A Comparison of Single and Multi-Site BMC Measurements for Assessment of Spine Fracture Probability

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In a prospective study of 699 women, 39 new spine fracture cases were observed during a mean follow-up of 3.6 yr. Spine fracture incidence was compared to initial bone mineral content (BMC) of the calcaneus, distal radius, proximal radius, and the lumbar spine. BMC at all four sites was significantly related to spine fracture incidence. Women at −1 s.d. for calcaneal BMC had a sevenfold greater probability of spine fracture than women at +1 s.d.; women at −2 s.d. had a 50-fold greater probability than women at +2 s.d., even after adjustment for the effects of age. Combinations of BMC at two sites further strengthened the relationship to spine fracture; the best two-site combination is calcaneus and distal radius BMC. Thus women can be categorized and stratified according to future fracture risk, and the selection of postmenopausal women for preventive treatments can be guided by measurements of BMC.

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A relationship between low bone mass and increased fracture probability has long been suspected. Based upon cross-sectional data, various investigators have proposed that bone mineral measurements be used in the selection of women for postmenopausal estrogen replacement (*1,2*). However, some important questions remain unanswered. The ability to estimate fracture risk prospectively with bone mineral measurements has been questioned (*3*). There is also disagreement concerning the ability of appendicular bone density measurements to assess spine fracture risk (*4*). Finally, it is not known whether a combination of bone mineral content (BMC) measurement sites, representative of both cortical and trabecular compartments, would improve the estimation of fracture probability.

In this prospective, cohort study we have explored the relationship of BMC measurements at four skeletal sites, both individually and in combination, to spine fracture incidence in a 6-year study of 699 postmenopausal women.

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METHODS

The original study population consisted of 1,098 Japanese-American women who were initially examined between February, 1981 and June, 1982. Details concerning the identification and recruitment of the original cohort have been reported previously (*5*). The women ranged in age from 43 to 80 yr, with an initial mean age of 63.3 yr. At the initial examination all subjects had single photon absorptiometric bone mineral content (BMC) measurements of the calcaneus, distal radius, and proximal radius, as previously reported (*5*). In addition, a 50% random sample had posteroanterior (PA) and lateral radiographs of the thoraco-lumbar spine. In 1984, the appendicular BMC measurements were repeated, along with PA and lateral radiographs of the thoraco-lumbar spine and lumbar spine BMC measurements by dual photon absorptiometry (DPA). All subjects received spinal radiographs at each examination beginning in 1984. Lateral radiographs of the thoracic and lumbar spine were repeated beginning in late 1986. The duration of follow-up for each individual varied according to the time of the initial BMC measurement or spinal radiograph; the mean duration was 3.6 yr.

The anterior, middle, and posterior heights of each vertebral body were measured on the lateral radiographs with the aid of a digitizing pad and microcomputer. A fracture was considered to be new if any of these heights diminished by 15% or more (*6*); in addition to the >15% height reduction, all fractures were confirmed by radiologist interpretation. Only

the 699 women who had two or more radiographs were included in the analyses.

In preliminary analyses of a subset (N=539), all subjects with pre-existing (prevalence) spine fractures (N=75) were excluded. This did not affect the relationship between BMC and spine fracture incidence. Therefore subjects with pre-existing spine fractures were not excluded from the analyses reported here.

Statistical Methods

Bone mineral content was treated as a continuous variable, adjusted for age by standard logistic regression methods (*7*). All significance values were calculated from the usual regression equations. However, results of logistic regression are often presented as a list of coefficients corresponding to estimated increments in log odds that have very little intuitive meaning. Therefore, we have transformed coefficients by solving the logistic equation for BMC values 1 s.d. below the mean and 1 s.d. above the mean, and taking the ratio to calculate an estimated relative risk (RR) value. Therefore, the estimated RR compares spine fracture risk for those with BMC 1 s.d. below the mean to those with BMC 1 s.d. above the mean value. Covariate-adjusted 95% confidence intervals (CI) were also derived from these logistic models to determine whether any RR was significantly different from 1.0. The utility of combined BMC measurements was evaluated by treating each BMC combination (e.g., calcaneus and distal radius) as a vector for each individual, that was then used in the age-adjusted logistic regression. The independent contributions of each of the two BMC measurement combinations were assessed by including both sites simultaneously in the age-adjusted logistic regression model.

RESULTS

There were new spine fractures in 40 women; nine of these women had pre-existing spinal fractures, as interpreted by a radiologist. None of the 40 new fracture cases were attributable to violent causes, such as auto accidents. The fracture types included 37 cases with wedge and three with crush fractures. One case of wedge fracture secondary to metastatic tumor was excluded.

In Table 1 are shown the age-adjusted spine fracture incidence rates for various BMC levels at each measurement site. At all sites the spine fracture incidence rate increases with diminishing BMC. Women who had initial calcaneus BMC levels 2 s.d.s below the mean have a fracture rate of 55 per 1,000 person-years contrasted with a rate of 1 for women 2 s.d.s above the mean.

In Table 2 are shown the age-adjusted relative risks for BMC values 1 s.d. below the mean versus values 1 s.d. above the mean, for each of the four measurement sites. There is a strong relationship between diminishing BMC and spine fracture incidence at all four sites. Women with calcaneal BMC 1 s.d. below the mean (244.0 mg/cm^2) have approximately seven times greater risk of spine fracture than women with calcaneal BMC 1 s.d. above the mean (377.4 mg/cm^2).

TABLE 1
Spine Fracture Incidence Rates (Fracture Cases per 1,000 Person Years) for Various BMC Levels

	Calcaneus	Distal radius	Proximal radius	Lumbar spine
+2 s.d.	1	2	2	4
+1 s.d.	3	4	4	5
Mean	9	9	10	9
−1 s.d.	23	22	22	18
−2 s.d.	55	49	45	35

Values of mean (s.d.) BMC were 311 (67), 0.699 (0.128), 0.725 (0.109), and 0.926 (0.153) for calcaneus, distal radius, proximal radius, and spine, respectively. These incidence rates are based on an average age of 63.7 yr and the indicated BMC values, using the coefficients from the logistic regression model.

The independent contributions of each of the BMC measurements were assessed by placing all combinations of two BMC sites into the age-adjusted, logistic model. Both calcaneus and distal radius BMC remain significant when any of the other three sites are included in the model (Table 3, column 2). Lumbar spine BMC remains significant only in the case of proximal radius BMC, and the proximal radius is not significant when any of the other three sites are included. The only two-site combination in which both sites provided significant, independent information is calcaneus and distal radius.

The extent to which a second BMC measurement contributes additional fracture risk information was explored in the following way. First, adjustments in the logistic model were performed for both age and the first BMC measurement. Then estimated relative risks for the second measurement were calculated as described above (Table 3, column 4). For example, given a group of women with similar distal radius BMC values, obtaining calcaneal BMC (Table 3, row 4) can further distinguish between individuals who differ in risk by a factor of 2.8 (95% CI = 1.4 to 5.7). Of all the various measurement site combinations, the calcaneus consistently provided the greatest amount of additional information about fracture risk.

In Figure 1 are shown representative plots from the logistic regression model for calcaneus BMC alone, and for calcaneus and distal radius BMC combined. The relative risks reported above can be calculated directly from this graph. For example, the spine fracture incidence rate at calcaneal BMC 1 s.d. below the mean (23.2 per 1,000 person-years) is taken as a ratio to the fracture rate at BMC values 1 s.d. above the mean (3.4 per 1,000 person-years, yielding an estimated RR of 6.9). From Figure 1 it can be seen that a greater RR will result from the two-site vector. It can also be seen that the estimated risk increases as BMC decreases. When a combination of calcaneus and distal radius BMC values are used in the logistic regression model

TABLE 2
Comparison of Age-Adjusted, Estimated Relative Risks for BMC Values 1 s.d. Below the Mean to Values 1 s.d. Above the Mean (Single BMC Site Model)

Site	Bone mineral content			Relative risk	95% C.I.
	Mean	−1 s.d.	+1 s.d.		
Calcaneus	310.7 mg/cm²	244.0	377.4	6.9	4.3, 10.6
Distal radius	0.699 g/cm	0.571	0.827	5.7	3.6, 8.7
Proximal radius	0.725 g/cm	0.616	0.833	4.8	3.0, 7.4
Lumbar spine	0.926 g/cm	0.773	1.079	3.9	2.4, 6.2

(Table 4), a relative risk of 10.6 results, as compared to 6.9 for calcaneus alone. In addition, only calcaneus and distal radius BMC remained significant in the presence of each other, suggesting that each contributes independent information about spine fracture risk.

The actual probabilities of spine fracture during the 3.6-yr duration of this study are shown in Table 5. The mean probability of spine fracture, irrespective of BMC, was 5.6%. However, fracture probabilities varied substantially at different levels of calcaneal BMC. Women with BMC 2 s.d. below the mean had a 19.9% probability, whereas women at +2 s.d. had an 0.4% probability. Women at −2 s.d. for both calcaneus and distal radius had a 25.0% probability of spine fracture, compared to an 0.2% probability for women at +2 s.d. for both sites.

DISCUSSION

There is a compelling clinical need to identify women who will be at risk for fractures in the postmenopausal years. Agents such as estrogen can slow bone loss, but the higher risk woman must be identified before or at the time of menopause, when estrogen can still influence ultimate outcome. The preventive use of other agents designed either to inhibit bone resorption (such as calcitonin), or stimulate bone formation, also requires objective measures of increased fracture risk prior to fracture occurrence. It is generally agreed that prevention of bone loss is more effective than attempting to replace lost bone structure and mass.

TABLE 3
Estimated Relative Risks of a Second BMC Measurement After Adjustment for Both Age and a First BMC Measurement

First measurement		Second measurement		
Site	p-value*	Site	RR	(95% CI)
Calcaneus	0.002	DR	1.9	(1.0, 3.9)
Calcaneus	0.008	PR	1.7	(0.9, 3.5)
Calcaneus	0.04	LS	1.5	(0.9, 3.4)
Distal radius	0.05	CA	2.8	(1.4, 5.7)
Distal radius	0.04	PR	1.4	(0.9, 2.9)
Distal radius	0.03	LS	1.7	(0.9, 3.8)
Proximal radius	0.1	CA	3.3	(1.5, 6.9)
Proximal radius	0.3	DR	1.9	(1.0, 3.6)
Proximal radius	0.2	LS	2.1	(1.0, 4.9)
Lumbar spine	0.3	CA	2.2	(1.0, 4.8)
Lumbar spine	0.2	DR	2.0	(1.0, 5.1)
Lumbar spine	0.05	PR	1.7	(0.9, 3.7)

*Significance level for association of the first BMC measurement with fracture incidence, after adjustment for age and the second measurement.

The method of identifying and selecting the higher risk woman is a source of disagreement. Some investigators have recommended that bone mass be measured at the time of menopause, and those women classified as high risk be given the choice of cyclic estrogen replacement (*1,2*). Riggs and Melton have proposed that bone mass measurements be reserved for those women with several risk factors (*4,8*). In any case, indiscriminate estrogen replacement for all postmenopausal women, irrespective of their actual fracture risk, is difficult to justify. Such an approach overtreats lower risk women who are not destined to fracture. In addition, if estrogens were prescribed only for higher risk women, the net effect upon ultimate fracture incidence might be comparable to that achieved by treating all women; the cost of selective treatment would also be substantially lower (*9,10*). Thus, the ability to identify higher risk women at the time of menopause would have considerable practical value, particularly if it could be done inexpensively.

In this prospective, cohort study, BMC at all four skeletal measurement sites is strongly and significantly related to spine fracture incidence, and this relationship persists after adjustment for age. The relationship of spine fracture incidence to the three appendicular BMC sites is actually equal to, or stronger than, the relationship to lumbar spine BMC. Although this may appear paradoxical, it may be explained by the high prevalence of conditions, such as aortic calcification and osteophyte formation, which artifactually increase spine BMC when measured by integral methods such as DPA (*11–13*). This would result in misclassification of such individuals, whose risk would be underestimated. In previous reports we have analyzed the relative contributions of various artifacts to measured BMC of the lumbar spine, and found that aortic calcification is the

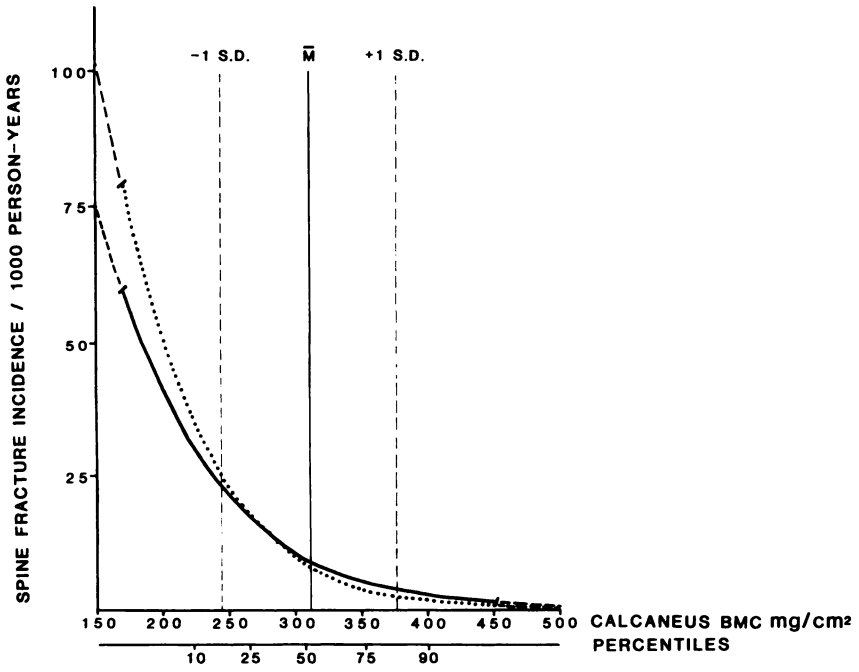

FIGURE 1
The relationship between spine fracture incidence and calcaneus BMC (solid line), and for calcaneus and distal radius BMC combined (dotted line). The best fit for the logistic regression model is shown. Spine fracture incidence increases substantially as BMC decreases; this relationship is approximately exponential. The addition of distal radius BMC to calcaneus BMC further strengthens the relationship.

strongest contributor to artifactually-increased BMC (*12,14*). Attempts to statistically adjust for the presence of aortic calcification increased the relative risk for lumbar spine BMC measurements by only 16%. Therefore exclusion of obvious artifacts such as osteophytes from the BMC calculation may improve the relationship to fracture marginally. However, it is possible that the inclusion of cortical, nonweight bearing bone in the posterior vertebral elements is a more important confounder for lumbar spine BMC.

In a previous report, we have shown that any of the four BMC measurements is a better indicator of spine fracture probability than is osteopenia on vertebral radiographs (*12*). Thus osteoporosis can be defined clinically by levels of fracture risk, using BMC. However, the question as to how much fracture risk should be considered osteoporosis is both complex and somewhat arbitrary, and has been addressed in other manuscripts (*12,15*).

These data also indicate that estimation of fracture risk at a given skeletal site, such as spine, does not necessarily require direct BMC measurement at the potential fracture site. Finally, the predominance of anterior wedging among new spinal fractures suggests that this phenomenon may be a common step in the evolution of vertebral collapse.

The fact that all four skeletal BMC measurements relate significantly to spine fracture incidence underscores the systemic nature of osteoporosis. However, the various BMC sites do differ somewhat in their relationship to spine fracture. These differences may be related to their relative cortical/trabecular composition, or their weight-bearing status. The fact that the two-site model improves the estimation of spine fracture probability may be secondary to the larger volume of measured bone, or alternatively to the sampling of both cortical and trabecular compartments.

Although these data are limited to spine fractures, previous data from this cohort study have also shown a strong relationship between BMC and nonspine fracture incidence (*16,17*). Other investigators have also reported a significant relationship between BMC of the

TABLE 4
Comparison of Age-Adjusted, Estimated Relative Risks for BMC Values 1 s.d. Below the Mean to Values 1 s.d. Above the Mean (Two BMC Site Model)

Sites	Relative risk	95% C.I.
Calcaneus, distal radius	10.6	6.4, 17.5
Calcaneus, proximal radius	9.1	5.6, 14.6
Calcaneus, lumbar spine	5.3	3.2, 8.6
Distal radius, proximal radius	6.3	4.1, 10.0
Distal radius, lumbar spine	5.5	3.3, 8.9
Proximal radius, lumbar spine	4.5	2.8, 7.3

TABLE 5
Percent Probability of Spine Fracture without testing, Following One Test (Calcaneus BMC), and Following Two Tests (Calcaneus and Distal Radius BMC)

	Probability of spine fracture without testing	Probability of spine fracture with one test	Probability of spine fracture with two tests
+2 s.d.	5.6	0.4	0.2
+1 s.d.	5.6	1.2	0.8
Mean	5.6	3.2	2.8
−1 s.d.	5.6	8.4	8.9
−2 s.d.	5.6	19.9	25.0

proximal radius and nonspine fracture incidence (*18*). In a cross-sectional study, Marshall et al. have shown substantial concurrence of wrist, spine, and hip fractures; the association between spine and hip fractures was particularly strong (*19*). In this context, the current data support the concept of osteoporosis as a systemic disease resulting in a generalized deficit of skeletal strength. Those afflicted are thus at increased risk for all fractures. Although the data relating hip fracture to bone mass are largely limited to prevalence rather than incidence fractures, it is generally believed that hip fractures are also related to osteoporosis, albeit at a later mean age than spine fractures (*18*). Comparative spine fracture incidence data for other ethnic groups are not available. However, there are no data to suggest that the relationship of BMC to fracture risk differs between ethnic groups. Patterns of bone loss in this cohort are similar to those observed in Caucasians (*20*).

The relationship between BMC and spine fracture incidence, as described by the logistic model, is strong and approximately exponential. Fracture occurrence rises rapidly for women with calcaneal BMC values below 300 mg/cm^2. Women with calcaneal BMC 1 s.d. below the mean have a sevenfold greater risk of spine fracture than women with BMC 1 s.d. above the mean.

Women at −1 s.d. for calcaneal and distal radial BMC combined have a tenfold greater risk of spine fracture than women at +1 s.d. Either calcaneal or distal radius BMC contributes significant, additional information about spine fracture risk, even if BMC at one of the other three sites is already known.

In order to illustrate the potential, clinical utility of such data, the probabilities of spine fracture for this cohort, in relation to BMC levels, can be calculated. For the total cohort, the mean probability of spine fracture is 5.6% during the mean follow-up of 3.6 yr. Thus if BMC is unknown, all women have the same, apparent risk, i.e., 5.6% (Table 5), since the combination of height, weight, and other risk factors did not relate significantly to spine fracture incidence (*21*). However, if calcaneal BMC is known, women with BMC 2 s.d.s below the mean have a 19.9% probability of spine fracture, compared to 0.4% for those 2 s.d. above the mean. This corresponds to a relative risk of nearly 50. If distal radius BMC is also known, then those women at −2 s.d. have a 25.0% probability, versus 0.2% for those at +2 s.d., that corresponds to a relative risk of 125. It should be emphasized that these relative fracture probabilities are based upon absolute BMC levels, and not upon comparisons to so-called, "normative" data. Thus knowledge of BMC alone substantially changes the future fracture probability of women, and this should influence the decision to use estrogen replacement or other treatment modalities.

In summary, both appendicular and spinal BMC are strongly related to spine fracture incidence, independent of age. Appendicular BMC measurements of the calcaneus, distal radius, and proximal radius can be used for the prospective assessment of spine fracture risk, and the selection of postmenopausal women for estrogen replacement can be appropriately influenced by these relatively inexpensive measurements. Cost and benefit considerations are complex, and have been addressed in a separate manuscript (*10*). Finally, the combination of two BMC measurements, (i.e., calcaneus and distal radius) may further improve the risk stratifications by BMC. Whether such combined measurements would be cost-effective remains to be determined.

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