

Bone mineral content and density in healthy subjects and in osteogenesis imperfecta

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Abstract

Lumbar spine bone mineral density in a cross sectional study of healthy subjects increased by 0.012 and 0.016 g/cm²/year in boys and girls respectively between 5 and 11 years of age. These rates increased five-fold in girls and threefold in boys between the ages of 11 and 13 years as a result of the bone mineral content increasing more rapidly than the coronal area at this age. By the age of 11 years the girls had 66% of the coronal area, 61% of the bone mineral density, and 41% of the bone mineral content of subjects aged 18-23 years. The ratio (lumbar spine bone mineral content/body weight) was constant in boys aged 6-13 years, but there were significant variations in girls. Femoral neck bone mineral density in both sexes changed little between 6 and 11 years and at 11 years was 69% of the adult values.

Subjects with osteogenesis imperfecta had a low bone mineral density and bone mineral content for their age and weight. The z score of bone mineral density at the femoral neck was significantly lower than at the lumbar spine.

In patients with recurrent fractures a low bone mineral density may help in identifying those with osteogenesis imperfecta and assist in their subsequent management.

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Bone mineral density measurements in children could be of value in the management of recurrent fractures, osteogenesis imperfecta, hypophosphataemic rickets, and other disorders.¹ Although dual energy x ray absorptiometry (DXA) is the most widely used form of bone density scanning, there are few reports of its use in children. The relation of bone mineral density with age has variously been plotted as linear² or cubic.³ Studies using either dual photon absorptiometry or DXA also suggest an increase in bone mass associated with puberty.^{1,4} Bone mineral density is related to the Tanner stage of pubertal development, though there is a slightly closer relation with weight.¹

Measurement of bone mineral density using DXA has been criticised because, unlike quantitative computed tomography, it does not exclude the posterior elements of the vertebrae and because the anteroposterior dimension of the vertebral body (vertebral depth) is not measured. DXA, however, gives low doses of radiation and is more suitable than quantitative computed tomography for use in children.

We investigated the changes in bone mineral density and bone mineral content in children aged from 5 to 13 years. We also used DXA to compare the relation of bone mineral density with weight in healthy children with that in children with osteogenesis imperfecta to identify the value of DXA measurements in such patients.

Subjects and methods

Normal healthy children were recruited from local schools. Subjects were excluded if they were attending a medical clinic regularly or were known to have a chronic disease. There were 75 girls (aged 5-13 years) and 57 boys (aged 6-13 years), all white. Height and weight were measured in all subjects but ethical permission precluded clinical examination or venepuncture. Permission was obtained from the subjects and their parents/guardians. This protocol was accepted by the Shropshire Health Authority research ethics committee.

Subjects with osteogenesis imperfecta had a mean (SD) age of 11 (3) years. There were three boys and six girls, all of whom had a history of fractures. Each had a family history of the disorder or blue sclerae, or both. All had type 1 osteogenesis imperfecta⁵ and all were usually mobile.

Bone mineral density was measured using a Hologic QDR1000 densitometer (Hologic Inc, Waltham, MA, USA). The second, third, and fourth lumbar vertebrae and the upper end of the left femur were measured. The densities of the lumbar vertebrae were expressed as an average measurement of L2-L4. This technique measures coronal vertebral area and bone mineral density directly and computes the bone mineral content as area multiplied by bone mineral density.⁶ The femoral neck site and Ward's triangle were measured in the left femur. The latter site is defined by the software program as the area with the lowest bone mineral density at the upper end of the femur. Body height was measured with a Harpenden stadiometer (Holtain, Crymmech, UK).

Statistical analysis was undertaken using techniques described in standard texts.^{7,8} Results are given as mean (SD) unless otherwise stated. Non-parametric tests were used to test significance between groups. As values for bone mineral density and area changed considerably from year to year, values for subjects with osteogenesis imperfecta were converted into z scores using values for the mean (SD) derived from the appropriate sex and age group of the healthy subjects. Differences between z scores were tested by the Mann-Whitney U test. The significance of the

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Table 1 Anthropometric data for healthy girls. Values are mean (SD)

	Age (years)								
	5 (n=5)	6 (n=4)	7 (n=5)	8 (n=10)	9 (n=7)	10 (n=12)	11 (n=12)	12 (n=14)	13 (n=6)
Weight (kg)	17.3 (1.30)	23.9 (6.4)	22.3 (0.91)	24.4 (2.60)	32.3 (7.06)	37.5 (7.2)	37.4 (8.0)	45.5 (15.1)	46.6 (10.3)
Height (m)	1.06 (0.018)	1.19 (0.05)	1.21 (0.02)	1.25 (0.04)	1.33 (0.07)	1.41 (0.06)	1.44 (0.08)	1.49 (0.09)	1.54 (0.06)
Bone mineral content lumbar spine (g)	9.6 (1.2)	12.1 (2.0)	14.3 (1.2)	14.1 (1.9)	15.3 (3.4)	18.4 (4.1)	19.2 (4.9)	25.4 (8.5)	29.9 (6.1)
Bone mineral density lumbar spine (g/cm ²)	0.535 (0.04)	0.593 (0.029)	0.651 (0.032)	0.636 (0.048)	0.590 (0.048)	0.670 (0.073)	0.657 (0.085)	0.764 (0.111)	0.833 (0.117)
Bone mineral density Ward's triangle (g/cm ²)	0.480 (0.028)	0.520 (0.04)	0.545 (0.043)	0.544 (0.053)	0.540 (0.067)	0.525 (0.064)	0.529 (0.085)	0.617 (0.100)	0.633 (0.109)
Bone mineral density femoral neck (g/cm ²)	0.540 (0.025)	0.605 (0.029)	0.611 (0.031)	0.625 (0.051)	0.635 (0.055)	0.646 (0.078)	0.636 (0.080)	0.740 (0.100)	0.769 (0.108)
Lumbar spine bone mineral content/weight (g/kg)	0.557 (0.066)	0.517 (0.062)	0.642 (0.051)	0.580 (0.054)	0.476 (0.062)	0.496 (0.092)	0.514 (0.070)	0.564 (0.076)	0.651 (0.096)

Table 2 Anthropometric data for healthy boys. Values are mean (SD)

	Age (years)							
	6 (n=6)	7 (n=4)	8 (n=6)	9 (n=5)	10 (n=10)	11 (n=12)	12 (n=6)	13 (n=8)
Weight (kg)	22.8 (3.8)	24.1 (1.9)	27.7 (2.9)	30.8 (2.9)	34.8 (5.7)	33.7 (4.1)	42.7 (8.0)	41.6 (4.9)
Height (m)	1.21 (0.05)	1.23 (0.06)	1.31 (0.09)	1.36 (0.06)	1.40 (0.05)	1.41 (0.053)	1.53 (0.07)	1.57 (0.09)
Bone mineral content lumbar spine (g)	13.5 (1.2)	14.1 (2.6)	14.4 (2.3)	17.0 (4.8)	18.4 (2.2)	17.3 (2.9)	23.8 (6.1)	25.3 (4.9)
Bone mineral density lumbar spine (g/cm ²)	0.574 (0.043)	0.600 (0.062)	0.601 (0.046)	0.619 (0.097)	0.643 (0.059)	0.625 (0.065)	0.692 (0.097)	0.704 (0.083)
Bone mineral density Ward's triangle (g/cm ²)	0.571 (0.033)	0.601 (0.069)	0.584 (0.100)	0.620 (0.119)	0.605 (0.074)	0.573 (0.064)	0.654 (0.071)	0.618 (0.063)
Bone mineral density femoral neck (g/cm ²)	0.624 (0.047)	0.672 (0.053)	0.653 (0.059)	0.702 (0.080)	0.698 (0.067)	0.697 (0.052)	0.746 (0.049)	0.734 (0.036)
Lumbar spine bone mineral content/weight (g/kg)	0.602 (0.094)	0.583 (0.062)	0.524 (0.053)	0.551 (0.135)	0.538 (0.075)	0.515 (0.066)	0.564 (0.127)	0.605 (0.061)

deviation from the expected frequencies in a normal distribution was tested by the Kolmogorov-Smirnov test.

Results

Tables 1 and 2 give the bone mineral measurements for healthy subjects. In the lumbar spine the mean bone mineral density in girls increased only slightly (0.016 g/cm²/year; $r=0.40$) between 5 and 11 years of age. After 11 years the rate increased to 0.089 g/cm²/year ($r=0.53$). The increase in bone mineral density obscured the difference in the changes of bone mineral content and area with age. The average lumbar bone mineral content in girls increased by 1.54 g/year from 5 to 11 years ($r=0.67$) and by 5.6 g/year from 11 to 13 years ($r=0.53$). Although the rate of increase of bone mineral content more than trebled, the rate of increase of the coronal area only doubled from 1.8 to 3.6 cm²/year over the same time intervals. Figure 1 gives the relations of bone mineral content, bone mineral density, and area with age in girls.

Lumbar bone mineral density in boys increased by 0.012 g/cm²/year from 6 to 11 years ($r=0.30$) and by 0.048 g/cm²/year between 11 and 13 years ($r=0.50$). Lumbar bone mineral content increased by 0.96 g/year up to the age of 11 years ($r=0.51$) and by 3.93 g/year from 11 to 13 years ($r=0.64$). The rates of change were not significantly different from those in girls.

In healthy children the bone mineral density in the lumbar spine correlated with weight with no difference between the sexes for subjects over the age ranges investigated ($r=0.74$) (fig 2). The intercept for bone mineral density was 0.43 g/cm². The lumbar spine bone mineral

content also correlated with body weight, with an intercept of 0.9 g in girls and 0.6 g in boys (difference in intercepts, $p=NS$).

The amount of mineral in the lumbar spine (L2-L4) as a proportion of body weight between 5 and 13 years of age was not constant in girls. There were peaks of $6.42 \times 10^{-2}\%$ at 7 years and $6.51 \times 10^{-2}\%$ at 13 years, and a nadir of $4.76 \times 10^{-2}\%$ at 9 years, the differences being greater than would be expected by chance at the 1% level (Kruskal-Wallis test). No significant difference was found in boys (mean (SD) $5.55 (0.84) \times 10^{-2}\%$).

In girls the bone mineral density in the femoral neck increased by 0.016 g/cm²/year between 5 and 11 years ($r=0.48$) and by 0.075 g/cm²/year between 11 and 13 years ($r=0.54$). In boys the increase (g/cm²/year) was 0.017

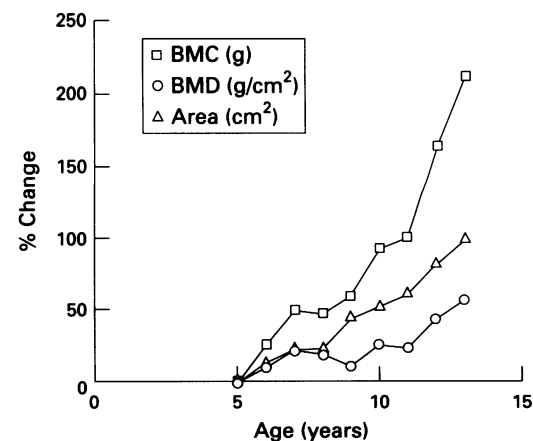


Figure 1 Cross sectional changes in bone mineral content (BMC), bone mineral density (BMD), and area in the lumbar spine of girls, expressed as the percentage change from values at 5 years. Bone mineral density does not change greatly between 5 and 11 years, whereas the BMC increases by 100%.

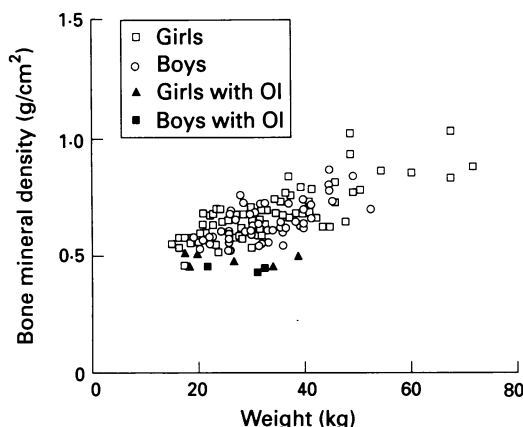


Figure 2 Bone mineral density plotted as a function of weight for healthy boys and girls. The regression equation is $y = 0.43 + 0.0067x$ ($r = 0.74$). Subjects with osteogenesis imperfecta (OI) have a low bone density for their weight.

between 6 and 11 years ($r = 0.40$) and 0.019 ($r = 0.44$) between 11 and 13 years. The relation between bone mineral density and age at Ward's triangle was not as close as at the femoral neck.

Subjects with osteogenesis imperfecta had had a mean of 0.65 fractures each year (range 0.28–0.91; table 3) over their lifetime. The most frequent fracture sites were the tibia (20 fractures), followed by the humerus (11), radius (10), femur (nine), and ulna (seven). We compared values of bone mineral density in the spine and femur, and of the bone mineral content and area in the spine in subjects with osteogenesis imperfecta with those in healthy subjects by converting the data for subjects with osteogenesis imperfecta into z scores (see under methods). Compared with values in healthy normal subjects, vertebral area ($p < 0.05$) and vertebral bone mineral density and bone mineral content ($p < 0.01$) were all low. The vertebral bone mineral density z score (-2.52 (0.49)) was significantly lower than vertebral area z score (-1.14 (0.49)) ($p < 0.02$; Mann-Whitney U test). Bone mineral density z scores were lower in the femoral neck than in the lumbar spine ($p < 0.05$). In relation to body weight both bone mineral content ($p < 0.05$) and bone mineral density ($p < 0.05$) were low in the subjects with osteogenesis imperfecta (fig 2; table 3).

Discussion

The pattern of increase in bone mineral density in the lumbar spine, with an increase to 7 years

followed by a plateau to 11 years and thereafter an acceleration in the rate of increase, more closely followed the cubic pattern^{1,3} than a linear relation.² Mean values for each age group were similar to those previously reported.^{1,3}

The bone mineral content, however, measures the total mineral present and provides a measure of mineral accumulation at particular sites. In this study the spinal bone mineral content increased slowly between 5 and 11 years at a rate of 1.54 g/year in girls, though in this sex the bone mineral content in the lumbar vertebrae as a proportion of body weight actually decreased between 5 and 9 years. This might arise as a result of bone being laid down at other sites. There was, however, a good correlation between the total lumbar and total femoral bone mineral content in girls aged 5–11 years ($r = 0.92$; slope = 0.99), suggesting that accumulation at these two sites was continuing at a similar rate. Tissue other than bone, such as fat, may have been accumulating preferentially at other sites. The minimal increase of lumbar spine bone mineral density between these ages in girls is similar to the lack of change of bone density measured by computed tomography over the same age group.^{9–12}

The changes in vertebral bone mineral occurring at the age of 11–13 years and thereafter are considerable. The rate of increase of bone mineral content increased threefold and bone mineral density fivefold in girls aged 11–13 years compared with the change between 5 and 11 years. The bone mineral density increase measured by DXA (12.2% /year) was itself higher than the rate of increase (3.1% /year) calculated from data obtained by computed tomography.^{9,11,12} To achieve the values measured in our unit for bone mineral density¹³ or bone mineral content and area (Haddaway M J, Davie M W J, unpublished data) for women aged 18–23 years, girls aged 11 years will increase their bone mineral density by 62%, their vertebral area by 44%, and their bone mineral content by 135%. The discrepancies between increases in bone mineral density found by computed tomography and by DXA and between the changes of bone mineral density and bone mineral content measured by DXA could result from a disproportionate increase in the anteroposterior dimension of the vertebral body, or in greater mineralisation of the posterior vertebral elements. Furthermore, the

Table 3 Anthropometric data for patients with osteogenesis imperfecta

Patient No	Sex	Age (years)	No of fractures/year	Weight (kg)	Weight z score	Height (m)	Weight/height ² (kg/m ²)	Bone mineral content spine (g)	Bone mineral content/weight (g/kg)	Bone mineral content/weight z score	Bone density (g/cm ²)			Bone mineral density z score		
											Lumbar spine	Femoral neck	Ward's triangle	Lumbar spine	Femoral neck	Ward's triangle
1	F	10.1	0.91	27.5	-1.389	1.31	16.0	11.13	0.405	-0.992	0.473	0.508	0.39	-2.70	-1.77	-2.11
2	F	12.3	0.82	40.0	-0.364	1.41	20.1	11.59	0.29	-3.609	0.49	0.308	0.196	-2.47	-4.32	-4.21
3	F	6.0	0.28	18.1	-0.906	1.13	14.2	8.46	0.467	-0.8	0.505	0.485	0.337	-3.03	-4.14	-4.58
4	F	10.8	0.46	35.0	-0.347	1.29	21.0	9.59	0.274	-2.413	0.447	0.488	0.265	-3.05	-4.03	-4.06
5	F	5.7	0.87	18.8	1.154	1.19	13.3	8.75	0.465	-1.387	0.454	0.475	0.413	-2.03	-2.6	-2.39
6	F	12.6	0.4	40.5	-0.331	1.44	19.5	16.19	0.399	-2.161	0.572	0.575	0.61	-1.73	-1.65	-0.07
7	M	11.5	0.7	33.5	-0.049	1.26	21.1	9.65	0.288	-3.438	0.449	0.47	0.35	-2.71	-4.37	-3.48
8	M	11.5	0.69	32.0	-0.415	1.27	19.8	9.46	0.296	-3.324	0.426	0.43	0.293	-3.06	-6.03	-4.38
9	M	7.6	0.69	22.5	-0.842	1.12	17.9	9.05	0.402	-2.916	0.448	0.465	0.279	-2.45	-3.91	-1.77

appearance at puberty of seven ossification centres in the posterior part of the lumbar vertebral body at the spinous processes, mammillary bodies, and cranial and caudal surfaces of the vertebra¹⁴ could also lead to a considerable increase of mineral, which would disproportionately increase the bone mineral density measured by DXA.

Values for bone mineral density at the femoral neck generally changed in a similar fashion with age as at the spine. At 11 years, however, the bone mineral density in the femoral neck expressed as a proportion of the bone mineral density in the femoral neck of subjects aged 18–23 years was 69.8 (0.8)%. This was higher than the value of 61.2 (0.9)% in the lumbar spine ($p < 0.01$; Wilcoxon paired ranks). The fact that a greater proportion of the adult bone mineral density has been achieved by 11 years of age in girls may indicate that the prepubertal accumulation of bone mineral density is relatively more important at the femur than at the spine.

Subjects with osteogenesis imperfecta had lower z scores for body weight (table 3). Height was more severely affected, but only three subjects had a height z score of less than -2.00 . The relative sparing of height deficiency suggests that repeated fractures are not as serious a handicap to growth as might be expected. In contrast, the bone mineral density was extremely low in all subjects, with the long bone (femur) being more severely affected (in terms of deviation from the mean) than the axial skeleton. At the spine the deficiency of bone mineral is partially attributable to the vertebrae having a lower coronal cross sectional area. As bone mineral density, which is independently measured, is even lower than the mean values, bone mineral within the vertebrae is also likely to be deficient. Whether the onset of puberty can overcome one or both of these deficiencies will require careful longitudinal study.

These data suggest that DXA might be of value in the management of fractures in childhood. In children with recurrent fractures a low bone density might help to define a cause and possibly detect mild osteogenesis imperfecta. These data suggest that the femur

might be a more valuable site to measure than the spine. Further work is required, however, to examine the bone mineral density at other sites such as the tibiae, humeri and wrists, which are the most common sites of fracture in our patients.

Measurements of bone density in children by DXA could also provide useful data to help with the management of patients with osteogenesis imperfecta. Patients have been treated with bisphosphonates,¹⁵ and it would be useful to be able to measure changes in bone mineral to ensure that a response was occurring and to avoid overtreatment that might hinder height gain.

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