CLINICAL AND LABORATORY OBSERVATIONS

Bone metabolism in children with epidermolysis bullosa

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We evaluated bone mineral density, vitamin D status, and biochemical markers of bone turnover in seven children with epidermolysis bullosa (EB). Four had osteopenia (*Z* score, –1.5) and four 25(OH) vitamin D <34 nmol/L (14 ng/mL), two of which had hyperparathyroidism. Children with severe EB should have evaluation of bone metabolism. (J Pediatr 2002;140:467-9)

Epidermolysis bullosa (EB) is a family of inherited disorders characterized by a reduced resistance of the skin and mucous membranes to trauma.[1] There are 3 main types: (1) EB simplex, caused by mutations in keratins 5 and 14; (2) dystrophic EB, caused by mutations in collagen VII; and (3) junctional EB, caused by mutations in laminin 5, collagen XVII, or α6β4 integrin.[2] This disorder is often associated with extracutaneous complications such as nutritional deficiencies, recurrent infections, and motor disabilities. Nutritional problems are a consequence of restricted nutritional intake, chronic constipation, and increased whole-body protein turnover,[3] probably caused by chronic nonhealing of wounds and infections. In addition, some children with EB have restricted physical activity as the result of painful lesions and joint contractures.[1]

Other nutritional disorders and conditions restricting physical activity have been shown to have deleterious effects on bone metabolism and bone mass.[4] No studies have been performed on bone metabolism in children with EB. The aim of this study was to evaluate bone mineral density, vitamin D status, and biochemical markers of bone turnover in 7 children with EB (dystrophic or non-Herlitz junctional EB). Such data may be helpful in optimizing patient treatment for this rare genodermatosis.

BMD	Bone mineral density
BMDba	Bone mineral density for bone age
BMDsa	Bone mineral density for statural age
BMI	Body mass index
EB	Epidermolysis bullosa
PTH	Parathormone

METHODS

Patients

Seven children (3 boys) ranging in age from 3 to 8 years old were recruited (Table). Patients 1 and 2 were sisters. The diagnosis of EB was established on the basis of the clinical findings, electron microscopy, and molecular studies. The methods for molecular studies have been described elsewhere.[5,6] Patients 1, 2, and 4 had dysphagia, patients 3 and 7 had chronic constipation, and all patients had anemia (hemoglobin level <110 g/L [11 g/dL]). Patient 1 had additional workup to rule out other causes of short stature (constitutional and endocrine diseases). No patient was taking vitamin supplements. Informed consent was obtained from all the parents, together with approval from the Ethics Committee of the Catholic University of Chile.

Anthropometric Findings

Standing height was measured with a stadiometer (Holtain Ltd, Crymych, Dyfed, UK). Body mass index (BMI)

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Table. Clinical, biochemical, and densitometric data on patients with EB

Patient No.	Sex M/F	Age (y/mo)	Type of EB	Height *Z* score	BMI *Z* score	Bone age (y/mo)	Physical activity	Albumin g/L (g/dL) NV:35-50 (3.5-5)	25OHD mmol/L (ng/mL) NV: 34-112 (14-45)	PTH ng/L or pg/dL NV: 10-70	BMD L2-L4 g/cm^2 (*Z* score)
1	F	3/2	D	–3	0.5	1/5	II	3.6 (36)	8.2 (20.5)	120	0.357 (–2.97)
2	F	4/2	D	–2	0.3	3/5	II	3.5 (35)	14.6 (36.4)	56	0.532 (–1.26)
3	F	3/0	D	0.8	–2.3	2/8	II	3.9 (39)	30.8 (76.9)	27.5	0.413 (–1.90)
4	F	5/3	D	–1.2	–1.8	3/0	III	2.9 (29)	8.7 (21.7)	82	0.278 (–4.53)
5	M	5/4	J	0.4	–0.4	5/0	I	3.5 (35)	29.6 (73.9)	13.5	0.577 (–0.79)
6	M	5/2	D	–1.8	–0.5	2/6	III	2.5 (25)	11 (27.5)	52	0.312 (–4.10)
7	M	7/11	D	0	–1.5	5/0	II	2 (20)	12 (29.9)	35	0.576 (–1.55)

M, Male; *F,* female; *D,* recessive dystrophic EB (Hallopeau-Siemens type); *J,* non-Herlitz junctional EB; *25OHD,* 25(OH) vitamin D; *NV,* normal values.

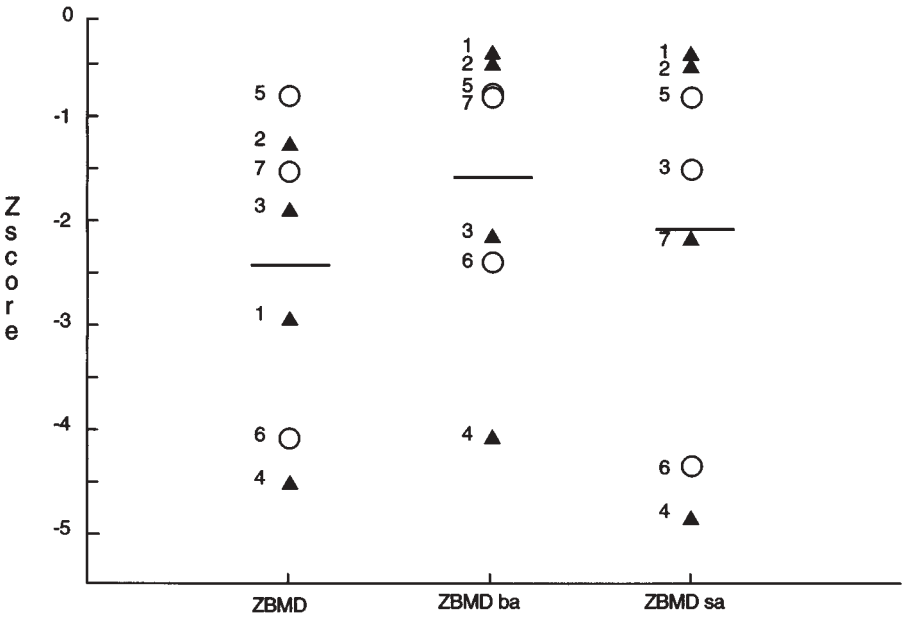

Figure. *Z* score of lumbar BMD *(ZBMD)*, BMDba *(ZBMDba)*, and BMDsa *(ZBMDsa)* in patients with EB. Male patients are represented as *white circles* and female patients as *black triangles*. *Lines* show means. Patient numbers are the same as in the Table.

was calculated by use of the formula: weight (kg)/height^2 (m^2). To allow a comparison between different ages and sexes, *Z* scores were calculated by use of the formula: individual value minus mean for age and sex/SD of normal mean.

Bone Mineral Density and Bone Age

Bone mineral density (BMD) of the lumbar spine (L2-L4) was measured by dual x-ray absorptiometry with the use of a Lunar densitometer, pediatric software version 4.7d (Lunar DPX-L, Lunar Radiation Corp, Madison, Wis), with a precision of 1% to 2%. Control data for BMD reported for Spanish children were used.[7] Bone mineral density for bone age (BMDba) and bone mineral density for statural age (BMDsa) *Z* scores were obtained by using bone age or statural age (age at which the patient's height would be at the 50th percentile) instead of chronological age to compute the *Z* scores, respectively. Bone age of the left hand was determined by the Atlas of Greulich and Pyle.[8]

Biochemical Measures

In each patient, serum levels of calcium, phosphate, magnesium, alkaline phosphatase, parathormone (PTH), creatinine, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, glucose and urine calcium/creatinine, and urine hydroxyproline/creatinine ratios were measured (methods reported previously[9]). In addition, serum 25(OH) vitamin D (commercial kit, DiaSorin, Stillwater, Minn) and copper and zinc content in hair were determined.

Physical Activity and Nutritional Intake

Physical activity level was classified arbitrarily in three categories: (1) normal: walking and running without limitation, (2) moderate limitation: running rarely, walking with limitation, and (3) severe limitation: rarely standing.

A dietitian using a questionnaire about the intake during the preceding week estimated the calorie, protein, phosphate, and calcium intake in each child.

RESULTS

BMD of the spine (L2-L4) and BMDsa and BMDba are shown in the Figure.

All children received the required amounts of calories, protein, phosphate, and calcium for normal children.[10] Bone ages are shown in the Table. Biochemical measures were normal, except for albumin in patients 4, 6, and 7, 25(OH) vitamin D in patient 1, 4, 6, and 7, and PTH in patient 1 (Table). All patients had calcium/creatinine ratios <0.2. There were no zinc or copper deficiencies detected in these children.

DISCUSSION

We found that children with EB have evidence of reduced BMD. Some of these children also had short stature and delayed bone age. After adjustment was made for bone age and statural age, 3 and 4 patients, respectively, fell below the range of osteopenia (*Z* score <–1.5). The most accurate method to adjust BMD for body size is still controversial,[11] and there are scant data on children under the age of 5 years. We do not have normative data of volumetric BMD in children in these ages, so we used BMDsa and BMDba as described above to adjust for these factors.

Reduced BMD is probably a result of multiple factors. Children with the lowest BMD were also the most malnourished and sedentary. Traditionally, physiotherapy in EB has been focused on maintenance of joint mobility and does not include regularly weight-bearing exercises. In central Chile, dairy products or cereals are not supplemented with vitamin D because ultraviolet radiation is sufficiently high all year.[12] However, children with EB are at risk of vitamin D deficiency from this source, probably because of extensive wound dressings and limited outdoor activities.

Many other factors could contribute to bone loss, including malnutrition and repeated episodes of infection. Although in this study caloric and protein intakes were within the normal range for normal children, they could not be enough for children with EB. The low levels of albumin found in three of these children support this.

We believe that any child with a severe form of EB should have periodic evaluation of BMD and vitamin D status. Children with EB may benefit from a weight-bearing exercise program that does not involve friction or any mechanical stress on the skin.

Prospective studies are necessary to determine the benefits and risks of a weight-bearing physical activity program and vitamin D supplements in children with EB.

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