Bone Scintigraphy: Part 3. Bone Scanning in Metabolic Bone Disease

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J Nucl Med 1993; 34:2247–2252

Whereas radionuclide bone scan appearances in various metabolic bone disorders have been extensively studied and reported upon, it is not widely performed in the routine evaluation of patients with classic metabolic bone diseases such as renal osteodystrophy and osteomalacia. However, the bone scan is well established in Paget's disease and there is increasing interest in osteoporosis, reflecting the fact that this is an extremely common disease with high morbidity. In recent years, there have been significant advances with regard to the treatment of Paget's disease and the investigation and treatment of osteoporosis. It seems opportune to review the role of radionuclide bone scanning in metabolic bone disease. Advances in bone density measurements and how they relate to osteoporosis will also be examined.

RENAL OSTEODYSTROPHY, OSTEOMALACIA AND PRIMARY HYPERPARATHYROIDISM

Metabolic bone disorders are characterized by increased tracer uptake throughout the skeleton and, in more severe cases, appearances are those of a "super scan" (*1,2*). In addition, several individual metabolic features such as faint or absent kidney images, prominent calvaria and mandible, beading of the costochondral junctions and a "tie sternum" sign may be present (*3*). In general, renal osteodystrophy leads to the most striking appearances with early primary hyperparathyroidism at the other extreme where scan findings are often normal (*4,5*). However, this will depend upon the severity of disease in individual cases. Some patients with primary hyperparathyroidism can have grossly abnormal scans, whereas mild renal osteodystrophy can appear normal. These conditions have in common excessive parathyroid hormone and the degree of abnormality of the bone scan is directly related to its severity and the duration of the disease. The problem with diffuse involvement of the skeleton is that recognition of increased uptake of tracer is subjective, unlike recognition of focal disease when metastases are present. This seems an ideal situation for quantitation which has been shown to be helpful (*6*), but in practice is seldom performed except in research protocols. Focal disease may be present in the metabolic disorders but is relatively uncommon and may arise with pseudofractures (*7*), brown tumors (*8*), ectopic calcification (*9*) and chondrocalcinosis (*10*). It should be recognized that there is no routine role for the bone scan in the diagnosis of these conditions (perhaps with the exception of renal osteodystrophy) and it is most helpful when answering specific questions such as in a case of osteomalacia, are pseudofractures the explanation for localized pain?

PAGET'S DISEASE

In many countries, Paget's disease is a common disorder that is generally polyostotic but may be monostotic in 20% of cases (*11*). However, there are wide geographical variations in incidence and even within a single country (*12*). While often grouped with the metabolic bone diseases, the cause is unknown, although currently thought to be due to a viral infection (*13,14*). It is of interest that there is no correlation between an individual's age and the extent of disease, suggesting that disease does not progress from bone to bone during an individual's lifetime (*15*), but progresses in involved bones which could be explained by prior invasion of these bones by a virus with a long incubation period. There are occasional reports of disease occurring in previously unaffected bones, although this situation seems to be rare. From radiological evidence, bone resorption progresses at a rate of 0.8 cm per year in an affected bone (*16*).

The bone scan appearances in Paget's disease are well known and there are several reviews on the subject (*17,18*). The exquisite sensitivity of the bone scan and the clear visualization of the whole skeleton make this the imaging modality of choice. However, x-rays are necessary whenever there is unexplained bone pain or other suspicion of fracture or sarcomatous change. Focal lesions may not always be apparent against a background of intense tracer uptake. With the newer bisphosphonates,

Received Jun. 22, 1993; revision accepted Jul. 18, 1993.
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FIGURE 1. Paget's disease. Bone scan of femur 6 mo after six weekly, 30-mg infusions of APD. Note nonhomogeneity of tracer uptake with focal defects. If unaware of treatment, there would be concern about the possibility of sarcomatous change.

there is an effective treatment for Paget's disease and prolonged remissions can be expected (*19*). However, after treatment some unusual and bizarre bone scan appearances can be seen when reactivation of disease occurs, and it is important to be aware that the patient has received therapy (Fig. 1) (*18,20*). While treatment is often perceived as being highly successful, this evaluation is generally based on an assessment of biochemical parameters. Even with second generation bisphosphonate therapy, it has been found that only 10% of bone scan lesions completely resolve, 65% improve and the remainder are essentially unchanged (*21*). There was no significant difference in response between various bony sites throughout the skeleton, but less active lesions are more likely to resolve completely. Thus, while many lesions improve, complete resolution is uncommon and the clinical significance of lesions which remain metabolically active is uncertain. In the past, usually only patients with symptomatic Paget's disease received treatment. Currently, with successful therapy available, it is much more likely that patients will receive treatment at an earlier stage of disease with a view to preventing progression and the development of complications.

A poor quality bone scan in patients receiving bisphosphonate therapy has been reported (*22*). There is controversy as to what extent bisphosphonate loading can affect the quality of a bisphosphonate bone scan (*18*). There are a large number of potential binding sites in the skeleton and this is essentially not a problem in clinical practice, particularly with oral therapy. However, if parenteral bisphosphonate is given in high dosage and a bone scan obtained shortly thereafter, then a study with poor tracer uptake by the skeleton and high background activity may result.

OSTEOPOROSIS

The radionuclide bone scan has no role in the initial diagnosis of osteoporosis and in cases of suspected fracture an x-ray should be obtained. The definition of osteoporosis is contentious at best. The term osteopenia is preferred for patients with low bone density who are at risk of osteoporosis, which is best defined as the established disease, i.e., with fractures (*23*). In recent years, a variety of "deformation" indices have been used to document changes in spinal vertebrae on x-ray, e.g., a reduction of 20% (*24,25*) or a reduction of three or four standard deviations in height when compared with normal vertebrae (*25,26*). This provides an objective measure of change and is used extensively in pharmaceutical studies. However, the clinical relevance of such changes is uncertain because patients are often asymptomatic and the affected vertebrae may not be positive on a bone scan. This is quite different from fractures at any other site in the skeleton and there must be doubt as to what exactly is being measured. We suggest that if clinically indicated, the bone scan should be used in such situations to confirm fracture.

The typical bone scan appearance of a vertebral fracture is intense linearly increased tracer uptake that gradually resolves over the following 6 to 24 mo (*27*). However, appearances can resolve more rapidly and complete resolution of multiple lesions over a three-month interval has been reported (*28*). The bone scan can be of particular value in the evaluation of a patient with known osteoporosis who presents with back pain to clarify whether further fracture has occurred or some other explanation for pain should be sought. In some cases, patients have lost 6–9 in. in height with multiple fractures, thus identifying new pathology becomes difficult. Bone scans clearly identify the recent fracture sites. On occasion, the bone scan will identify coexistent disease such as a rib fracture or metastases that may be the cause of, or contribute to, symptoms. It should always be remembered that even when scan appearances are typical of a vertebral fracture, the findings are not specific to osteoporosis and a coexistent lesion cannot be excluded. However, when multiple vertebral fractures are present, particularly when showing different stages of resolution, osteoporosis is the probable diagnosis. Occasionally a disease which causes generalized demineralization such as myeloma can mimic this situation.

Recently, it has been found that back pain in osteoporosis may often be due to coexistent degenerative disease that can be unrelated to the site of fracture (*29*). This is generally due to facet joint arthritis. SPECT provides increased sensitivity for diagnosis and localization of lesions

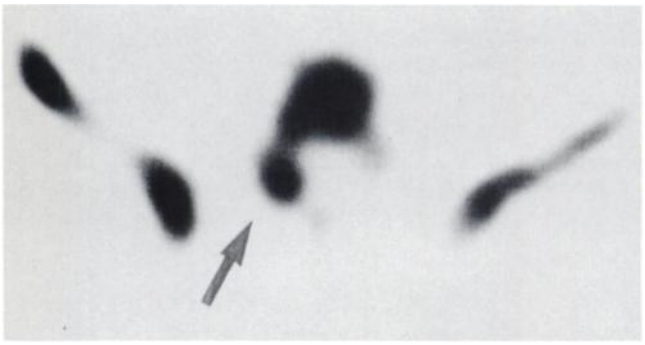

FIGURE 2. Transaxial SPECT image shows focal, increased tracer uptake in facet joint due to arthritis (arrow).

(Fig. 2). Such findings have potentially important implications for therapy (*30*).

The bone scan is of value in confirming suspected fractures when initial x-rays are negative at sites such as forearms or hips. Bone scans may also provide diagnostic information in other less common situations such as osteoporosis of pregnancy, transient regional osteoporosis (*31–33*), reflex sympathetic dystrophy syndrome (*34–37*) and the detection of microfractures in patients receiving fluoride therapy (*38,39*).

BONE DENSITY MEASUREMENTS

While there has been considerable research interest in the measurement of bone density, it is only in recent years, with the advent of dual x-ray absorptiometry (DXA), that such measurements have become established in routine clinical practice (*40–42*). DXA utilizes an x-ray tube as the radiation source rather than ^{153}Gd which is used in dual-photon absorptiometry (DPA). This has the attraction of eliminating difficulties relating to calibration with a continuously declining source strength due to radioactive decay and providing significant savings on the isotope purchases. The major advantages of DXA are its practicality because scan time is reduced from 20 to 40 min with DPA to 2 to 5 min. Further, the greater photon flux means higher precision, approximately 1% compared to 2%–4% with DPA (*42,43*). There is also improved resolution and image quality is greatly enhanced. In addition, there have been improvements in software, in particular the "compare" facility for serial studies, which ensures that regions of interest (ROIs) around bone and soft tissue can be accurately reproduced.

The standard DXA examination includes the lumbar spine and the proximal femur. In the elderly, DXA measurements of the spine may not accurately reflect bone density because of confounding factors such as degenerative disease, vertebral fractures and aortic calcification that may be apparent on x-ray. There are no technical difficulties in measuring spinal bone density. The femur is more problematic, however, and results can be affected by patient positioning and subsequent analysis of the study, e.g., ROI placement (*44*). Rigorous quality control, appropriate training of technicians and review of scans by an experienced observer is important, particularly for research protocols and serial studies where clinical decisions could be affected. Until recently, there have been relatively limited data on the femur when compared with the spine, and what data are available generally relate to the femoral neck. Routine DXA analysis provides data for the femoral neck, trochanter and Ward's triangle. Ward's triangle is the most sensitive site for the detection of trabecular change in the proximal femur. Although theoretically attractive as a means of detecting postmenopausal bone loss, its clinical use is limited by relatively poor precision of approximately 3% (*44*).

The Scientific Advisory Board of the National Osteoporosis Foundation has suggested four clinical indications for measurement of bone density (*45*):

1. The estrogen-deficient female who may need treatment with estrogen.
2. Vertebral abnormalities identified on x-ray.
3. Patients receiving long-term steroid therapy.
4. Asymptomatic primary hyperparathyroidism in which an abnormal result may influence the decision to proceed with surgery.

Measurement of bone density is likely to arise in one of two situations: (1) to assess whether bone density for an individual is in the normal range or (2) as part of a research protocol to monitor the effect of a drug on the skeleton. In this context, it should be noted that much recent information pertaining to pharmacological effects in the skeleton could not have been obtained without the benefit of such measurements, e.g., effectiveness of cyclical etidronate therapy in osteoporosis (*46,47*), tamoxifen protecting the skeleton (*48,49*) and fluoride, although it leads to a substantial increase in bone density in the spine, causing bone loss in the femur in some cases (*50,51*). The major potential area for bone density measurements is in identifying those individuals who are at risk for developing osteoporosis (*52*). Once established, osteoporosis is difficult to treat and it is generally agreed that prevention of bone loss is important. There is now no doubt that bone density measurements provide the best, albeit not perfect, means of identifying those at risk of fracture. This has been confirmed in several prospective studies (*53–57*). A clinical profile of risk factors does not contribute to the evaluation of risk in this situation (*58,59*). In many cases, an individual may be concerned about osteoporosis, e.g., a menopausal woman whose mother had osteoporosis, patients with early menopause, patients receiving steroids, patients with a history of prolonged amenorrhoea, patients who have sustained after trivial trauma and patients in whom an x-ray has suggested osteopenia. In these situations, bone density measurements will help to resolve the problem and patients can be reassured that all is well or be given precise information about the severity of the problem.

The issue is how to define normal bone density. In practice, an individual's results are generally compared to normal age-related curves provided by individual manufacturers. There is some discussion as to whether it is better to relate results to age-matched controls or to values expected for young normals. In practice, both sets of data are provided as the Z or T scores, respectively. There is at least a theoretical problem with Z scores since these assume a normal distribution for the reference population. The assumption is also made by manufacturers when presenting reference ranges that the standard deviations for various age groups do not alter with advancing age. This is unlikely to be the case. The use of percentiles resolves some of these issues (*52*) and are also much simpler to comprehend, e.g., a patient is in the lowest 30th percentile for her age rather than this information being given as

either a multiple or a fraction of a standard deviation. There is also the concept of a "fracture threshold," i.e., a value below which an individual is at risk of fracture (*60*). While this is somewhat artificial, it is nevertheless useful when considering risk. The "fracture threshold" has either been defined as two standard deviations below the value for a young normal (*61*) or as the 90th percentile of values taken from a population who has sustained osteoporotic fractures (*62*). In practice, the two definitions agree well.

The concept of mass screening of the female population to identify those at risk of osteoporosis remains contentious and there is no case to be made for this at the present time. However, this is not because bone density measurements are not of clinical value, but because there is no consensus as to how to manage an abnormal result. If, after full discussion of the issues with an individual patient, she states that if she is at risk she wishes to take hormone replacement therapy (HRT), then clearly bone density measurements will be important in influencing this decision. However, it is apparent that the majority of women are not prepared to take long-term HRT (*63*). Advances in HRT are occurring with several bleed-free regimens and progestogens, which have a lower incidence of side effects. It is probable that compliance with HRT will improve, but there remains the long-term safety issues, particularly, concerns about associations with breast cancer (*64,65*).

Screening is only a concept that applies to younger women because it is apparent that virtually all women over 75 who have never received hormone replacement therapy will have bone density values which place them at risk of fractures (*62*). Should there be a suitable safe treatment for osteoporosis, it is likely that bone density measurements will be used not only to decide who to treat, but also to determine the duration of therapy. In the future, there may be sets of tables to assist a physician in making a decision on treatment based on an individual's age, menopausal status and site-specific bone density measurements, because it is now apparent that the best predictor of fracture risk at a specific site is bone density measurement at that site. For example, it has been shown that the risk of fracture increases approximately threefold for each decrease of ISD in bone density at either the spine (*66*) or femur (*57*).

Although DXA is a relatively recent introduction into clinical practice, there are continuous and rapid developments in the technology. There have been new scanning modes and specialized software applications that supplement the standard spine and femur measurements. New sites include the distal forearm (with DXA this site can be scanned in air in comparison to single-photon absorptiometry which uses a water bath) (*67*), total body mineral measurements (*68*) and the lateral lumbar spine and calcaneus (*69–71*). Specialized applications include body composition measurements (*68,72*), evaluation of the prosthetic hip (*73*), pediatric studies and small animal studies (*74*). With regard to the equipment itself, there has been the introduction of a fanbeam configuration for the x-ray beam coupled to a multidetector scanning head (*75,76*).

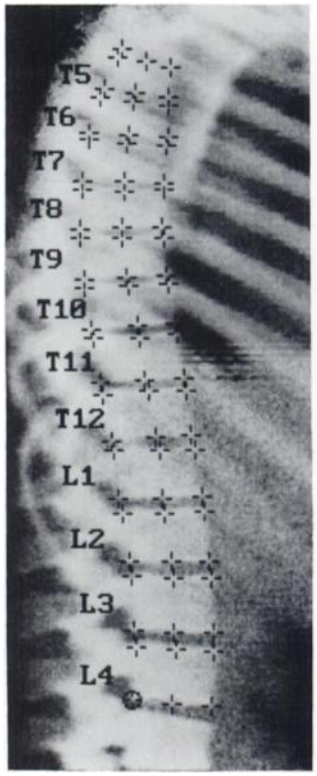

FIGURE 3. Morphometric DXA scan shows markers for measuring anterior, mid and posterior vertebral heights. (Image provided Dr. Steiger, Hologic)

This has led to a significant reduction in scanning time; it is now possible to obtain an adequate spinal measurement in 5 sec (*77*).

There is further improvement in precision, particularly for lateral spine studies (*75,78*). With this methodology, it is now possible to obtain a true volumetric analysis of vertebrae (*79*). The most important potential use for lateral DXA is evaluation of vertebral morphometry (*80*), an area of active interest and research. It is probable that in the near future it will be possible to monitor changes in vertebral height by automated studies of digital DXA (Fig. 3). If the precision should prove adequate, patients with osteoporosis will be able to have serial spine x-rays using approximately 1/1000 of the radiation used in standard x-rays.

REFERENCES

1. Sy WM, Mittal AK. Bone scan in chronic dialysis patients with evidence of secondary hyperparathyroidism and renal osteodystrophy. *Br J Radiol* 1975;48:878–884.
2. Fogelman I. The bone scan in metabolic bone disease. In: Fogelman I, ed. *Bone scanning in clinical practice*. London: Springer-Verlag: 1987:73–87.
3. Fogelman I, Citrin DL, Turner JG, et al. Semi-quantitative interpretation of the bone scan in metabolic bone disease. *Eur J Nucl Med* 1979;4:287–289.
4. Sy WM. Bone scan in primary hyperparathyroidism. *J Nucl Med* 1974;15: 1089–1091.
5. Wiegmann T, Rosenthall L, Kaye M. Technetium-99m-pyrophosphate bone scans in hyperparathyroidism. *J Nucl Med* 1977;18:231–235.
6. Fogelman I, Bessent RG, Turner JG, et al. The use of whole-body retention of ^{99m}Tc-diphosphonate in the diagnosis of metabolic bone disease. *J Nucl Med* 1978;19:245–248.
7. Singh BN, Kesala BA, Mehta SP, et al. Osteomalacia on bone scan simulating skeletal metastases. *Clin Nucl Med* 1977;2:181–183.
8. Evens RG, Ashburn W, Bartter FC. Strontium-85 scanning of a 'brown tumour' in a patient with parathyroid carcinoma. *Br J Radiol* 1969;42:224–225.

9. de Graaf P, Schicht IM, Pauwels EKJ, et al. Bone scintigraphy in uremic pulmonary calcification. *J Nucl Med* 1979;20:201–206.
10. Sy WM, Mottola O, Lao RS, et al. Unusual bone images in hyperparathyroidism. *Br J Radiol* 1977;50:740–744.
11. Fogelman I, Carr D. A comparison of bone scanning and radiology in the assessment of patients with symptomatic Paget's disease. *Eur J Nucl Med* 1980;5:417–421.
12. Barker DJ, Clough PW, Guyer PB, et al. Paget's disease of bone in 14 British towns. *Br Med J* 1977;1:1181–1183.
13. Rebel A, Basle M, Pouplard A, et al. Towards a viral etiology for Paget's disease of bone. *Metab Bone Dis Rel Res* 1981;3:235–238.
14. Mills BG, Singer FR. Nuclear inclusions in Paget's disease of bone. *Science* 1976;194:201–202.
15. Meunier PJ, Salson C, Mathieu L. Skeletal distribution and biochemical parameters of Paget's disease. *Clin Orthop* 1987;217:37–44.
16. Maldague B, Malghem J. Dynamic radiological patterns of Paget's disease of bone. *Clin Orthop* 1987;217:126–151.
17. Serafini AN. Paget's disease of the bone. *Semin Nucl Med* 1976;6:47–58.
18. Fogelman I. Bone scanning in Paget's disease. In: Freeman LM, ed. *Nuclear medicine annual 1991*. New York: Raven Press Ltd: 1991;99–128.
19. Ryan PJ, Sherry M, Gibson T, et al. Treatment of Paget's disease by weekly infusions of 3-aminohydroxypropylidene-1, 1-biphosphonate (APD). *Br J Rheumatol* 1992;31:97–101.
20. Anderson DC, O'Driscoll JB, Buckler HM, et al. Relapse of osteoporosis circumscripta as a lytic ring after treatment of Paget's disease with intravenous 3-amino-1-hydroxyproplidene-1, 1-biphosphonate. *Br J Radiol* 1988; 61:996–1001.
21. Ryan PJ, Gibson T, Fogelman I. Bone scintigraphy following intravenous pamidronate for Paget's disease of bone. *J Nucl Med* 1992;22:1589–1593.
22. Krasnow AZ, Collier BD, Isitman AT, et al. False-negative bone imaging due to etidronate disodium therapy. *Clin Nucl Med* 1988;13:264–267.
23. Kanis JA. Osteoporosis and osteopenia. *J Bone Min Res* 1990;5:209–211.
24. Steiger P, Block JE, Steiger S, et al. Spinal bone density measured with quantitative CT: effect of region of interest, vertebral level and technique. *Radiology* 1990;175:537–543.
25. Melton III LJ, Lane AW, Cooper C, et al. Prevalence and incidence of vertebral deformities. *Osteoporosis Int* 1993;3:113–119.
26. Eastell R, Ledel SL, Wahner HW, et al. Classification of vertebral fractures. *J Bone Min Res* 1991;6:207–213.
27. Matin P. The appearance of bone scans following fractures, including immediate and long-term studies. *J Nucl Med* 1979;20:1227–1231.
28. Fogelman I. Bone scanning in osteoporosis: the role of the radionuclide bone scan and photon absorptiometry. In: Freeman LM, ed. *Nuclear medicine annual 1990*. New York: Raven Press Ltd; 1990:1–36.
29. Ryan PJ, Evans P, Gibson T, et al. Osteoporosis and chronic back pain: a study with single-photon emission computed tomography bone scintigraphy. *J Bone Min Res* 1992;7:12:1455–1460.
30. Scott AM, Schwartzer A, Cooper R, et al. Methods with zygaphyseal joint infection in the evaluation of chronic low back pain [Abstract]. Comparison of SPECT and planar bone scintigraphy. *J. Nucl Med* 1992;31:868.
31. Strashun A, Chayes Z. Migratory osteolysis. *J Nucl Med* 1979;20:129–132.
32. Bray ST, Partain CL, Teates CD, et al. The value of the bone scan in idiopathic regional migratory osteoporosis. *J Nucl Med* 1979;20:1268–1271.
33. Kim SM, Desai AG, Krakovitz M, et al. Scintigraphic evaluation of regional migratory osteoporosis. *Clin Nucl Med* 1989;14:36–39.
34. Genant HK, Kozin F, Bekerman C, et al. The reflex sympathetic dystrophy syndrome. *Radiology* 1975;117:21–32.
35. Carlson DH, Simon H, Wegner W. Bone scanning and diagnosis of reflex sympathetic dystrophy secondary to herniated lumbar disks. *Neurology* 1977;27:791–793.
36. Kozin F, Soin JS, Ryan LM, et al. Bone scintigraphy in the reflex dystrophy syndrome. *Radiology* 1981;138:437–443.
37. Demangeat JL, Constantinesco A, Brunot B, et al. Three-phase bone scanning in reflex sympathetic dystrophy of the hand. *J Nucl Med* 1988;28:26–32.
38. Schulz EE, Libanati CR, Farley SM, et al. Skeletal scintigraphic changes in osteoporosis treated with sodium fluoride: concise communication. *J Nucl Med* 1984;25:651–655.
39. O'Duffy JD, Wahner HW, O'Fallon WM, et al. Mechanism of acute lower extremity pain syndrome in fluoride-treated osteoporotic patients. *Am J Med* 1986;80:561–566.
40. Wahner HW, Dunn WL, Brown ML, et al. Comparison of dual-energy x-ray absorptiometry and dual photon absorptiometry for bone mineral measurements of the lumbar spine. *Mayo Clin Proc* 1988;63:1075–1084.
41. Kelly TL, Slovik DM, Schoenfeld DA, et al. Quantitative digital radiography versus dual photon absorptiometry of the lumbar spine. *J Clin Endocrinol Metab* 1988;67:839–844.
42. Mazess R, Collick B, Trembe J, et al. Performance evaluation of a dual-energy x-ray bone densitometer. *Calcif Tissue Int* 1989;44:228–232.
43. Sorenson JA, Duke PR, Smith SW. Simulation studies of dual-energy x-ray absorptiometry. *Med Phys* 1989;16:75–80.
44. Wilson CR, Fogelman I, Blake GM, et al. The effect of positioning on dual-energy x-ray bone densitometry of the proximal femur. *Bone Min* 1991;13: 69–76.
45. Johnston CC, Melton LJ, Lindsay R, et al. Clinical indications for bone mass measurement. *J Bone Min Res* 1989;4(suppl):1–28.
46. Storm T, Thomasborg G, Steiniche T, et al. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* 1990;322:1265–1271.
47. Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* 1990;323:73–79.
48. Fentiman IS, Caleffi M, Rodin A, et al. Bone mineral content of women receiving tamoxifen for mastalgia. *Br J Cancer* 1989;60:262–264.
49. Love RR, Mazess RB, Barden HS, et al. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med* 1992;326:852–856.
50. Riggs BL, Hodgson SF, O'Fallon WM, et al. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. *N Engl J Med* 1990;322:802–809.
51. Inkovaara J, Heikinheimo R, Jarvinen K, et al. Prophylactic fluoride treatment and aged bones. *Br Med J* 1975;286:1283–1288.
52. Ryan PJ, Blake GM, Fogelman I. Postmenopausal screening for osteopenia. *Br J Rheumatol* 1992;31:823–828.
53. Jensen GF, Christiansen C, Boesen J, et al. Relationship between bone mineral content and frequency of postmenopausal fractures. *Acta Med Scand* 1983;213:61–63.
54. Gardsell P, Johnell O, Nilsson BE. Predicting fractures in women using forearm bone densitometry. *Calcif Tissue Int* 1989;44:235–242.
55. Ross PD, Wasnich RD, Vogel JM. Detection of prefracture spinal osteoporosis using bone mineral absorptiometry. *J Bone Min Res* 1988;3:1–11.
56. Wasnich RD, Ross PD, Heilbrun LK, et al. Prediction of postmenopausal fracture risk with use of bone mineral measurements. *Am J Obstet Gynecol* 1985;153:745–751.
57. Cummings SR, Black DM, Nevitt MC, et al. Bone density at various sites for prediction of hip fractures. *Lancet* 1993;341:72–75.
58. Cohn AJ, Vaswani AN, Yeh JK, et al. Risk factors for postmenopausal osteoporosis. *Am J Med* 1985;78:95–100.
59. Elders PJM, Netelenbos JC, Lips P, et al. Perimenopausal bone mass and risk factors. *Bone Min* 1989;7:289–299.
60. Mazess RB. Bone density in diagnosis of osteoporosis: thresholds and breakpoints. *Calcif Tissue Int* 1987;41:117–118.
61. Nordin BEC. The definition and diagnosis of osteoporosis. *Calcif Tissue Int* 1987;40:57–58.
62. Riggs BL, Wahner HW, Dunn WL, et al. Differential changes in bone mineral density of appendicular and axial skeleton with aging. *J Clin Invest* 1982;67:328–335.
63. Ryan PJ, Harrison R, Blake GM, et al. Compliance with hormone replacement therapy (HRT) after screening for postmenopausal osteoporosis. *Br J Obstet Gynecol* 1992;99:325–328.
64. Bush TL, Barrett-Connor E, Criqui MH, et al. Estrogen use and all-cause mortality. *JAMA* 1983;249:903–906.
65. Dupont WD, Page DL. Menopausal estrogen replacement therapy and breast cancer. *Arch Intern Med* 1991;151:67–72.
66. Ross PD, Davis JW, Epstein RS, et al. Pre-existing fractures and bone mass predict vertebral fracture incidence in women. *Ann Intern Med* 1991;114: 919–923.
67. Ryan PJ, Blake GM, Fogelman I. Measurement of forearm bone mineral density in normal women by dual energy x-ray absorptiometry. *Br J Radiol* 1992;65:127–131.
68. Herd RJM, Blake GM, Parker JC, et al. Total body studies in normal British women using dual x-ray absorptiometry. *Br J Radiol* 1993;66:303–308.
69. Slosman DO, Rizzoli R, Donath A, et al. Vertebral bone mineral density measured laterally by dual energy x-ray absorptiometry. *Osteoporosis Int* 1990;1:23–29.
70. Uebelhart D, Duboeuf F, Meunier PJ, et al. Lateral dual-photon absorptiometry: a new technique to measure the bone mineral density at the lumbar spine. *J Bone Min Res* 1990;5:525–531.
71. Waud CE, Lew R, Baran DT. The relationship between ultrasound and densitometric measurements of bone mass at the calcaneus in women. *Calcif Tissue Int* 1992;51:415–418.

72. Kohrt W, Snead D, Rupich R, et al. Bone and soft tissue assessment with the QDR-1000/W [Abstract]. *Osteoporosis Int* 1991;1:199.
73. Trevisan C, Cherubini R, Ulivieri FM, et al. Dual-energy x-ray absorptiometry in the evaluation of periprosthetic bone mineral status: analysis protocols and reproducibility [Abstract]. *Osteoporosis Int* 1991;1:191.
74. Ammann P, Rizzoli R, Slosman D, et al. Sequential and precise in vivo measurement of bone mineral density in rats using dual-energy x-ray absorptiometry. *J Bone Min Res* 1992;7:311–316.
75. Steiger P, von Stetten E, Weiss H, et al. Paired AP and lateral supine dual x-ray absorptiometry of the spine: initial results with a 32-detector system [Abstract]. *Osteoporosis Int* 1991;1:190.
76. Pommet R, Chambellan D, Reverchon P, et al. Array multidetector bone densiometer for supine lateral vertebral measurement in lateral projection [Abstract]. *Osteoporosis Int* 1991;1:190.
77. Buxton FMA, Blake GM, Parker JC, et al. Spinal bone density measured with a 5-sec scan. *Br J Radiol* 1993;66:275–277.
78. Devogelaer JP, Baudoux C, Nagant de Deuxchaisnes C. Reproducibility of BMD measurements on the Hologic QDR-2000 [Abstract]. *Calcif Tissue Int* 1993;52:164.
79. Sabin MA, MacLaughlin SM, Blake GM, et al. A study of the accuracy of lateral and volumetric spinal bone density measurements with the Hologic QDR-2000 [Abstract]. *Calcif Tissue Int* 1993;52:154.
80. Kelly TL, Pomeroy M, Richardson TL. New developments in x-ray densitometry [Abstract]. In: Ring EFJ, ed. *Current research in osteoporosis and bone mineral measurement*. London: British Institute of Radiology 1990; 19–20.