Bone Densitometry for Diagnosis and Monitoring Osteoporosis (42918)

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There has been a dramatic increase of public and medical attention paid to osteoporosis over the past several years (1–5). Osteoporosis is a disease characterized by excessive bone loss, or osteopenia, particularly in the axial skeleton at sites of fracture like the spine and proximal femur. Since strength of both the spine and femur (6–8) is directly proportional to bone mass regardless of age (r about 0.9), this osteopenia always increases the risk of fracture. A clear gradient of increased fracture risk with decreasing density has been demonstrated in both retrospective and prospective studies (9–14). Fractures occur in only half of osteopenic women as a group, but those osteopenic women with the lowest axial density have a 50–100% lifetime risk of osteoporotic fracture. This compares with about a 20–30% risk for all postmenopausal women and less than a 5% risk for women whose bone density remains at the premenopausal level. The lifetime risk for hip fracture at the menopause is about half that for all osteoporotic fractures (11). Normal women lose about 20–25% of their bone following the menopause, which does increase risk, but the osteopenia that produce osteoporotic fractures involves an even greater diminution of bone to levels 25–50% below the average for young normal women (15–17).

As a consequence of the close association of fracture risk and bone mineral density (BMD), there has been a growing use of bone densitometry in both biomedical research and clinical practice (3, 18, 19). Also, there still are no suitable biochemical indices that accurately reflect ongoing bone loss or that indicate bone increases with therapy (20). Existing tests, such as osteocalcin, urinary calcium, or alkaline phosphatase only reflect the transient state of bone turnover (20, 21). Consequently, clinicians must use densitometry for monitoring bone loss in those at high risk for osteopenia, as well as bone increases in those receiving therapy influencing the skeleton. The use of densitometry for mass screening of asymptomatic subjects, however, has not yet been conclusively demonstrated to be valuable (19, 22).

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Measurement Methods

A variety of methods are available today for bone assessment (18, 23–25). These include single photon absorptiometry (SPA), dual photon absorptiometry (DPA), dual energy x-ray absorptiometry (DEXA), and quantitative computed tomography (QCT). One major functional difference among methods, apart from factors such as cost, availability, and radiation dose, is the anatomical location measured, including the amount of bone actually incorporated in the measurement (Table I). Prior to axial densitometry, appendicular bone had to be measured; it was assumed that small appendicular regions represented large areas of the skeleton. Appendicular QCT was assumed to represent all trabecular bone, a compartment 2500 times greater than that measured; however, the correlation is only moderate ($r = 0.7$). Appendicular SPA on compact bone often is assumed to represent all compact bone, a compartment 2000 times greater. This assumption is more reasonable than the first because the correlation is higher ($r > 0.9$). Other methods also involve assumptions that are rarely questioned. Spinal QCT measures only a small proportion (1%) of spinal trabecular bone. Studies have shown that the small region measured by QCT does not accurately represent other areas of the spine (r about 0.8 and SEE about 10–15%). Finally, DPA/DEXA measurements of the lumbar spine, or of the femur, are assumed to represent compartments about twice the size of those actually measured (thoracic spine and contralateral femur); the correlation is good ($r > 0.9$). For total body measurement, extrapolation is not necessary.

It should be noted that even greater assumptions are sometimes made about the representivity of histomorphometry of iliac crest biopsies. The small region sampled on one ilium is not even representative of adjacent areas, let along "remote" areas such as the spine or hip (26). There is a modest correlation ($r \sim 0.7$) between TBV from iliac crest biopsy and bone density of the spine (27). However, the latter can be measured with 1–5% precision, whereas the former has

Table I. Noninvasive Methods Measure a Fixed BMC But Often Are Extrapolated to Represent a Larger Anatomical Zone

Method	Measured BMC (g)	Extrapolation		
		Zone	BMC (g)	Factor
Appendicular QCT	0.2	Trabecular	500	2500
Appendicular SPA	1.0	Compact	2000	2000
Spinal QCT	0.5	Spine Trabecular	50	100
Femur DPA/DEXA	3.0	Both femurs	6	2
Spine lumbar DPA/DEXA	35.0	Total spine	105	3
Total body DPA/DEXA	2500.0	Total skeleton	2500	1

a 15–25% precision error (28). Delmas *et al.* (27) showed that TBV is no more sensitive than peripheral densitometry in diagnosis of spinal osteoporosis (Z-score compared to with age-matched controls was 1.1 vs 1.9 for spinal DPA).

There are some differences in both diagnostic sensitivity and monitoring specificity among methods of peripheral densitometry as well as among methods of axial densitometry, but there are definite advantages of axial vs peripheral densitometry for both diagnosis and monitoring. Even the least reliable axial measurement is superior to the best appendicular measurement. The commonest methods are described below.

SPA. Single photon absorptiometry is a method for peripheral densitometry that utilizes a radionuclide source, such as ^{125}I (28 keV) or ^{241}Am (60 keV), emitting at a single energy (18, 24). The source is coupled to a radiation detector, usually a sodium iodide crystal mounted on a photomultiplier tube, or more recently to solid state detectors. The narrow beam (1–3 mm) of radiation is passed across an area. Measurements usually are made on the shaft of a long bone; the distal third (not "midshaft") of the radius shaft is the standard site because its anatomical uniformity allows routine precision of about 2%. The radiation dose is a few mrem. The major recent advance in SPA has been use of rectilinear scanners that allow measurements over an area several centimeters long. This permits scans on anatomically variable regions, such as the distal radius (15, 29, 30) or the os calcis (31), that have more trabecular bone. Linear scanners cannot be used in these regions because large changes of results occur with small changes in location. Even though precision at these sites is comparable to that on the radius shaft in research laboratories, the clinical precision is 3–4%. Moreover, the distal radius and os calcis are of much less diagnostic sensitivity for spine or hip fractures (15, 30, 33) and monitoring specificity than the radius shaft itself (16, 17, 33) because peripheral trabecular bone like compact bone is not as responsive both to aging decreases and to therapeutic intervention as is axial bone (21, 34–36). Hence, the radius shaft provides identical changes that are easier to ascertain. The radius shaft also is particularly useful in relation to hyperparathyroidism where compact bone is strongly affected (36). On the other hand, the distal radius is sensitive for Colles' fracture (12, 15 37) and the os calcis is closely related to ankle and tibia fractures (13, 14).

DPA. Dual photon absorptiometry is a widely used modality for spine and femur densitometry (18, 24, 38). Over 1000 hospitals and clinics use DPA for management of metabolic bone disease. A rectilinear scanner is typically employed in which the radioisotope source (^{153}Gd with emissions at 44 and 100 keV) is coupled to a scintillation detector. Scans of the total body, spine, and femur have had a precision error of 1, 2, and 3%, respectively, in a number of laboratories (39–44). Careful attention to detail in the best laboratories has reduced the precision error of spine (see Table II) and femur scans to about 1.5% and total body precision to <1% (39–42). The total body scan takes 60–70 min, while spine and femur scans take under 20 min with standard scanners. Second-generation DPA scanners, with multiple detectors, do regional scans in as little as 10–15 min with lower activity sources. The basic DPA method has an accuracy error of <3% (7, 44, 45) and a radiation dose of about 1 to 5 mrem. In the past, a higher dose (10 mrem) was quoted for DPA because older ^{153}Gd sources had high-energy contaminants (europium) that could not be shielded.

The limited output flux from the typical 1-Ci source of ^{153}Gd demands relatively large pixels (usually 2 × 3 mm) so that scans can be done in a reasonable time. Also, the size of the source and beam (3 mm) limits inherent spatial resolution to about 3–4 mm. This is not usually a problem in femur scans or even in spine measurements of nonosteoporotic subjects. Crush fractures within the lumbar spinal region increase the apparent density by only 3% on the average, which is not a problem for diagnostic applications (46). However, in the elderly a variety of artifacts in the spine area (osteophytes, endplate hypertrophy, disc degeneration, calcified aorta, and fractures) not only cause quantitative problems but obscure the image so that a precise region of interest (ROI) cannot be identified. This has led some physicians to focus on measurement

Table II. The Precision Error of Dual Photon Absorptiometry, Dual Energy X-Ray Absorptiometry, and QCT for Spine BMD *In Vivo*

Authors	Precision (%)
DPA	
Isaia *et al.*, 1988 (47)	1.1
Shipp *et al.*, 1988 (48)	1.3
Baran *et al.*, 1988 (49)	1.4
Slemenda and Johnston, 1988 (43)	1.4
Tummon *et al.*, 1988 (50)	1.5
Al-Azzawi *et al.*, 1987 (51)	1.7
Dalsky *et al.*, 1988 (52)	1.8
LeBlanc *et al.*, 1986 (53)	1.9
Braillon *et al.*, 1987 (54)	2.1
Schaadt and Bohr, 1982 (44)	2.1
Krolner, 1985 (55)	2.1
Liel *et al.*, 1988 (56)	2.2
Pouilles *et al.*, 1988 (46)	2.2
Pocock *et al.*, 1986 (57)	2.6
Crilly *et al.*, 1988 (58)	2.8
Nilas *et al.*, 1988 (59)	3.7
DEXA	
Mazess *et al.*, 1989 (62)	0.9
Kelly *et al.*, 1988 (60)	1.0
Pacifici *et al.*, 1988 (61)	1.0
Wahner *et al.*, 1988 (63)	1.3
QCT[a]	
Genant *et al.*, 1987 (25)	2.2
Banks and Stevenson, 1986 (72)	2.2
Firooznia *et al.*, 1984 (70)	2.5
Cann and Genant, 1980 (67)	2.8
Harma *et al.*, 1985 (108)	2.8
Rosenthal *et al.*, 1985 (69)	5.0

[a] For normals in research laboratories; precision in clinical practice is 2 times greater.

of the proximal femur rather than the spine in patients over age 65. At that age, femoral fracture is of greater clinical interest than crush fracture, suggesting a higher priority for femoral densitometry. Recent studies have shown that femoral neck BMD is a sensitive indication not only of the risk of hip fracture but of spine fracture (33). In contrast, spine BMD is not specifically diagnostic for hip fracture even though spine BMD (from DPA but not QCT) is reduced somewhat in hip fracture cases (16).

DEXA. Problems of spine imaging can be overcome with the new method of dual energy x-ray absorptiometry. The higher radiation flux achievable using x-ray sources provides several advantages over conventional DPA (38), including improved spatial resolution (1–2 mm vs 4 mm), improved precision (1 vs 2%), and greatly decreased scan times (10 min for total body and around 5 min for spine or femur). One commercial system even provides 1-min regional scans with only slightly compromised images. There is a high degree of correlation between scans obtained with DEXA systems and those using ^{153}Gd-DPA (60–64). The typical precision error for spine scans *in vitro* is about 0.5% while the precision *in vivo* is about 1% (Table II).

There are two approaches to DEXA. One approach uses a constant voltage x-ray tube with a K-edge filter to produce a dual energy beam (62). One system (Lunar DPX) with a cerium filter has effective energies of 40 and 70 keV, while another system (Norland XR26) will use a samarium filter to give slightly higher energies. Alternatively, the x-ray energy can be rapidly switched between high and low kVp settings, but the results vary widely with changes of energy. One system (Hologic QDR) compensates for the wide fluctuations in results on a pixel-by-pixel basis by using a rotating wheel containing known materials (38). There appears to be no particular advantages of the inherently stable K-edge approach vs the second approach other than the lower dose achievable for any given precision (1 vs 3 mrem) with the former method (65). It is likely that DEXA systems will replace DPA in larger hospitals with a high caseload; simpler DPA scanners may continue to be used in specialty clinics that do not demand high throughput (>5 patients/day).

QCT. An alternative method for spinal densitometry, QCT was pioneered by researchers at UCSF (25, 66, 68). A conventional x-ray tomographic scanner is used to obtain cross-sectional images of the lumbar spine. The x-ray output and energy of such scanners are highly variable, even over the short term, so calibration standards must be measured together with the patient or immediately before and/or after a patient scan. Even with such calibration, however, density results may vary over time. The typical precision error in careful research laboratories is 5 mg/cm^3 (69), which is 3% in young normal subjects, but about 7–15% in an osteoporotic patient. The results also vary (±7%) among different scanners (68) so that repeat measurements must be made on the same scanner; sometimes extensive recalibration is needed even with changes of x-ray tube on the same scanner (70, 71). Again in research laboratories, where these factors can be rigorously controlled, better results are obtainable (25, 68).

Two approaches to QCT measurement are used. Researchers often obtain at least several contiguous transverse slices from each vertebra in order to reconstruct a larger volume of interest with each of several vertebral bodies (72, 73). This procedure gives better precision (1–3% vs 5%) than the typical clinical approach in which only a small ROI (3 cm^3 or <5% of vertebral mass) is analyzed from a single slice of each of 2–4 lumbar vertebrae. The latter approach (25) is very dependent on (i) congruence of the lateral scout view and the tomographic slice; (ii) angulation of each vertebra; and (iii) selection of the region within the vertebra. A small change of 1 mm in any direction can cause relatively large changes (74). New software programs for automatic localization can minimize the very large variation associated with these factors (75, 76).

The small ROI in the anterior body of the vertebra is not representative of the entire vertebral body (77, 78), and, as noted earlier, it represents only a small part (1%) of trabecular bone throughout the spine. The usual small ROI is not a good indicator of strength (78–81), which may make it a less sensitive indicator of fracture risk than larger regions. On the other hand, this region may be the area that changes first with disease (oophorectomy, immobilization) or with treatment, i.e., a harbinger of changes that subsequently influence the entire vertebral body albeit to a lesser extent (35, 82).

Typically, computed tomography for imaging is done at a high kilovoltage (120–130 kVp) and exposure. Radiologists and technicians use these same factors for QCT even though a lower voltage (80 kVp) and exposure are recommended for this quantitative, nonimaging method (68). As a consequence, the usual radiation dose is relatively high; at 6 mrem/mas the typical dose would be about 1000 mrem. It is possible to reduce this 5-fold (66, 69). A high kilovoltage also is undesirable because it increases the large accuracy errors (at least 15–25%) associated with variable marrow fat and varying osteoid (83–98). Gluer *et al.* (99) showed an error of ash density of 8 mg/cm^3 for every 100 mg/cm^3 change of marrow fat, but the error at higher energies is 10–13 mg/cm^3, i.e., 30–50% greater (85, 92, 99–101). The usual bias of QCT results due to fat is shown in Figure 1. This systematic error, which is due to the varying organic constituents of trabecular bone, may be responsible for (i) the systematic overestimation of aging decreases (92); (ii) overestimation of the effects of estrogen withdrawal (102); and (iii) overestimation of drug effects. With regard to the first point the QCT density decrease in women at the menopause (5–10%/year) is about double the actual decrease. Regarding the second point, there appears to be a large effect of estrogen on marrow composition (102). Finally, fluoride increases both osteoid and red marrow; since QCT is subject to erroneous overestimation due to these factors (88, 98), QCT cannot accurately indicate true bone increases due to fluoride therapy. Dual energy methods for QCT have been proposed (85, 87, 91, 95, 103, 104), but they only partially correct the problem due to variable marrow and osteoid. Dual energy QCT does not increase the diagnostic sensitivity of the method (99, 105), but it doubles the radiation dose and increases the precision error. Consequently, experts (25, 99) view dual energy QCT as useful chiefly for research studies.

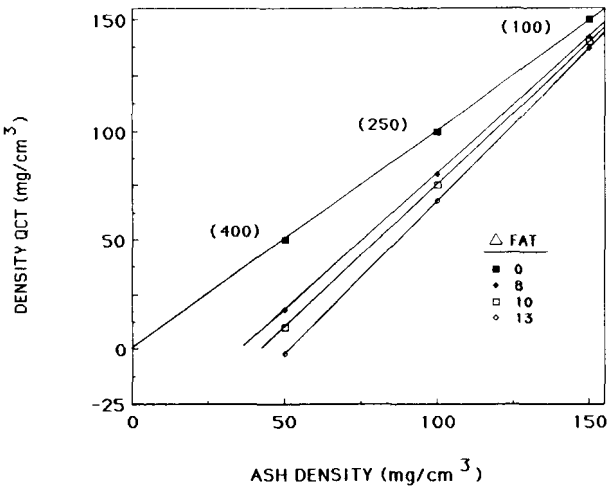

Figure 1. *Actual ash density is plotted vs QCT density for three levels of "fat error" (change in observed QCT density for each 100 mg/cm^3 increase in fat). The typical amount of fat in trabecular bone is given by the quantities in parentheses at ash densities of 50, 100, and 150 mg/cm^3. At 150 mg/cm^3 of ash, there is only a 8–10 mg/cm^3 bias due to fat, while at the 50 mg/cm^3 level seen in osteoporosis there is a negative bias of 30–50 mg/cm^3. The larger bias (13 mg/cm^3 per 100 mg/cm^3 of fat) is encountered only at higher kVp settings (>120 kVp).*

QCT has been used experimentally for examination of the proximal femur (106, 107), since spinal QCT is of no value in relation to hip fracture (108, 109).

Fracture Risk and Density

The risk of fracture increases with age because bone density at most sites decreases with age in nonobese women (110–115). Table III shows the decrease of BMC and BMD with age in normal women; the area of the lumbar spine and the femoral neck does not change with age. In those who maintain density, for example, overweight women or men, fracture risk is markedly reduced. Black women who have a density 8% above their white peers (56) have about half the overall fracture incidence, whereas older males, who have a spine density substantially above age-matched females, have at least five times lower fracture rates at that site. The sex difference of aging bone loss in femur density is much less marked than in the radius or the spine (Fig. 2). Consequently, femoral fracture is 2–3 times less

Table III. Bone Results Using DPA of the Spine (L2–L4) and Femur (1.5-cm slice across neck) in Normal Subjects with No Fractures (Adapted from Mazess *et al.* (114))

Age	*n*	Area (cm^2)	BMC (g)	BMD (g/cm^2)
Femur neck				
20–29	34	4.72 (0.42)[a]	4.73 (0.57)	1.00 (0.11)
30–39	67	4.73 (0.69)	4.66 (0.71)	0.97 (0.12)
40–49	13	4.69 (0.49)	4.06 (0.76)	0.86 (0.13)
50–59	39	4.62 (0.60)	3.71 (0.69)	0.80 (0.12)
60–69	101	4.56 (0.44)	3.44 (0.58)	0.75 (0.11)
70–79	137	4.75 (0.45)	3.43 (0.58)	0.72 (0.10)
L2–L4 spine				
20–29	164	42.29 (4.49)	52.53 (8.73)	1.239 (0.13)
30–39	248	41.63 (4.03)	52.50 (8.40)	1.259 (0.13)
40–49	58	40.08 (4.77)	48.47 (8.48)	1.208 (0.12)
50–59	76	40.48 (5.17)	44.41 (9.34)	1.091 (0.14)
60–69	70	40.03 (4.19)	40.15 (7.07)	1.002 (0.13)
70–79	15	39.57 (5.35)	37.16 (7.41)	0.939 (0.16)

[a] Mean (±SD).

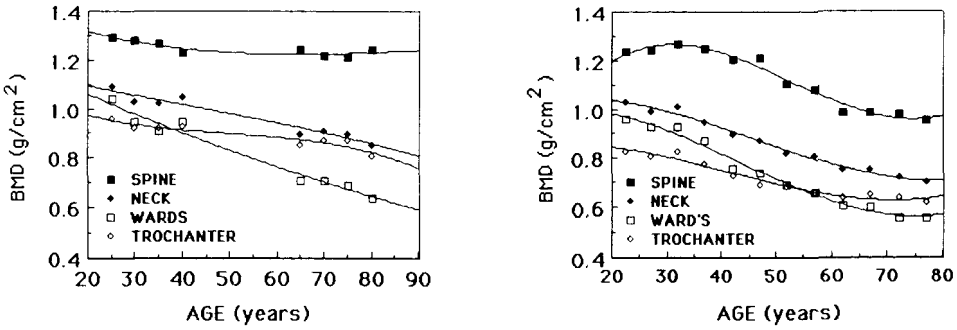

Figure 2. Aging bone changes in the lumbar spine and proximal femur (neck, Wards triangle and trochanter) using DPA in normal men and women.

common in men than women rather than 10 times less common as with spine and Colles' fractures. These rough correlations of density and fracture among population segments are indicative of a causal relationship. More detailed studies, within homogeneous populations (between 50 and 80 years) have demonstrated a close association between bone density and fracture rate. The influence of an increased frequency of falls, or decreased mechanical strength, apart from osteopenia, while significant, is probably not of great magnitude. No significant *incremental* influence of such factors has ever been demonstrated in a population nor have epidemiologists shown that the attributable risk of such factors is above 10%. It should be recognized that an increased frequency of falls, poorer muscular protection in falls, and diminished structural integrity of bone may covary with bone density (116).

Investigators at Mayo Clinic have demonstrated that bone mineral density measured by DPA at fracture sites is closely associated with fracture risk (10, 11, 15). Each 10% decrease of spine or femur BMD increased the relative risk of fracture about 2-fold. Prospective studies using densitometry on the peripheral skeleton have demonstrated a similar but slightly lower increase of risk vs degree of osteopenia (9, 14). Each 10% decrease of appendicular density increases fracture risk about 1.3 times rather than 2-fold. The predictive accuracy of peripheral densitometry is comparable to that of cholesterol for coronary heart disease. The predictive accuracy of measurement at axial fracture sites would be better given the extent to which diagnostic sensitivity at axial sites is superior to that at peripheral sites.

Numerous studies have shown that the diagnostic sensitivity of peripheral densitometry is about half that of axial densitometry in the immediate postmenopausal years (30, 33, 57, 108, 117–121). We have recently examined this question in 1600 female patients referred for densitometric examination (122). These patients were intermediate to normals and osteoporotic women in their bone density values. In those decades between 30 and 60 years, there were about 2–3 times more osteopenic (>20% loss) cases for the spine than for the radius (Table IV). By age 70, however, appendicular loss caught up to the earlier axial loss and the degree of osteopenia and proportions of significantly osteopenic cases were similar for both sites.

Table IV. Spine Misclassification Based on Radius (Adapted from Mazess *et al.* (122))

Age group	*n*	% young normal		% with spine deviant		
		Radius	Spine	10–19%	>20%	>10%
30–39	39	91	85	23	13	36
40–49	137	92	84	31	13	34
50–59	320	83	78	28	11	39
60–69	587	75	72	22	9	31
70–79	461	69	69	16	5	21
80–89	61	63	65	13	3	16

Table IV shows that the average spine BMD in patients prior to the menopause was 16% below that of young normal women, while the radius BMD was only 8% low. Significant misclassification of patients could occur if the radius was used for diagnostic purposes in women prior to age 65 or 70. The spine BMD was more than 20% more osteopenic than the radius in over 10% of such women and the spine was more than 10% more osteopenic in 30–40% of patients. This difference of 10% is clinically significant because it reflects a doubling of fracture risk, i.e., 30–40% of patients have twice the risk of fracture that would be inferred from appendicular density alone.

We have examined a large population of normal white women (114) to determine normal age changes in spine and femoral density. This population had significantly higher BMD values (+20%) than patients with vertebral or proximal femur fracture (16). The diagnostic sensitivity of femoral measurements for hip fracture was excellent. Femoral neck BMD accounted for 81% of the area under the receiver operating characteristic curve (33) compared with the typical finding of 70% for lumbar spine BMD in relation to spinal osteoporosis. The lumbar spine is not sensitive for hip fracture, and may be no more sensitive than the femur for spine fracture because most spine fractures occur in

the thoracic region. Age, body weight, and radius BMD are about equally insensitive (ROC area <60%).

The distribution of BMD values in about 600 older (age 50–89 years) women, including fracture cases, and the percentage with fractures, are given in Table V. About 25% of the population had spine or hip fractures (18% spine, 10% hip). Half of the women with hip fractures had spine fractures as well. Most fractures (85%) occur below the mean value for normal older women (under 1.0 g/cm^2 for the spine or 0.75 g/cm^2 for the femoral neck). The fracture risk for each site increases as BMD at that site decreases. The relationship is not completely site specific; the spine affords some indication for femoral fracture and the femur provides a fairly good indication of spine fracture risk. Most hip fractures (62%) occur in 20% of women with femoral neck BMD under 0.6 g/cm^2 and 90% occur in the lowest 47% of the entire population (normal + fracture) with BMD <0.7 g/cm^2. Most spinal fractures (58%) manifest in the 35% with spine BMD under 0.90 g/cm^2. In examining the prevalence of both types of fracture in relation to density, it is obvious that there is relatively little fracture risk at spine BMD >1.00 or femoral neck BMD >0.8. These are the "thresholds" of fracture risk that lie about 2 SD below the mean values in young normal women (17). Definite osteoporosis with marked fracture risk is manifest by the increase of fracture prevalence at spinal BMD <0.9 (overall prevalence 36%) and femoral neck BMD <0.7 (overall prevalence 41%). The fracture prevalence above these density breakpoints is several times lower (2–4 times) than the prevalence below the breakpoints (17). Severe osteoporosis occurs for a spinal BMD below 0.8 g/cm^2.

Table V. Distribution of Spine and Femur BMD (g/cm^2) in Women 50–89 Years with the Observed Prevalence of Spine and Proximal Femur Fracture[a]

	Total		Spine fracture		Hip fracture		Either fracture		Lifetime risk
	n	%	*n*	%	*n*	%	*n*	%	
Spine BMD									
>1.10	100	17	6	6	3	3	7	7	0%
1.00–1.09	111	19	11	10	6	5	15	14	6%
0.90–0.99	159	28	27	17	10	6	35	22	25%
0.80–0.89	134	23	31	23	13	10	40	30	35%
0.70–0.79	49	9	20	41	6	12	22	45	65%
0.60–0.69	20	3	10	50	3	15	12	60	95%
Total	573		105		41		131		
Femur BMD									
>0.80	133	22	5	4	0	0	5	4	0%
0.70–0.79	178	30	19	11	6	4	23	13	5%
0.60–0.69	164	28	35	21	17	10	51	31	10%
0.50–0.59	89	15	29	33	26	29	46	52	20%
0.40–0.49	26	4	10	39	12	46	20	77	40%
Total	590		98		61		145		

[a] The estimated lifetime risk of spine and femur fracture for a woman at the menopause at each BMD level is also given.

At these density levels, fracture is more common than normality; the risk of fracture is above 50%.

These prevalence data give the relative risk of fracture and do not provide the lifetime risk that clinicians often desire. The cumulative incidence of fractures indicates a lifetime risk for femoral fracture of about 15% for a women at the menopause (1, 11). The lifetime risk for spinal osteoporosis is about twice this. Given these facts, plus (i) the increase of relative risk with each 10% decrease in BMD and (ii) the distribution of BMD, one can approximate the lifetime risk of fracture in relation to BMD. Table V shows that there is almost no risk at normal densities but that there is an exponential increase of risk as density decreases. The lifetime risk of spinal fracture is approximately equal to the centile score of crush fracture osteoporotics for a given spine BMD over a limited range. Similarly, the lifetime risk of hip fracture is approximately half the centile score for a given femoral neck BMD. It should be noted that the lifetime risk apparently decreases with age at any given density because the life expectancy decreases (11).

Monitoring Bone Changes

Monitoring the course of disease or therapy is a major clinical application of bone densitometry. There is a broad consensus among clinical leaders that bone disease, including osteoporosis, should not be treated without monitoring using both densitometry and clinical chemistries (1–3). The ability to monitor depends critically on both the magnitude of change occurring at a skeletal site and the precision error of the densitometric method used at that site. There are obvious advantages, in terms of signal to noise ratio, in choosing both a responsive skeletal area and a method with a low precision error. Figure 3 shows the bone decrease of untreated women during the first 5 years after the menopause for various sites. Also shown is the average response to estrogen therapy over the first two years in postmenopausal women. Typically there is a 5–10% increase of spinal density during the first few years of treatment with estrogen (123–126), exercise (52), or fluoride (127–129). Other agents/treatments also can

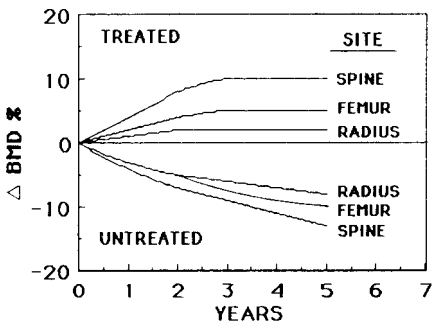

Figure 3. Typical bone changes in the lumbar spine (DPA), proximal femur (DPA), and radius (SPA) following the menopause in untreated and treated (estrogen, calcitonin, or fluoride) women.

Table VI. Differences between Treated (Estrogen or Fluoride) Women and Untreated Women after 1 Year Relative to the Precision Error of Each Method

Site	Method	Untreated (%)	Treated (%)	Difference	Error (%)	Difference ÷ error	Sign
Radius	SPA	−2	0	2	2	1.0	NS
Spine	QCT	−5	+2	7	5	1.4	NS
Radius	QCT	−1	0	1	0.5	2.0	$P < 0.10$
Spine	DPA	−2	+4	6	2	3.0	$P < 0.05$
Total	DPA/DEXA	−2	+1	3	1	3.0	$P < 0.05$
Spine	DEXA	−2	+4	6	1	6.0	$P < 0.01$

increase spinal density. Younger hypogonadal women who are made eumenorheic show large, rapid increases in spinal density, up to 1%/month (130–134). Rapid bone increases also are observed in the spine after correction of corticosteroid excess (135, 136).

The difference between treated and untreated patients after 1 year is shown in Table VI relative to the precision error of each method. SPA of the peripheral skeleton and spinal QCT are similar in that the precision error of the method is on the order of the changes. Peripheral QCT done with radionuclide sources is no better than the simpler SPA approach, but the better precision obtained with x-ray QCT of the peripheral skeleton (0.5%) affords some benefit. DPA of the spine or of the total body have about twice the specificity of conventional spinal QCT or of peripheral SPA for measuring changes. If the lower precision error (2% vs 5%) obtained in research laboratories with dedicated CT scanners can be obtained in clinical practice, then spinal QCT can give results comparable to DPA. The best results are obtained with DEXA which gives a smaller precision error than DPA yet retains the advantages of that approach.

It should be noted that conventional spine DPA with a precision of 2% provides a significant ($P < 0.05$ for Type I error) treatment difference compared with untreated cases on the average. About 50% of patients treated with estrogen or fluoride will show at least the 4% spinal increase in 1 year that is the critical level for $P < 0.05$. It is doubtful, however, if such a rigorous criterion for clinical effectiveness (rejection of the null hypothesis with 95% confidence) is required for interim assessments of accepted drugs like estrogen. A criterion of 50% confidence would be comparable to that used for other clinical tests. About 85% of treated cases would exceed the +2% increase (4% difference from untreated) that is the critical level for $P < 0.5$. This should not be misconstrued, as some have done (22), to indicate that lesser increases are "insignificant." For a change in treated patients to be demonstrably without significance (i.e., Type II error testing), there would have to be a bone loss of about −2% (i.e., $P < 0.05$ for the alternative hypothesis). With less specific methods, more measurements or longer time periods of observation would be necessary. The new DEXA method, with 1% precision, allows clinical efficacy to be judged with high confidence within 6–12 months.

Table VII. Indications for Bone Densitometry (Adapted from the Southern California Bone Club)

- Premenopausal women with high risks including
  - Surgical menopause
  - Amenorrhea
  - Anorexia nervosa
  - Hyperprolactinemia; neuroleptic drugs
  - GnRH and LHRH agonists
- Postmenopausal women with two or more major risk factors including
  - Positive family history
  - Stature <160 cm, weight <50 kg;
  - Loss of >3 cm height;
  - Hypercalciuria, elevated GLA protein
  - Previous fracture in adult years with minimal trauma
  - Evidence of osteopenia on plain radiograph
  - Age over 65 years
- Males with major risk factors including
  - Hypogonadism
  - Osteoporosis on radiograph
  - Fracture with minor trauma
- Prolonged immobilization
- Calcium deficiency for more than 10 years and
  - Hypercalciuria (24-hr, 4 mg/kg/day), kidney stones
  - gastrointestinal diseases
- Rheumatoid arthritis over a 5-year duration
- Chronic corticosteroid excess, or methotrexate treatment
- Anticonvulsant therapy over a 5-year period.
- Kidney disease with a creatinine clearance of <50 ml/min, or renal tubular disorders.
- Osteomalacia, indicated by low serum calcium, and phosphorus
- Hyperparathyroidism (including mild cases to assess the need for therapy)
- Prolonged use of thyroid replacement (over 10 years)
- Monitoring of treatment programs for osteoporosis

Conclusions

Bone densitometry is used in over 1000 institutions in the United States to aid in diagnosis of bone disease and to monitor bone changes with disease and therapy. The leading method (DPA) has a low radiation dose (1 mrem) and modest cost ($125/scan) compared with the QCT alternative (1000 mrem and $250). These methods are generally considered to be essential to basic clinical management (3, 19). Insurers have used the

controversy about "screening" in a normal population without symptoms to avoid payment for medically indicated densitometry in patients with symptoms. The Southern California Bone Club has provided a guideline for medical use (Table VII). Responsible application of any densitometric method can enhance clinical control; this is particularly the case for the new x-ray absorptiometry approach that allows rapid and precise assessments hitherto impossible.

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