Calcif Tissue Int (1985) 37:594–597

Calcified Tissue
International

The Role of Three-Dimensional Trabecular Microstructure in the Pathogenesis of Vertebral Compression Fractures

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Summary. We compared indices of three-dimensional microstructure of iliac trabecular bone between 26 patients with vertebral compression fractures due to postmenopausal osteoporosis and 24 control subjects without vertebral fracture, who were matched for age, sex, race, menopausal status, and several densitometric and histologic indices of both cortical and trabecular bone mass. The patients with fracture had a significantly lower mean value (1.03 ± 0.15 vs. 1.26 ± 0.26; $P < 0.005$) for indirectly calculated mean trabecular plate density, an index of the number and connectivity of structural elements, and as a necessary corollary, a significantly higher mean value for the mean thickness of structural elements. Plate density was more than one standard deviation below the age-adjusted mean value for normal postmenopausal white females in 19 (73%) of the fracture caes and in only 5 (21%) of the nonfracture cases ($P < 0.001$). We conclude that the biomechanical competence of trabecular bone is dependent not only on the absolute amount of bone present but also on the trabecular microstructure.

Key words: Osteoporosis — Fractures — Trabecular microstructure.

There is a direct relationship between bone mass, however measured, and skeletal strength [1, 2]. As a result, older individuals, females, and whites all have less bone [3] and more fractures [4] than younger individuals, males, and blacks respectively, and persons with less bone subsequently experience more fractures than otherwise similar persons with more bone [5]. Patients with atraumatic vertebral fractures have less trabecular bone than individuals without fractures of the same age, sex, and race, whether measured by iliac bone histomorphometry [6], dual photon absorptiometry [7], or quantitative computed tomography [8] of the spine. However, there is considerable overlap between fracture and nonfracture groups by each of these techniques, which consequently have limited ability to predict the occurrence of fracture in an individual. Clearly, factors other than bone mass must contribute to fracture risk.

We have recently demonstrated that the loss of trabecular bone that accompanies normal aging results predominantly from a reduction in the number of structural elements with only a slight reduction in the thickness of those that remain [9]. Furthermore, in patients with vertebral compression fractures this structural change is more pronounced, and indirectly calculated mean trabecular plate density produces better separation between osteoporotic and nonosteoporotic subjects than does trabecular bone volume alone [9]. This suggests that an alteration in three-dimensional trabecular architecture could be an additional contributory factor to the pathogenesis of fractures [10]; we now provide further evidence for this hypothesis.

Subjects and Methods

All subjects were postmenopausal white females aged 50 years or more. The control group of 24 subjects consisted of 9 normal volunteers, 10 patients suspected of osteoporosis because of an X-ray report or a low value for photon absorptiometry of the radius, but in whom vertebral body dimensions were radiographically normal, and 5 previously healthy persons autopsied after sudden death. They were selected because iliac trabecular bone volume (TBV) was less than the mean predicted from the regression of TBV on age [9] and so fell within the lower half of the

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Table 1. Indices of cortical and trabecular bone mass

	Nonfracture	Fracture	*P*
Trabecular bone volume (%)	15.3 ± 3.2 (24)	14.8 ± 1.7 (26)	—[a]
Cortical bone volume (%)	93.0 ± 2.9 (20)	93.8 ± 2.5 (22)	NS
Mean cortical thickness (mm)	1.088 ± 0.411 (20)	0.943 ± 0.273 (22)	NS
Radial bone mineral content/bone width (z)	−1.41 ± 1.83 (18)	−1.45 ± 1.02 (26)	NS

Results expressed as means ± SD Numbers of observations in parentheses
[a] Significance not tested because values used to define the groups

Table 2. Indices of trabecular microstructure

	Nonfracture	Fracture	*P*
n	24	26	
Mean trabecular plate thickness (μm)	123.4 ± 25.1	146.7 ± 27.8	<0.005[a]
Mean trabecular plate density (/mm)	1.262 ± 0.260	1.027 ± 0.153	<0.001[b]
Mean trabecular plate separation (μm)	705 ± 181	851 ± 148	<0.005[a]

Results expressed as means ± SD
[a] Unpaired *t* test (variances not significantly different)
[b] Wilcoxon rank-sum test (variances significantly different)

age-adjusted normal range. The study group consisted of 26 patients with one or more nontraumatic vertebral compression fractures attributed to postmenopausal osteoporosis. They were selected because iliac TBV was >12.8%, a value arbitrarily chosen to ensure that the mean value for TBV was the same as in the nonfracture group. In the control group all indices of resorption and formation were within reference ranges for normal white postmenopausal females and in all cases the relative osteoid volume was < 5%, and the bone appeared qualitatively normal.

The methods for obtaining, processing, and analyzing the bone specimens have previously been reported in detail [9]. In brief, with simultaneous measurement by digitizer of total perimeter, bone area and tissue area in thin histologic sections, excluding only the cortices, indirect estimates of mean trabecular plate thickness (MTPT) and mean trabecular plate density (MTPD) can be derived, such that TBV (%) = MTPD (/mm) × MTPT (μm). MTPD is an index of the probability that a scanning or test line will intercept a structural element of bone. Mean trabecular plate separation (MTPS), given by MTPS (μm) = 1000/MTPD-MTPT, is an index of the distance between structural elements of bone. A reduction in MTPD and an increase in MTPS both indicate that the two-dimensional profiles of bone are more isolated and less completely connected [9]. Mean cortical thickness (MCT) was measured in the same histologic sections by dividing the mean area of the two cortices by the periosteal perimeter length; this takes account of varying obliquity of the biopsy core to the plane of the ilium. Cortical bone volume (%) is calculated as 100-porosity, the latter measured as (soft tissue area/total tissue area) × 100. The between-observer precision is less than 5% for primary area and perimeter measurements [11] and less than 10% for derived indices [9, 12].

The bone mineral content (BMC) of the radius of the nondominant side was measured by single beam photon absorptiometry (using the Norland-Cameron Bone Mineral Analyzer) at the standard proximal site one-third of the distance from the radial styloid to the olecranon process, where > 95% of the bone is cortical. BMC is divided by bone width (BW) to partly correct for variation in body size, and the value for BMC/BW expressed as a z score, which is the number of standard deviations by which the observed value differs from the mean value expected for the patient's age [7,13]. For statistical calculation, comparison of means was performed by an unpaired *t* test or by the nonparametric Wilcoxon rank-sum test, depending on equality of variance, and comparison of proportions by the chi-squared test with Yates correction [14, 15].

Results

The mean ages in years (± SD) of the nonfracture group (63.3 ± 7.2) and the fracture group (66.3 ± 7.8) were not significantly different. Also, as shown in Table 1, the groups did not differ in any of the indices of cortical or trabecular bone mass. By contrast, as shown in Table 2, there were differences in each of the indices of trabecular microstructure. Fracture cases had significantly lower values for plate density (by 19%) and significantly higher values for plate thickness (by 19%) and separation (by 21%). Individual values for plate density are plotted against age in Fig. 1. In relation to the regression on age in normal subjects, the distribution of values was shifted significantly downward in the fracture group (Table 3).

Discussion

Biomechanically, one can liken trabecular bone to a simple cubic lattice [16]. For a given type of struc-

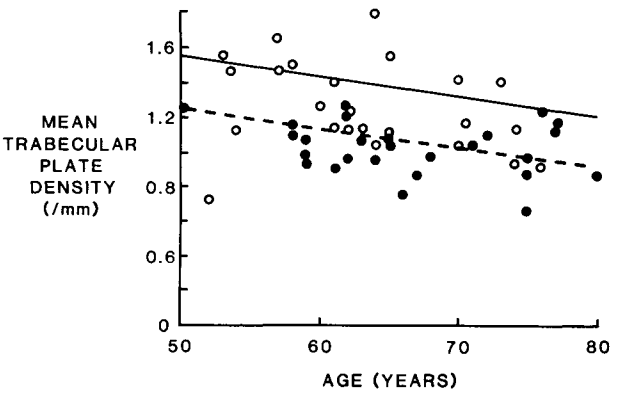

Fig. 1. Relationship between mean trabecular plate density and age. *Closed circles*—subjects with fracture, *open circles*—subjects without fracture. *Solid line* is regression line for normal female subjects [9]; the *parallel interrupted line* is lower by 0.276, which is 1 SD for normal postmenopausal subjects. Note that the majority (73%) of fracture cases are below the −1 SD line, whereas the majority (79%) of nonfracture cases are above this line.

Table 3. Frequency distribution of mean trabecular plate density in relation to predicted mean

	Nonfracture	Fracture
	n (%)	n (%)
Above predicted mean[a]	0 (0)	7 (29)
Less than 1 SD below[a]	7 (17)	12 (50)
More than 1 SD below[a]	19 (73)	5 (21)

[a] Relationship of individual values to regression on age depicted in Fig. 1.
Significance of difference in distribution: $\chi^2 = 16.4$, $P < 0.001$

tural material the strength of such a lattice depends not only on the amount of material present, but also on its spatial distribution; measurements of bone mass address only the first of these components of strength. We have focused on the area of overlap in iliac TBV between persons with and without vertebral compression fracture. Our two groups were matched with respect to age, sex, race, menopausal status, and various indices of both cortical and trabecular bone mass. Furthermore, there are only minor or no differences in the composition and density of bone tissue between normal subjects and patients with osteoporosis [17, 18]. Since the groups differed only in fracture frequency and trabecular microstructure, our data suggest that the same amount of trabecular bone is biomechanically less competent when distributed as thicker plates that are fewer, more widely separated, and less completely connected, than when distributed as thinner plates that are more numerous, less widely separated, and more completely connected.

There are several limitations to our study. First, there are important aspects of three-dimensional structure that cannot be derived from two-dimensional histologic sections such as preferential orientation *in vivo* [19], and a rigorous measurement (rather than an intuitive description) of connectivity [20]. Second, there are important anatomic differences between trabecular bone at different sites [19], although our concept of the structural basis of age-related bone loss probably applies to the vertebral bodies as well as to the ilium [9, 21], and there is a significant correlation ($r = 0.83$) between their TBV measurements [22]. Third, we have not taken account of factors other than bone strength that may contribute to fracture risk [4, 23], although there were no obvious differences in lifestyle or neuromuscular function between the two groups. These limitations should be addressed in future studies, but we do not think they are serious enough to vitiate our conclusions.

Our study is not directly concerned with the recognition of osteoporosis in individuals, for which bone biopsy is not especially useful, but mean trabecular plate density evidently discriminates more efficiently between patients with and without vertebral fracture than does TBV alone (Fig. 1). As is discussed in detail elsewhere [9, 24], the deficit in structural elements that characterizes symptomatic osteoporosis could be brought about by exaggerated depth of osteoclastic resorption cavities during the period of accelerated bone loss that occurs after menopause. An alternative possibility is a stochastic process whose frequency is dependent on the rate of bone remodeling [25]. Deficient accumulation of structural elements during growth is probably a contributory factor in some cases. The increased plate thickness in the fracture group reflects the method of case selection and we are unable to say whether it represents a difference acquired during bone growth and consolidation, or resulted from preferential removal of thinner structural elements or from compensatory thickening of those that remain. But whichever is the case, the thicker plates failed to compensate for the weakness resulting from disruption of the normal trabecular architecture.

Our hypothesis is also of potential importance in predicting the success of attempts to increase bone strength in osteoporosis. So far as is known, once skeletal maturity is attained, trabecular bone can be added only by increasing the thickness of existing trabeculae and not by replacing those that have been removed [26]. Whether or not existing trabeculae can become more connected in response to therapy is unknown. For a given TBV, patients with fewer trabeculae would be less likely to experience

a reduction in fracture rate, even if bone mass was increased. Confirmation of our hypothesis must await the direct examination of trabecular architecture in three dimensions [27] and correlation with direct testing of biomechanical properties [2, 16].

Acknowledgments. We thank B. Frame for referring patients, and L. Feldkamp, S. Goldstein, R. Freeling and M. Flynn for helpful discussions. These studies were supported in part by NIH Grant #R01 AM28583

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