC patients have higher urinary calcium excretion than the combination of LA and FTA patients. FTWC patients are less physically active than their ambulatory counterparts and therefore suffer from “relative immobilization” and immobilization hypercalcuria.

Bone mineral density in normal children of both sexes increases with age until it peaks in early adulthood.9,10 In our cohort of boys, bone mineral density was 1 to 2 SD units below normal, but, nevertheless, increased with age until the observed peak at 19 years. It is interesting, however, that bone mineral density in girls demonstrates no significant change between the ages of 6 and 19 years. The divergent rise in bone mineral density versus age seen in the boys may be related to a central role of testosterone in postpubertal skeletal maturation. The absence of a rise in bone mineral density versus age in girls may be related to the lack of high levels of serum testosterone. Indeed, osteoporosis in adult men is usually related to testosterone deficiency.20 Alternatively, cultural biases in the different levels of physical activity encouraged between the sexes also may play a role in this divergence in bone mineral density.

It is unknown at this time whether pharmacologic therapy with inhibitors of urinary calcium excretion (ie, thiazide diuretics) or inhibitors of bone reabsorption (ie, bis-phosphonates) would be of help in increasing bone mineral density or decreasing the incidence of multiple bone fractures. Use of thiazide diuretics might be particularly helpful in lowering urinary calcium excretion in FTWC patients. The efficacy of bis-phosphonates to increase bone mineral density seems promising as was demonstrated recently in three nonambulatory patients with cerebral palsy.21 In general, this population of patients would seem appropriate for future therapeutic trials to improve bone disease and quality of life.

In summary, patients with myelomeningocele have decreased bone mineral density (1 to 2 SD units below norm) from 6 to 19 years of age. This reduced bone mineral density may, in large part, explain the higher incidence of bone fractures in patients with myelomeningocele. Measurement of bone mineral density may be an important clinical tool to help identify those patients particularly at high risk for pathologic fractures. This low bone mineral density was associated with a greater frequency of abnormally elevated PYR levels in the FTWC and LA subjects versus the FTA subjects. There also were higher levels of urinary calcium excretion in the
Acknowledgments

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