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Vertebral Bone Mineral Content in Osteogenesis Imperfecta

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Summary. Quantitative computed tomography of the lumbar spine was carried out in 28 patients with osteogenesis imperfecta (OI) in order to measure vertebral trabecular bone mineral concentration (BMC). The patients ranged in age from 6–73 years, and included 3 of the 4 major clinical subtypes of the disease. The findings underscore the heterogeneity of osteogenesis imperfecta even among family members with the same disease type. In addition, cross-sectional analysis of Type I OI patients suggests that BMC during young adulthood averages about 70% of normal, and subsequently falls more rapidly than in normal patients. BMC tends to be lower in the more severe forms of OI. Decreased BMC was not found in a few otherwise normal relatives with scoliosis or joint laxity.

Key words: Osteogenesis imperfecta—Bone densitometry—Computed tomography.

Osteogenesis imperfecta (OI) is a heterogeneous inherited disorder with multiple clinical and biochemical subtypes [1–5]. Bony fragility with a history of multiple fractures characterizes the clinical history. Additional clinical findings can include blue sclerae, joint laxity, growth retardation, presenile hearing loss, and abnormal dentition. Radiographs reveal variable degrees of osteopenia along with evidence of fractures or bony deformities. Chemical studies using dermal fibroblasts have demonstrated abnormal synthesis of type I collagen in some OI patients [6–8] but it is not yet possible to firmly relate a specific chemical defect to the occurrence or severity of a particular phenotype. The skeletal X-rays in OI show varying degrees of osteopenia but there has been no systematic effort to relate the degree of osteopenia to other parameters of the disease. We feel that accurate quantification of bone mineral concentration (BMC) would provide information of prognostic importance in OI, and possibly diagnostic or therapeutic importance should therapy become available.

Recently, a technique has been developed for the measurement of vertebral trabecular BMC using a commercial-type CT scanner [9]. We have evaluated a series of patients with OI using this method to determine whether vertebral BMC is related to other indices of the severity of the disease or its genetic transmission. None of the patients were receiving medical therapy trials.

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Materials and Methods

The vertebral body measurements were carried out using a GE 8800 CT/T scanner and a scanning phantom (Imatron Associates, South San Francisco, CA) as described by Cann and Genant [9]. A scout image of the patient was used to align the gantry for CT slices through several adjacent vertebral bodies. Separate 10 mm slices were obtained through the vertebral bodies of L1 to L4, unless collapsed. In small patients, 5 mm slices were used. Regions of interest in the trabecular portion of each vertebral body 1–2 mm inside the cortical rim were chosen for measurement. The attenuation value of this selected bone volume was then compared with a linear regression of the measured values simultaneously obtained in the scanning phantom. This gave an estimate of bone mineral concentration in milligrams per cubic centimeter of K_2HPO_4 mineral equivalent. Vertebral bodies demonstrating crush fractures or severe scoliotic angulation were not scanned. T12 or L5 provided suitable substitutes in a number of cases. In some patients, it was not possible to obtain four accurate vertebral body measurements because of spinal deformity. In these cases, an average of the two or three acceptable measurements was used.

Calculations performed by James Vucich in the Diagnostic Radiology Department, NIH, based on test data from the CT

Table 1. Classification of OI[a]

Type	Inheritance	Severity of deformities	Scleral color
I	Dominant	Mild, few deformities	Blue
II	Recessive	Lethal, grossly deformed	Blue
III	Recessive	Severe, major deformities including scolioses, wheelchair bound	White
IV	Dominant	Moderate severity, with scolioses and peripheral deformities	White

[a] Modified after Sillence DO, Senn A, Danks PM (1979). Genetic heterogenity in osteogenesis imperfecta, J. Med Genet 16:101–116

Table 2. Summary of findings in OI patients, with listing in order of increasing BMC

Patient	Age (yrs)	Sex	Disease type	Vertebral BMC	Comments
1	25	F	III	26	
2	45	F	I	36	Scoliosis
3	48	M	III	38	
4	45	M	I	42	
5	28	M	III	43	Scoliosis
6	56	M	III	45	Scoliosis
7	60	F	IV	54	
8	73	M	I	55	
9	30	M	IV	60	
10	26	M	I	64	Brother of pt. #17
11	54	F	I	65	
12	48	F	III	69	Scoliosis
13	16	F	IV	101	
14	39	F	I	102	
15	16	M	IV	104	
16	34	F	I	109	
17	24	M	I	112	Brother of pt #10
18	36	F	I	116	
19	34	M	I	122	
20	36	M	I	123	
21	30	F	I	131	
22	34	F	I	178	
23	12	M	IV	50	Not included in
24	10	F	III	76	statistical
25	11	F	III	77	analysis due
26	6	M	I	98	to age less than 20 yrs
27	33	F	III/IV	133	Uncertain type of OI

scanner, showed the maximum local radiation dose to be less than 500 mR (based on 120 kVp and 80 mas). This is comparable to the maximal local dose from a plain radiograph of the abdomen. The gonadal dose from this study was substantially less than that of a single abdominal X-ray.

The technique was applied in 28 patients with osteogenesis imperfecta who were followed in the genetics and endocrinology clinics at the National Institutes of Health. Five of these patients were scanned a second time after periods of 6–15 months. One patient exhibited such severe vertebral collapse deformities that accurate measurements were not possible. Nine family members of patients with OI were also evaluated, two of whom had a hyperextensibility of the joints without bony fragility or blue sclerae.

Informed consent was obtained from all patients and their relatives prior to study. Normal data was derived from literature-based controls [10] and a series of 22 patient controls studied concurrently. No major difference was found between these controls and those described in the literature. The OI classification used, a modification of that proposed by Sillence et al. [1], is described in Table 1. Note that this classification is clinical, and is not based on firm chemical or metabolic findings.

Reproducibility of this technique is better than 3%, based on repeat studies in phantoms. In normal subjects, our interverte-

Table 3. BMC findings in family members of OI patients. No evidence of reduced BMC was found

Relative	Age (yrs)	Sex	No. of related patient	Bone density mg K_2HPO_4/cm^3	Comments
1	50	F	7	102	
2	38	F	26	130	
3	27	M	9	132	
4	41	M	26	155	
5	31	F	23	169	
6	33	M	23	171	
7	14	F	23	188	
8	13	F	16	205	Hyperextensible joints
9	19	F	13	228	Hyperextensible joints

bral reproducibility was about 4%. This compares with a literature reproducibility of 3% [10]. The accuracy is affected by the quantity of marrow fat, and actual mineral content (measured by biopsy) would be higher than the numbers given here. However, this does not preclude measurement with comparison to an established normal range.

Results

The stated OI subtypes are defined in Table 1 as modified from Sillence et al. [1]. Table 2 summarizes the findings in the patients with osteogenesis imperfecta. Table 3 gives the results for the examined family members along with their relationships to the patients. All statistical analyses excluded patients under 20 years of age, as reference data has not been established for this group.

Half of the patients suffered from type I disease. Of these, all but one were over 20 years of age. The trabecular BMC in K_2HPO_4 equivalents from these 13 patients are plotted against age in Fig. 1, along with the linear regression for the data. Osteopenia is defined as BMC in the lowest 5% of the population based on our normative data, and was found in about 80%. Results suggest an average rate of bone mineral loss of 2.3% per year over the entire patient age range from 24–73 years. However, the slope is not statistically significantly different than the normal negative slope with age [11, 12]. In addition, the 9 type I OI patients aged 20–40 had a bone mineral content of 117 ± 30 mg/cm^3 (SD), smaller than the value of 167 ± 27 mg/cm^3 (SD) for our group of 22 normal female controls aged 20–40 ($P < .001$, Wilcox). The ages of the two groups were not different ($P > .05$, Wilcox).

The data on types III and IV osteogenesis imperfecta were insufficient to analyze independently. However, they could be compared with that of the type I subjects. Analysis using the Wilcoxon statistic indicated that trabecular bone density of the four patients over 20 years of age with type IV OI was less than that of patients with type I OI with a

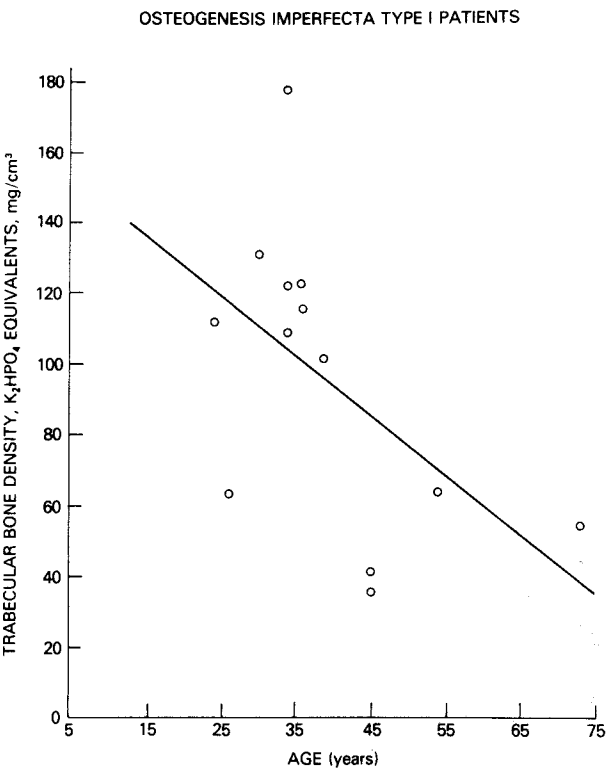

Fig. 1. Age vs. vertebral BMC for 13 patients with type I OI. Regression line is superimposed, with intercept 163, slope −1.7, and correlation coefficient −.53 ($P < .05$).

P value of less than .04. A similar comparison showed that the trabecular BMC of the type III OI patients was less than that of type I patients at a P value of less than .02. It is important to mention that comparison of the groups was performed for potential statistical bias due to age or sex. This analysis did not demonstrate any bias by sex. However, the type IV patients on the average were considerably younger than those in the other two groups. Since BMC tends to be negatively correlated with age, the P value of .04 is probably conservative.

The data in healthy family members shown in

Table 4. Summary of follow-up findings in 5 patients. The first and last patients of this group had significant scolioses, which could impair positioning reproducibility

Patient	Initial Age	Sex	Disease type	Bone density measurements (mg K_2HPO_4/cm^3)		Time between measurements (Months)
	(Years)			First	Second	
6	56	M	III	45	76	14.8
7	60	F	IV	54	42	6.5
11	54	F	I	65	52	12.2
12	48	F	III	69	61	14.2
24	10	F	III	76	51	6.4

Table 3 do not reveal osteopenia as a separately transmissible characteristic. All of the values in this table are within the 95% confidence interval of our normative data except for relative 1, who is 50 years old, which is older than our established normal population. Her value is within the 95% confidence interval of literature controls [10]. It is interesting to note that the two family members (numbers 8 and 9) without clinical OI, but with hyperextensible joints, had measurements that were higher than average. This is not of statistical significance, but further studies on such individuals are warranted.

Only five patients have returned for follow-up thus far. Four demonstrated a reduction (8, 12, 13 and 25 mg/cm^3) in vertebral BMC, one an increase (31 mg/cm^3), after intervals of 6–15 months (Table 4). Further studies are necessary to determine if any of these differences are significant. A substantial portion of these differences may be due to reproducibility error, since two patients had moderate scoliosis and the remaining three patients had mild scoliosis. None of the patients had significant radiographic changes or received medical therapy in the time interval.

Discussion

The results of this study underscore the clinical heterogeneity of patients with osteogenesis imperfecta. The scatter observed in Fig. 1 shows that large variations exist among patients with a single disease type. Patients 10 and 17 (Table 2) are brothers, illustrating that this variation can be found even in patients with presumably identical genotype. Clinically, these two patients were quite similar. Obviously, in any one subject, vertebral BMC will vary with age, disability, medication, and the severity of the underlying chemical metabolic defect. Because of this, the fact that type I patients tend to have higher bone densities than type III and type IV patients may not prove useful for differentiating among the clinical and biochemical subtypes. The results do suggest that average bone mineral concentration is better with certain categories of OI than with others. Since reduced bone density has been associated with an increased incidence of fractures, BMC may be of useful prognostic value in OI patients, especially with follow-up. Note that measurement of vertebral trabecular BMC is preferred over radiographic evaluation of cortex in the hand or long bones, since Paterson [13] has reported normal cortical thickness in adult OI patients based on metacarpal measurements.

In addition to use as a prognostic tool, we anticipate that this technique will prove valuable in assessing the results of therapy. Previous studies of efficacy of treatments have been based on comparisons of numbers of fractures [14], and no treatment has been proven beneficial thereby. This may not be due to unsuccessful therapy, but rather to the crude measure of effectiveness used. Quantitative CT bone densitometry offers an objective, reproducible, and sensitive way to measure vertebral trabecular BMC, particularly in type I OI patients without scoliosis, and may permit physicians to evaluate treatment modalities more effectively. Further, correlation of fracture rates with BMC would be valuable. Since the fracture rate is known to diminish after puberty, measurement of pre- and postpubertal BMC would be interesting.

An intriguing result of this study is the suggestion that type I OI patients lose vertebral bone density with age at a rate of more than 2% per year. More data will be needed to confirm statistically that the negative slope is indeed increased over that of normal subjects. Note that previous studies of bone turnover in OI have suggested that both bone formation and resorption are accelerated. However, treatment with calcitonin in an attempt to decrease bone resorption has not proven useful [15].

Conclusion

An established method for CT measurement of trabecular bone density in vertebral bodies has been

applied to a series of patients with osteogenesis imperfecta. The results demonstrated that the disease is heterogeneous with respect to this parameter, even among patients with the same phenotype. Patients with the more severe types III and IV OI tended to have lower trabecular bone densities than those having milder type I disease. Young type I OI subjects can be expected to exhibit bone densities averaging about 30% lower than normal, and may lose bone mineral faster than normal controls.

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