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The Predictive Value of Bone Loss for Fragility Fractures in Women: A Longitudinal Study over 15 Years

Per Gärdsell, Olof Johnell, and Bo E. Nilsson

Department of Orthopaedics, Malmö General Hospital, S-214 01 Malmö, Sweden

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Summary. Fifteen years after their forearm bone mineral content was measured, 366 women were measured again with the same single photon technique. 96 of the women had sustained one or more fragility fractures during that period. The initial bone mineral content was less in those women who were to have fractures. The rate of loss over the years did not differ between fracture and non-fracture women—the initial bone mass was the better predictor. Peak bone mass in the women in this study occurred before the age of 40.

In a prospective study [1] we measured forearm bone mineral content (BMC) using single photon absorptiometry (SPA). BMC predicted future fragility fractures but only in women below the age of 70. Also, a history of a previous fragility fracture [2] and a short fertile period were of predictive value. In women over 70 it was not possible to differ between those who were to have fractures and those who were not. Instead, differences in function variables, weight, and hand grip strength became important.

The objective of the present study was to learn whether an initially low bone mass or the subsequent bone loss is the most important predictor of future fragility fractures.

Material and Methods

From 1970 to 1976, 1,076 women had their forearm BMC measured using SPA according to the method of Nauclér et al. [3]. This method employs a ^{241}Am radiation source. Transverse scans of the radius and ulna were taken of both arms at a distance of 1 cm (BMC 1) and 6 cm (BMC 6) from the tip of the styloid process of the ulna. BMC was expressed as mg/cm^2.

From the National Population Records 1987 it was possible to find all women in the cohort still living in the city (n = 519). Except for 70 women with only a non-fragility fracture, they were all invited to have a repeat BMC measurement. Three hundred and sixty-six women responded (82%). The same equipment and technique were used as in the first BMC measurement. This technique was used continuously over the years and checked against the same standard. Also, several prospective studies have been going on.

All fractures that had occurred after the initial measurement, i.e., from 1975–1987, were recorded. This was possible because all emergency roentgenogram examinations in Malmö are undertaken in the Department of Diagnostic Radiology at the Malmö General Hospital. There is only one Department of Orthopedics in the city. All reports are being kept on file for each patient. Fractures of the vertebrae (presenting symptoms), the proximal ends of the humerus and femur, the distal end of the forearm, the ramii of the pelvis, and tibia condyle compression fractures were classified as fragility fractures. The cohort was separated into age groups (age at initial measurement): 20–29 (n = 12), 30–39 (n = 31), 40–49 (n = 60), 50–59 (n = 112), 60–69 (n = 124), and above 70 (n = 27). The latter group was small due to death or senility.

The initial BMC for all individuals in the age groups 40–49, 50–59, 60–69 was stratified into quartiles (only three groups in age groups 40–49) for studying the rate of loss at different BMC levels. The rate of loss was also divided into quartiles. Risk ratio was calculated by dividing the number of fractures per 1,000 women years in the lowest quartile of rate of loss with the number in the highest. In addition, a logistic regression analysis and analysis of covariance were performed.

Results

The time interval between the first and the second measurements was 14.6 years (±2.2). One hundred women in the age group 40–69 years sustained one or more fragility fractures during the observation period from 1975 to 1987. It was not possible to measure BMC in 1987 in 4 of these women with vertebral fractures in age group 60–69. Ninety-six women had not had any fracture during their adult lives. The mean age within the age groups at initial measurement did not differ between women with and those without fracture. As the vertebral fractures are commonly used to define osteoporosis, these fractures were calculated separately.

The initial BMC was less, regardless of age group, in those women who were to have a fragility fracture during the observation period (Table 1) and the difference remained,

Offprint requests to: P. Gärdsell

Table 1. Deviation of initial BMC-value (prior to the fracture) from the non-fractured group (means)

Age at initial BMC		40–49			50–59			60–69	
	No.	BMC 1	BMC 6	No.	BMC 1	BMC 6	No.	BMC 1	BMC 6
Vertebral fracture	5	−19%	−6%	17	−21%[b]	−18%[c]	31	−8%	−12%
Other fragility fractures	12	−15%	−4%	20	−18%[b]	−7%	15	−3%	−10%[a]
All fragility fractures	17	−16%[a]	−4%	37	−20%[c]	−13%[c]	46	−6%	−11%[b]

[a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$

Table 2. Deviation of second BMC value (after the fracture) from the non-fractured group (means)

Age at initial BMC		40–49			50–59			60–69	
		BMC 1	BMC 6		BMC 1	BMC 6		BMC 1	BMC 6
Vertebral fracture	(58)	−6%	−10%	(69)	−20%[b]	−18%[c]	(79)	+5%	−9%
Other fragility fractures	(61)	−9%	−8%	(70)	+2%	−11%[a]	(78)	−5%	−14%[a]
All fragility fractures		−8%	−8%		−8%	−14%[c]		+2%	−11%[a]
Non-fracture	(62)			(69)			(78)		

Age at time of remeasurement in parentheses

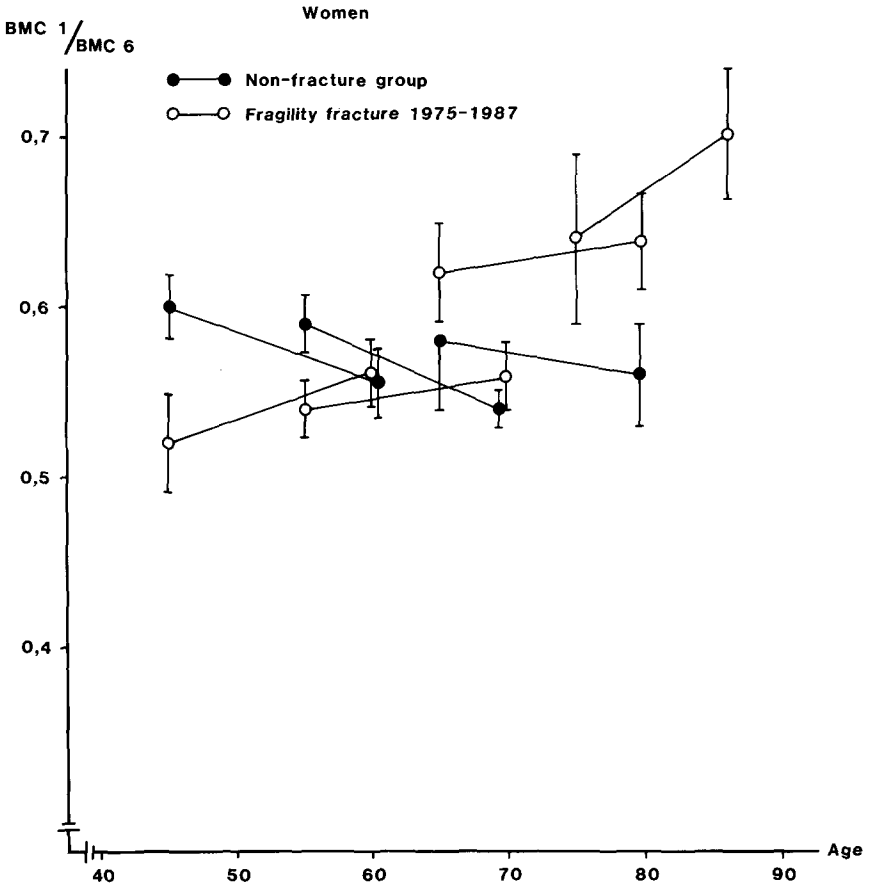

Fig. 1. Changes in BMC 1/BMC 6 ratios over a 15-year period for the age groups (age at initial BMC measurement) 40–49, 50–59, 60–69 and, only for the fracture group, >70 years. Means ± SEM.

Table 3. Bone loss (mg/cm^2)/year

Age at initial BMC	40–49		50–59		60–69	
	BMC 1	BMC 6	BMC 1	BMC 6	BMC 1	BMC 6
No fracture	−4.9 (−1.4)	−6.3 (−1.2)	−4.8 (−1.5)	−5.7 (−1.1)	−2.7 (−1.0)	−4.3 (−0.9)
Vertebral fracture	−2.2 (−0.2)	−8.8 (−1.5)	−3.7 (−1.1)	−3.8 (−0.7)	−0.2 (−0.4)	−3.4 (−0.9)
Other fragility fractures	−3.3 (−0.9)	−7.6 (−1.3)	−0.3 (−0.1)	−6.1 (−1.1)	−3.1 (−1.1)	−5.0 (−1.2)

Rate of loss %/year in brackets

but was less at the second measurement in 1987 (Table 2). Measurement of trabecular bone mass (BMC 1) appeared to be an earlier predictor than cortical bone (BMC 6). We calculated the ratio BMC 1/BMC 6—an "osteoporotic index" on an individual basis—and the ratio increased between the two measurements in the fracture group but decreased in the nonfracture group (Fig. 1).

The rate of loss, did not correlate with fracture risk. It declined with age, which was even more obvious in absolute values (mg/cm^2/year) (Table 3). The non-fracture group appeared to be the fastest losers in middle-age at the trabecular site (BMC 1). In an analysis of rate of loss using analysis of covariance, there was no significant difference in the slope between the fracture and the non-fracture group at both mea-

Table 4. Non-fracture group

Age at initial BMC	No.	Rate of loss (%/year) BMC 1	BMC 6
20–29	10	+0.7	−0.1
30–39	26	−0.2	−0.4
40–49	28	−1.42	−1.11
50–59	35	−1.46	−1.05
60–69	33	−1.02	−0.92

suring sites. The rate of loss in the non-fracture population 20–70 years is presented in Table 4 and it is apparent that peak bone mass is attained before the age of 40.

In Table 5 the initial BMC values have been divided into quartiles (in age group 40–49 only three groups) and compared with the rate of loss in percent. Also, patients with a fragility fracture before the initial BMC measurement were included, so that the fracture group now included 196. The rate of loss was correlated with the initial BMC value, so that a high initial BMC was associated with a high rate of loss. However, those individuals with fracture in the quartile with the highest BMC 6 who were 50–69 years old had a significantly higher rate of loss than their corresponding non-fracture group (Table 5). The outcome was the same when studying only those who sustained fractures during the observation period.

The patients were separated into quartiles according to rate of loss. In the fracture group, at both sites, there was a positive correlation between rate of loss and initial BMC value. This was also the case for the group with fractures during the observation period. However, this was not a consistent finding in the non-fracture group. Significant differences between the two groups with regard to BMC levels were primarily seen in the lower quartiles, with lower initial BMC for the fracture group. Within the quartiles, there was no difference for the various age groups with regard to the distribution of different fractures.

The number of fractures per 1,000 women years in the various quartiles of rate of loss are presented in Figure 2. The risk ratio for sustaining a fragility frature was about doubled in age group 40–49 in the group with the lowest as compared with the highest rate of loss of BMC 1 and nearly doubled in age groups 50–59 and 60–69; at the BMC 6 site, this was not seen.

Logistic regression analysis was used to assess the relative risk of a fragility fracture for a 1 SD reduction of BMC. The relative risk for the initial BMC measurement was 2.6 for BMC 1, 3.2 for BMC 6, whereas the relative risk for BMC after the fracture (second BMC measurement) was 1.4 and 2.6, respectively. Consequently, the initial BMC measurement has the stronger predictive value. When we included rate of loss in the model, no change for BMC was observed.

Discussion

The relationship between BMC and fracture risk is recognized whereas the usefulness of BMC for fracture risk screening is not all that clear [4]. However, Ross et al. [5] recently reviewed the usefulness of various bone mineral techniques and found that most studies were able to show an association between reduced bone mass and increased fracture risk. The magnitude of the relationship varied less in prospective studies now being carried out, compared to cross-sectional studies. Several studies have demonstrated the reliability of SPA in measurements of bone mass [6–12]. Hui et al. [13] found that an initial SPA measurement is predictive of future fractures. The same authors found, in a 6.5 year prospective study using SPA, that aging is a better predictor of hip fracture than decreasing forearm bone mass [14]. Vogel et al. [12] also showed a good predictive value for a BMC measurement. We have demonstrated the predictive value of bone mass measurements of the distal end of the

Table 5. Rate of loss (%/year)

	Initial BMC	No.	No fracture BMC 1	No.	BMC 6	No.	Fragility fracture BMC 1 a b	No.	BMC 6 a b
40–49	I	6	−1.08	6	−0.72	13	+0.01 (−0.07)	13	−0.98 (−1.09)
	II	11	−1.45	13	−1.27	9	−1.19 (−1.23)	7	−1.21 (−1.33)
	III	12	−1.56	10	−1.15	7	−1.98 (−2.10)	10	−1.8 (−1.71)
50–59	I	2	−0.23	5	−1.22	26	0.4 (+0.17)	23	−0.49 (−0.28)
	II	6	0.20	5	−0.93	21	−0.36 (−0.30)	21	−1.09 (−1.29)
	III	18	−1.8	10	1.07	9	−0.88 (−0.63)	18	−1.5 (−1.57)
	IV	9	−2.21	15	−1.05	18	−2.31 (−2.28)	14	−1.45 (−1.36)
60–69	I	5	−0.79	3	0.74	26	1.44 (+2.02)	27	−0.6 (−0.72)
	II	8	−1.17	9	0.95	21	−0.41 (−0.69)	21	−1.20 (−1.36)
	III	10	−0.57	11	−1.26	19	0.22 (−0.87)	20	−0.86 (−0.93)
	IV	10	−1.5	10	−1.02	20	−2.00 (−1.65)	19	−1.64 (−1.75)
50–69	I	8	−0.91	8	−0.27	53	1.03 (+1.0)	50	−0.57 (−0.44)
	II	15	−0.39	13	−1.15	40	−0.44 (−0.21)	44	−1.05 (−1.10)
	III	22	−1.32	21	−1.23	32	−0.47 (0.98)	37	−1.21 (−1.41)
	IV	23	−1.86	26	−0.94	35	−2.14 (−1.86)	32	−1.6** (−1.63**

Initial BMC value has been divided in quartiles (I = lowest BMC) except for age groups 40–49
a = fragility fractures before and/or after first BMC measurement
b = fragility fractures after first BMC measurement
** $P < 0.01$

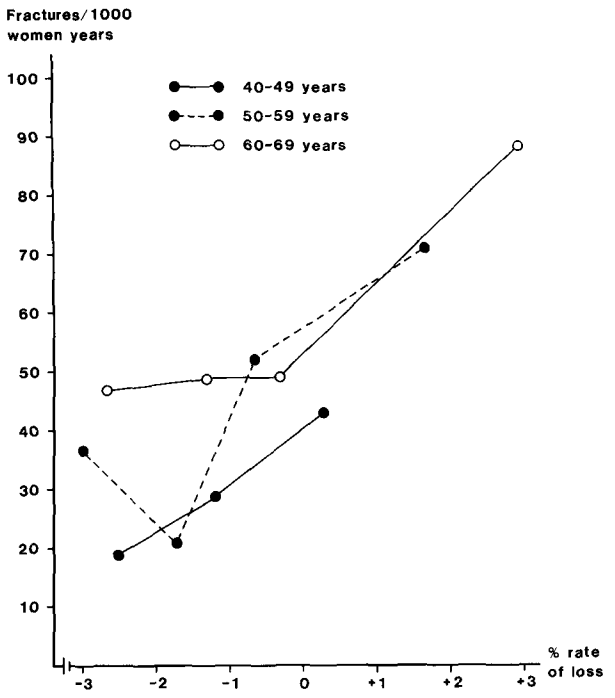

Fig. 2. Fragility fractures per 1,000 women years for quartiles of rates of loss, in age groups 40–49, 50–59, and 60–69 years. Mean values are used to label the quartiles. Negative percent means a loss.

forearm using SPA [1]. In that study, measurements of both trabecular and cortical bone were predictive but only before the age of 70. In a stepwise logistic regression analysis, the BMC 6 appeared to be a stronger predictor of future fragility fractures than BMC 1. This was surprising because postmenopausal osteoporosis is considered to be mainly a loss of trabecular bone. One reason may be that trabecular bone loss levels off in the seventh decade whereas cortical loss is continuous, and that the cortices contain more bone mass.

Prevention of fragility fractures is possible today but only at a cost—in risks—that requires selection. In a longitudinal study, Davis et al. [15] found that the rate of bone loss in the distal end of the radius decreased with age. The relationship between BMC/rate of loss in our study supports the view of Stevenson et al. [16], Nordin et al. [17], Genant et al. [18], and Schaadt and Bohr [19] that the rate of loss is positively correlated with bone mass, i.e., the greater the bone mass the greater the loss.

This is the first study of these variables which also includes the fracture risk. Our conclusion is that bone mass predicts fracture better than the rate of bone loss. However, we did identify a small subset of fast losers, age 50–69, in the fracture group in the highest quartile of BMC 6. The information obtained regarding rate of loss might have been biased by the fact that fracture occurred before the second measurement. The event of fracture causes disability and possibly alters behavior in ways that alter rates of bone loss. Post-fracture bone loss have been reported to persist for years [20]. This could mean that the "true" rate of loss prior to fracture in our fracture group should be less. Hui et al. [21] have demonstrated that those who are fast losers after menopause do not continue to be so later in life. The same authors also calculated the relative risk for fracture with a bone mass 1 SD below the mean [13]. For the younger subjects, relative risk was found to be 2.2; their measuring site corresponds with our BMC 6. Our relative risk was higher, i.e., 3.2.

In certain groups the rate of loss, established by repeated measurements, may have a predictive value in describing the bone metabolic state in individual subjects—possibly also predicting fractures. The best fracture predictive variable beside age, sex, and menopausal age, is the bone mineral content.

In this longitudinal study, it was possible to verify that peak bone value in women occurs before the age of 40.

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