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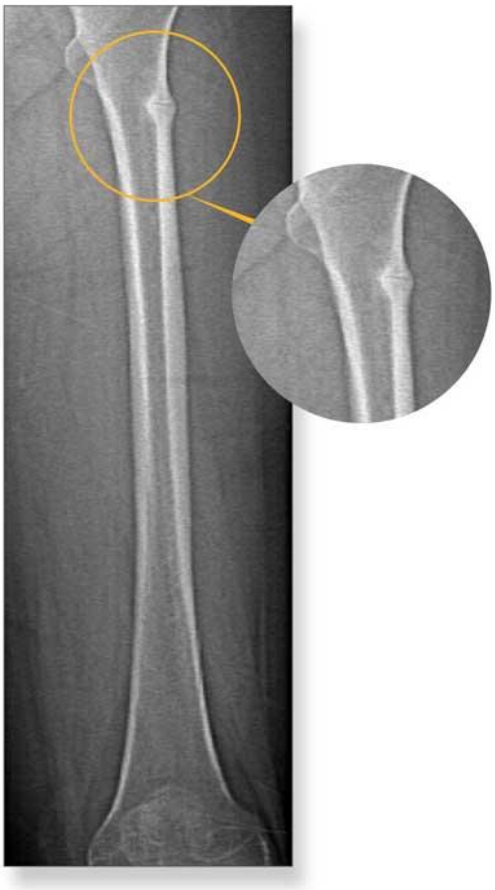

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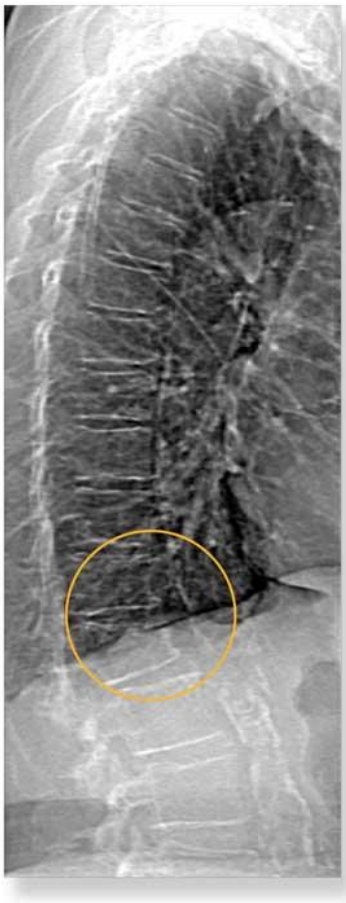

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Trabecular Bone Microarchitecture, Bone Mineral Density, and Vertebral Fractures in Male Osteoporosis

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ABSTRACT

Some studies have indicated that the risk of fragility fractures in men increases as bone mineral levels decrease, but there is an overlap in the bone mineral density (BMD) measurements between patients with or without fractures. Furthermore, it has been suggested that the biomechanical competence of trabecular bone is dependent not only on the absolute amount of bone present but also on the trabecular microarchitecture. In the present study, 108 men (mean age 52.1 years) with lumbar osteopenia (T score < -2.5) were recruited to examine the relationships between BMD, architectural changes in trabecular bone, and the presence of vertebral fractures. Lumbar BMD was assessed from L2 to L4 in the anteroposterior view with dual-energy X-ray absorptiometry. At the upper left femur, hip BMD was measured at the transcervical site. Spinal X-ray films were analyzed independently by two trained investigators, and vertebral fracture was defined as a reduction of at least 20% in the anterior, middle, or posterior vertebral height. Transiliac bone biopsy specimens were obtained for all patients. Histomorphometric studies were performed on an image analyzer, and the following parameters were determined: trabecular bone volume (BV/TV), trabecular thickness (Tb.Th), number (Tb.N), and separation (Tb.Sp), interconnectivity index (ICI), characterization of the trabecular network (node count and strut analysis), and star volume of the marrow spaces. Spinal radiographs evidenced at least one vertebral crush fracture in 62 patients (group II) and none in 46 patients (group I). After adjusting for age, body mass index, and BMD, there were no significant differences between the two groups in BV/TV, Tb.Th, or star volume. In contrast, the mean values of ICI, free end–to–free end struts (FF/TSL), and Tb.Sp were significantly higher, whereas Tb.N and node-to-node struts (NN/TSL) were lower in patients with at least one vertebral fracture. Logistic regression analysis showed that only ICI, FF/TSL, NN/TSL, and Tb.N were significant predictors of the presence of vertebral fracture: odds ratios for an alteration of 1 SD ranged from 1.7 (1.0–3.2) for NN/TSL to 3.2 (1.1–10.1) for ICI. Patients with at least three vertebral fractures ($n = 23$) were categorized as "multiple fractures." The results of logistic regression showed that spine BMD, BV/TV, and all architectural parameters were significant predictors of multiple vertebral fractures: odds ratios for an alteration of 1 SD ranged from 2.2 (1.1–4.6) for star volume to 3.7 (1.4–9.7) for ICI. These results strongly suggest that bone trabecular microarchitecture is a major and independent determinant of vertebral fractures in middle-aged men with osteopenia. (J Bone Miner Res 2000;15:13–19)

Key words: osteoporosis, men, bone histomorphometry, bone microarchitecture, bone mineral density, vertebral fractures

INTRODUCTION

OSTEOPOROSIS HAS BEEN defined as a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in risk of fracture.[1] In men the impact of osteoporosis has often been underestimated. Several recent epidemiologic studies have shown that ~30% of hip fractures occurred in men. Perhaps as a result of a higher prevalence of concomitant disease, the mortality

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associated with hip fractures in elderly men is at least twice as great in women.[2,3] It has been estimated that in the United States the lifetime risk of hip fracture is ~6% and the risk of vertebral fracture is ~5% in 50-year-old white men.[2] Furthermore, a recent multicenter European study has shown that the prevalences of vertebral deformity were similar in both sexes and that middle-aged men (aged 50–64 years) had a higher prevalence of deformity compared with similarly aged women.[4] The same findings were reported by Davies et al. in a cohort of 529 men and 899 women: men in their 50s have a 29% prevalence of vertebral deformity compared with 10% in women.[5] Finally, sequelae of spine fractures have been reported in 63 men: loss of height was documented in 49%, kyphosis in 54%, and pain on standing in 64%; 52% of patients used analgesics daily.[6]

In men, some studies using single- or dual-photon absorptiometry have indicated that the risk of fragility fractures increases as bone mineral levels decrease.[7–9] There is a considerable overlap, however, in BMD measurements between controls and patients with fractures, and it has been suggested that BMD alone does not explain the fracture risk and that bone quality could play a key role in the biomechanical competence of trabecular bone in the vertebrae. Few studies have analyzed bone remodeling and bone architecture in men. They suggest that bone formation is reduced in men with alcoholic osteoporosis,[10,11] hypercalciuria[12] or primary osteoporosis.[11,13,14] Bone resorption is more difficult to assess but seems to be increased in hypogonadal osteoporosis.[14] The microarchitectural changes of age-related bone loss have been compared in men and women. Compston et al., using a computerized method which measures trabecular nodes and free ends, have shown that removal of trabeculae occurs in males, but to a lesser extent than in women.[15] By using the trabecular bone pattern factor technique (TBPf), Hahn et al. reported that male subjects presented an age-dependent loss of bone volume with only minor changes in bone connectivity.[16] Mosekilde et al. have studied the microarchitectural evolution of age-related bone loss in men and women and found a greater preservation of trabecular bone architecture in men.[17]

However, except in corticosteroid induced osteoporosis,[18] the architectural changes in the trabecular network have been poorly investigated in men with severe osteoporosis and vertebral fractures. A reduction in the trabecular number was reported in men with primary osteoporosis.[13] The three-dimensional network (appreciated by scanning electron microscopy and numerized image reconstructions of microscopic bone sections) was found to remain well connected in a group of patients with alcoholic osteoporosis.[10]

The purpose of the present study was to evaluate a cohort of 108 osteoporotic men for the prevalence of vertebral fractures, for spine and hip bone mineral density (BMD), and for microarchitectural changes in trabecular bone.

MATERIALS AND METHODS

Patients

From January 1993 to December 1997, 335 men were referred to our unit (by their general practitioner or rheumatologist) for measurement of BMD because they had risk factors for osteoporosis, apparent osteopenia, or vertebral fractures on X-ray films.

One hundred and eight men with significant lumbar osteopenia (BMD >2.5 SD below the normal young adult value) were included in a prospective study to examine the relationships between the bone mineral density, the architectural changes of trabecular bone and the presence of vertebral fractures. Their ages ranged from 19 to 76 years (mean 52.1 years). Of these 108 patients, 72 (66.7%) had relevant medical disorders associated with their osteoporosis (alcohol abuse, cigarette smoking, hypogonadism, glucocorticosteroid therapy). The remaining thirty six patients (33.3%) had no apparent cause for their bone fragility and were categorized as idiopathic osteoporosis.

Bone densitometry

We measured bone mineral density (areal density in g/cm2,BMD) using dual-energy X-ray absorptiometry (DXA) operating in fan beam mode (Hologic QDR 2000 densitometer; Hologic Inc., Waltham, MA, U.S.A.). Quality-control scans were performed daily, using the manufacturer-supplied anthropomorphometric spine phantom; the long-term (<2-year) coefficient of variation was 0.40%. Lumbar BMD was assessed from L2 to L4 in the posteroanterior view, and fractured vertebrae were excluded from analysis. At upper left femur, hip BMD was measured at the transcervical site. The mean precision error of DXA measurement is <1.5% for the lumbar spine and <2% for hip BMD.

Radiographic assessment

Anteroposterior and lateral spinal X-ray films were taken at the time of the bone biopsy. They were analyzed independently by two trained investigators who were unaware of the patient status. A patient was classified as having a vertebral fracture if both readers independently found a definite fracture; he was classified as normal if both readers independently found that the films were normal. When the readers disagreed, the films were reviewed in conference between both investigators. Vertebral fracture was defined as a reduction of at least 20% in the anterior, middle, or posterior vertebral height according to the following criteria: (1) anterior wedge deformity: ratio of anterior to posterior height <80%; (2) concavity deformity: ratio of middle to posterior height <80%; (3) compression deformity: ratio of posterior height to posterior height of the adjacent vertebra <80%.

Bone biopsies

Transiliac bone biopsy specimens were obtained with subjects under local anesthesia by using a 7.5-mm internal

diameter trephine 2 cm below the iliac crest and 2 cm behind the anterosuperior iliac spine. All specimens were complete and unbroken. They were fixed in 70° alcohol acidified with 1% acetic acid and embedded in methylmethacrylate-based media as previously reported.[19] Six undecalcified sections (7 μm thick) were cut dry on heavy-duty microtomes and were stained with Solochrome cyanin and/or Goldner's trichrome.

Histomorphometric analysis

The histomorphometric analysis was performed on a Leica Quantimet Q570 image analyzer (Leica France, Rueil Malmaison, France) as previously reported.[18] In this way, basic histomorphometric measurements can be obtained. Cortical thickness (Ct.Th) is the mean of external + internal cortical thickness, expressed in micrometers. Trabecular bone volume (BV/TV) is the amount of trabecular bone within the spongy space (expressed as a percentage). BV/TV is derived from measurements of bone area (B.Ar) and cancellous tissue area (T.Ar) and expressed as

$$\mathrm{BV/TV} = 100 * \mathrm{B.Ar/T.Ar}$$

In addition, four stereological methods were computed in order to appreciate the spatial distribution of trabeculae and their connectivity.

Trabecular thickness, number, and separation: Trabecular thickness (Tb.Th, in micrometers) was derived from trabecular perimeter (B.Pm) and B.Ar according to Parfitt's formula[20]:

$$\mathrm{Tb.Th} = 1.199 * \mathrm{B.Ar/2/B.Pm}$$

Trabecular number (Tb.N, expressed per millimeter) and trabecular separation (Tb.Sp, expressed per micrometer) were calculated assuming that trabecular bone can be modeled by the parallel plates and bar model:

$$\mathrm{Tb.N} = \mathrm{Tb.Ar} * 10/\mathrm{Tb.Th}$$

$$\mathrm{Tb.Sp} = 1000/\mathrm{Tb.N} - \mathrm{Tb.Th}$$

Interconnectivity index: The method was originally proposed by Le et al. to appreciate the connectivity of porous biomaterials such as corals.[21] The connectivity of the marrow cavities can be measured by taking the skeletons of their profiles. On the pruned skeleton, the total number of nodes (N), node-to-node branches (NN), and node–to–free end branches (NF) were determined. Also, the number of "trees" (T) was obtained, a tree being the structure composed of interconnected node(s) with node-to-node and/or node–to–free end branch(es). The interconnectivity index (ICI) of the bone marrow cavities is then defined as

$$\mathrm{ICI} = (\mathrm{N} * \mathrm{NN})/(\mathrm{T} * (\mathrm{NF} + 1))$$

(NF + 1 is preferred to NF in order to avoid cases where division by zero may lead to computational problems).

The higher the level of connectivity of the marrow cavities (given by a high number of nodes and segmental branches associated with a low number of trees), the higher the ICI and, conversely, the higher the fragmentation of the bone trabecular network.

Characterization of the trabecular network: The binary images of the trabeculae were skeletonized and pruned with the same algorithms as described for ICI determination.[22–24] On the skeleton, nodes, free ends, and the various types of trabeculae were measured: node-to-node struts (NN/TSL) and free end–to–free end struts (FF/TSL). Core boundaries struts were not considered for measurements. Measurements of strut lengths were expressed as a percentage of the total strut length (TSL).[22]

Star volume of the bone marrow: The star volume of the marrow space was determined according to the chord length distribution method described by Levitz and Tchoubar for porous glasses or cements.[25]

A series of grid of parallel lines (with angles from π to 2π) was used to explore the marrow cavities. The cubed length of each overimposed chord 1_o^3 was measured, and the star volume was defined as

$$V^* = \pi/3 * \overline{1_o^3}$$

With these methods, a decreased trabecular bone connectivity is characterized by an increase in Tb.Sp, ICI, star volume, and FF/TSL and a decrease in Tb.N and NN/TSL.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS release 6.1.3; SPSS Inc., Chicago, IL, U.S.A.). All results are expressed as the mean ± one standard deviation. The nominal significance level was set at 0.05. Correlations were searched between parameters: linear correction analysis used Pearson's r based on the model $y = ax + b$, where y is the dependent variable and x the predictor variable. When nonlinear relationships between two variables appeared evident on graphic examination, polynomial (in x^2 and x^3), logarithmic (model: $y = a \cdot \log(x) + b$), hyperbolic (model: $y = a + 1/(b \cdot x)$, and exponential (model: $y = a \cdot \exp(b \cdot x)$) relationships were computed.

Subjects were categorized according to the presence or absence of vertebral fracture. Comparisons between group I (patients without vertebral fracture), group II (patients with at least one vertebral fracture) were tested by multivariate analysis of variance. The associations of age, BMD, and architectural parameters with vertebral fractures were explored by using logistic regression analysis: the outcome variable was the presence of vertebral fracture (yes/no) or multiple fracture (yes/no), and the possible predictor variables were age (10 years increase), body mass index (BMI), hip or spine BMD (1 SD decrease), and histomorphometric, and microarchitectural parameters: BV/TV, Tb.Th, Tb.N, NN/TSL (1 SD decrease) ICI, V*, and FF/TSL (1 SD increase). Backward-stepwise algorithms were used to arrive at the best model. Variables were included in the final model if the p value was <0.05.

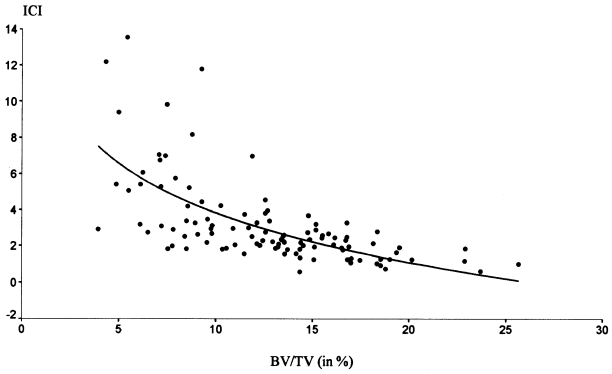

FIG. 1. Logarithmic relationship between BV/TV and ICI.

RESULTS

Radiographic vertebral evaluation

Anteroposterior and lateral spinal radiographs evidenced at least one vertebral crush fracture in 62 patients (who constituted group II) and none in 46 men (group I).

In group II, 21 patients had only 1 vertebral fracture, whereas 31 men had 2–4 fractures. Ten patients had severe osteoporosis with 5–10 vertebral fractures.

Relationships between microarchitectural parameters and bone mineral density

The different sterological methods seemed to yield nearly similar results: good correlations (logarithmic models) were obtained between ICI and FFS/TSL ($r = 0.83$, $p = 0.001$), ICI and NN/TSL ($r = -0.65$, $p = 0.001$), ICI and star volume ($r = 0.60$, $p = 0.001$), NNS and Tb.N ($r = 0.60$, $p = 0.001$), and Tb.N and V* ($r = 0.69$, $p = 0.001$).

Logarithmic regressions were found to best describe the relationships between BV/TV and ICI ($r = 0.62$, $p = 0.001$) and BV/TV and FFS/TSL ($r = 0.74$, $p = 0.001$) (Figs. 1 and 2).

Exponential regression described the relationship between BV/TV and star volume ($r = 0.66$ $p = 0.001$) (Fig 3). On these curves, the inflection point appeared for a value of BV/TV near 11%.

After adjustment for age and BMI, we did not find any significant relationship between spinal BMD and microarchitectural parameters, with the exception of a weak correlation with FFS/TSL ($r = 0.26$, $p = 0.02$). Hip BMD was correlated with ICI ($r = 0.34$, $p = 0.01$) and FFS/TSL ($r = 0.28$, $p = 0.03$).

Bone mineral density, bone microarchitecture and vertebral fractures

We compared bone mineral density and histomorphometric parameters between patients without vertebral fracture (group I) and patients with at least one vertebral fracture (group II). As shown in Table 1, there were no significant differences between the two groups according to age, BMI, or spine or hip BMD. After adjusting for age, BMI, and BMD, there were no significant differences between groups I and II in BV/TV, Tb.Th, or star volume. In contrast, the multivariate analysis of variance showed that the mean values of ICI, FF/TSL, and Tb.Sp were significantly higher, whereas Tb.N and NN/TSL were lower in patients with at least one vertebral fracture.

As shown in Table 2, logistic regression analysis showed that age, BMI, spine BMD, hip BMD, BV/TV, Tb.Th, and V* were not significant predictors of the presence of at least one vertebral fracture. On the other hand, five microarchitectural parameters were significantly associated with the presence of vertebral fracture: odds ratios for an alteration of 1 SD ranged from 1.7 for NN/TSL to 3.2 for ICI.

Patients with at least 3 vertebral fractures ($n = 23$) were categorized as ''multiple fractures.'' Logistic regression analysis showed that spine BMD, hip BMD, BV/TV (but not Tb.Th) and all architectural parameters were significant predictors of the presence of multiple vertebral fractures (Table 3).

DISCUSSION

In the present study we examined the relationships between bone mineral density, trabecular bone microarchitecture, and the presence of vertebral fracture in a large cohort of men suffering from osteoporosis. We have confirmed that the correlation between the four different stereological methods was high, with correlation coefficients ranging from 0.60 to 0.83. As previously reported by Chappard et al.,[18] Croucher et al.,[26] and Thomsen et al.,[27] bone trabecular volume and most three-dimensional descriptors (which are not derived from B.Ar and T.Ar measurements) are not linearly correlated. An important increase in these stereological parameters that indicate the lack of trabecular connectivity occurs when BV/TV was below the value of 11%. This value was recognized several years ago as the spontaneous vertebral fracture threshold by Meunier et al.[28]

Hip BMD was correlated with two microarchitectural indices (ICI and FF/TSL), whereas spine BMD was only correlated with FF/TSL. However, correlation coefficients were relatively low. These results have to be examined carefully. On the one hand, methodological problems may exist. The measurements of BMD (in the spine and hip) and the estimation of bone architecture (in iliac crest biopsy specimens) did not concern the same skeletal site. Morever, measurements of spine or hip BMD capture trabecular bone and also a large proportion of cortical bone. On the other hand, the weak correlation between BMD and microarchitectural indices could argue in favor of the independent contribution of bone mass and bone microstructure in the pathogenesis of osteoporosis.

The most striking observation in our study was the marked alteration of trabecular bone connectivity in patients with vertebral fractures. Multivariate analysis of variance showed that mean values of ICI and FF/TSL were significantly higher, whereas Tb.N and NN/TSL were lower in patients with at least one vertebral fracture. Furthermore, after adjusting for age, BMI and BMD, odds ratios for an alteration of 1 SD ranged from 1.8 for NN/TSL to 3.2 for

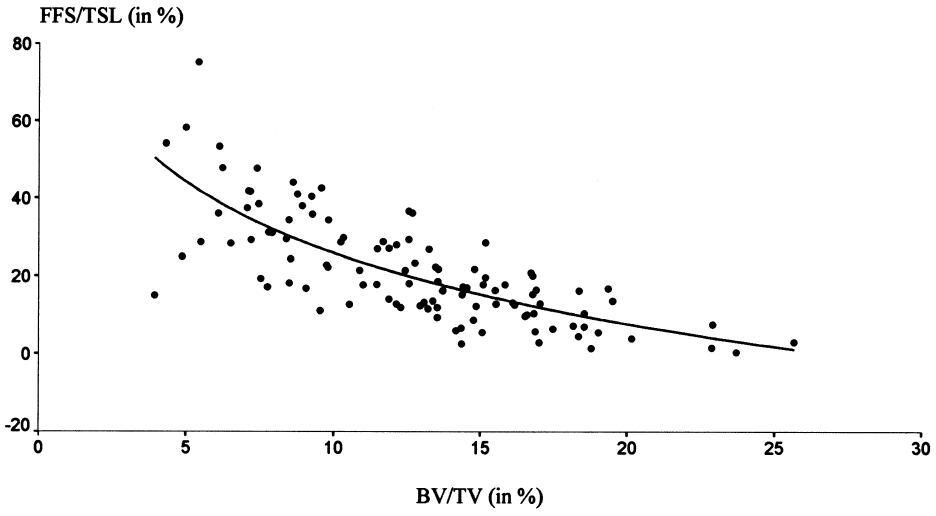

FIG. 2. Logarithmic relationship between BV/TV and FFS/TSL.

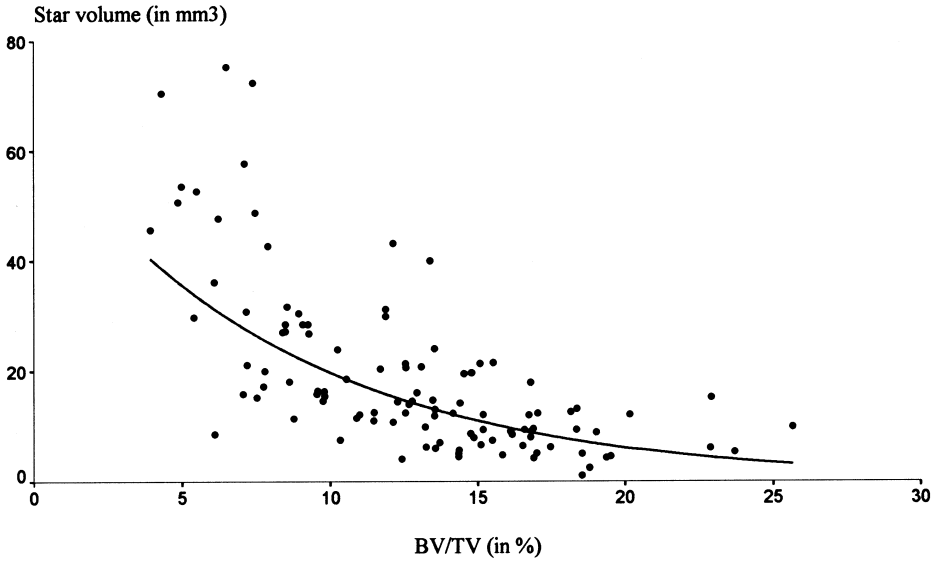

FIG. 3. Exponential relationship between BV/TV and star volume of the marrow spaces.

ICI. These results strongly suggest that bone trabecular microarchitecture is a major and independent determinant of vertebral fractures in middle-aged men with severe osteopenia; in addition to traumatic factors, differences in bone trabecular microstructure could explain, in part, the difference in fracture prevalence observed in men, even for an identical BMD.

It has already been shown that the risk of vertebral deformity was equal and even greater in young men than in women and it has been suggested that these deformities are in part "traumatic."[4,5] This is a crucial methodological problem in assessing the influence of bone mass or bone quality in vertebral fracture risk in men. However, the higher the number of vertebral deformities in a patient, the higher the probability that these deformities are osteoporotic and not traumatic. We observed that the decrease of femoral or spine BMD was clearly associated with the risk of multiple vertebral fractures: after adjusting for age and BMI, odds ratio ranged from 1.9 to 2.2 per SD. The magnitude of this effect agrees with findings in previous studies of nonselected men[8,9,29] or in postmenopausal women.[30,31,32] On the other hand, we observed that the alteration of trabecular connectivity was more strongly associated with multiple fractures than BMD. After adjusting for age, BMI and BMD, odds ratios for an alteration of 1 SD ranged from 2.2 for star volume to 3.7 for ICI. This result strongly suggests that an altered bone trabecular microarchitecture is an important criterion to estimate the severity of osteopenia in middle-aged men.

By using a model of vertebral trabecular bone architecture, Jensen et al.[33] showed that the apparent bone stiffness varies by a factor of 5–10 from a perfect cubic lattice to a network of maximal irregularity, even if trabecular bone volume remains constant. Our data confirm in vivo that the biomechanical competence of trabecular bone is dependent not only on the absolute amount of bone present but also on its three-dimensional configuration.

In conclusion, this histomorphometric study shows that not only BMD but also trabecular bone connectivity are

TABLE 1. COMPARISONS BETWEEN GROUP I (PATIENTS WITHOUT VERTEBRAL FRACTURE) AND GROUP II (PATIENTS WITH AT LEAST ONE VERTEBRAL FRACTURE) TESTED BY MULTIVARIATE ANALYSIS OF VARIANCE FOR AGE, BMI, BMD, AND HISTOLOGICAL PARAMETERS

	No fracture (group I) (n = 46)	*At least 1 fracture (group II) (n = 62)*	*p*
Age (years)	50.3 ± 13.3	53.4 ± 12.8	NS
Body mass index (kg/m^2)	24.5 ± 4.2	24.1 ± 3.8	NS
Spinal BMD (g/cm^2)	0.73 ± 0.08	0.71 ± 0.08	NS
Hip BMD (g/cm^2)	0.69 ± 0.08	0.67 ± 0.11	NS
C.Th (μm)	781.7 ± 365.9	765.7 ± 255.0	NS
BV/TV (%)	13.9 ± 4.0	11.9 ± 4.7	NS
Tb.Th (μm)	97.3 ± 26.7	98.3 ± 34.5	NS
Tb.N (/μm)	1.4 ± 0.3	1.2 ± 0.4	0.002
Tb.Sp (μm)	635.3 ± 189.1	806.9 ± 275.9	0.005
ICI	2.2 ± 0.9	3.83 ± 2.8	0.01
$V^*_{m.space}$ (mm^3)	15.4 ± 13.4	21.7 ± 16.5	NS
NN/TSL	30.6 ± 13.8	20.0 ± 12.5	0.01
FF/TSL	15.6 ± 8.9	25.7 ± 15.2	0.01

Values are means ± SD.

TABLE 2. ASSOCIATIONS BETWEEN AGE, BMI, BMD, AND HISTOMORPHOMETRIC PARAMETERS WITH AT LEAST ONE VERTEBRAL FRACTURE IN LOGISTIC REGRESSION MODELS IN 108 MEN

	At least 1 vertebral fracture	
Predictor	*Odds ratio (95% CI)*	*p*
Age (10-year increase)	1.0 (0.7–1.6)	NS
BMI (1-kg/m^2 increase)	1.0 (0.9–1.2)	NS
Hip BMD (1-SD decrease)	1.7 (0.9–3.4)	NS
Spine BMD (1-SD decrease)	1.5 (0.9–2.5)	NS
BV/TV (1-SD decrease)	1.7 (0.9–3.2)	NS
Tb.Th (1-SD decrease)	0.9 (0.6–1.8)	NS
Tb.N (1-SD decrease)	2.8 (1.1–7.3)	0.02
Tb.Sp (1-SD increase)	3.1 (1.2–6.5)	0.02
NN/TSL (1-SD decrease)	1.7 (1.0–3.2)	0.03
FF/TSL (1-SD increase)	2.5 (1.2–5.2)	0.02
ICI (1-SD increase)	3.2 (1.1–10.1)	0.01
$V^*_{m.space}$ (1-SD increase)	1.3 (0.7–2.4)	NS

Odds ratios shown represent the increase in odds of vertebral fracture corresponding to a 10-year increase in age, a kg/m^2 increase in BMI, 1 SD decrease in BMD, or 1 SD alteration in histological parameters.

CI, confidence interval.

major determinants of vertebral deformities in men with mild osteoporosis. To predict the fracture risk and the severity of osteoporosis in middle-aged men, BMD measurements may to be combined with information about bone quality and particularly bone trabecular microarchitecture.

TABLE 3. ASSOCIATION BETWEEN AGE, BMI, BMD, AND HISTOMORPHOMETRIC PARAMETERS WITH THE PRESENCE OF MULTIPLE VERTEBRAL FRACTURES IN LOGISTIC REGRESSION MODELS IN 108 MEN

	Multiple fractures (at least 3 fractures)	
Predictor	*Odds ratio (95% CI)*	*p*
Age (10-year increase)	1.2 (0.9–1.7)	NS
BMI (1-kg/m^2 increase)	1.1 (1.0–1.2)	NS
Hip BMD (1-SD decrease)	1.9 (0.9–4.2)	NS
Spine BMD (1-SD decrease)	2.2 (1.1–4.3)	0.02
BV/TV (1-SD decrease)	3.3 (1.2–9.0)	0.02
Tb.Th (1-SD decrease)	1.5 (0.7–3.8)	NS
Tb.N (1-SD decrease)	2.6 (1.2–5.8)	0.02
Tb.Sp (1-SD increase)	2.6 (1.1–6.2)	0.02
NN/TSL (1-SD decrease)	3.0 (1.1–8.5)	0.03
FF/TSL (1-SD increase)	2.6 (1.2–5.8)	0.01
ICI (1-SD increase)	3.7 (1.4–9.7)	0.01
$V^*_{m.space}$ (1-SD increase)	2.2 (1.1–4.6)	0.02

Odds ratios shown represent the increase in odds of vertebral fracture corresponding to a 10-year increase in age, a kg/m^2 increase in BMI, 1 SD decrease in BMD, or 1 SD alteration in histological parameters.

CI, confidence interval.

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