Different Approaches to Bone Densitometry*

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From 1990 to 2000, several effective new treatments were introduced for the prevention of osteoporotic fractures; these treatments were proven effective in large, international, clinical trials. At the same time, there was rapid technologic innovation, with the introduction of new radiologic methods for the noninvasive assessment of patients' bone density status. These developments led to the publication of guidelines for the clinical use of bone densitometry that include criteria for the referral of patients for investigation as well as recommendations for intervention thresholds for the initiation of preventive treatment of osteoporosis. Dual-energy x-ray absorptiometry scanning of the spine and hip remains the technique of choice for bone densitometry studies, although there is now a wider appreciation of the need for smaller, cheaper devices for scanning the peripheral skeleton if the millions of women most at risk of a fragility fracture are to be identified and treated. This article reviews these developments, concentrating in particular on the advantages and disadvantages of the different types of equipment available for performing bone densitometry investigations, the guidelines for the referral of patients, and the principles for the interpretation of the scan findings.

Key Words: bone densitometry; osteoporosis; dual-energy x-ray absorptiometry; quantitative CT; quantitative ultrasound; radiographic absorptiometry

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Over the past decade, osteoporotic fractures have come to be recognized as one of the most serious problems in public health. For a 50-y-old white woman, the lifetime risk of suffering a fragility fracture of the spine, hip, or forearm is estimated to be 30%–40%, which compares with the percentages for breast cancer and cardiovascular disease of 9%–12% and 30%–40%, respectively (*1*). For men, the risk of an osteoporotic fracture is about one third of that in women. In the United States in 1995, the total health care costs attributable to osteoporotic fractures exceeded $13 billion (*2*), a figure that is expected to rise to between $30 and $40 billion by the year 2020 (*3*). Of these costs, about two thirds are attributable to hip fractures. In addition to incurring greater costs, hip fractures also cause greater morbidity and mortality than other types of fractures. One quarter of hip-fracture patients die within a year after their fracture (*4*), and survivors frequently suffer sustained disability and loss of independence (*5*). However, it should not be forgotten that fractures at other sites may also cause substantial pain and disability.

The increased recognition of the scale of morbidity and mortality attributable to osteoporosis has led to a major effort by the pharmaceutical industry to develop new therapeutic strategies for the prevention of fractures (*6–8*). Estrogen deficiency after menopause is one of the most documented causes of osteoporosis and can be prevented by hormone replacement therapy (HRT). However, although HRT has additional benefits that include the prevention of cardiovascular disease (*9*), it may also cause an increase, of approximately 35%, in the risk of breast cancer in long-term users (*10*). In addition to such fears, compliance with HRT may also be a problem because of side effects such as bleeding, weight gain, and breast tenderness. Consequently, much effort has been devoted to developing alternative treatments for osteoporosis. Among these treatments, bisphosphonates are becoming increasingly recognized as the treatment of choice at the present time (*11–13*). Another new class of therapeutic agents recently introduced is the selective estrogen receptor modulators (SERMs), which are compounds that have a unique ability to mimic the beneficial effects of HRT on osteoporosis and cardiovascular disease while antagonizing the effects of estrogen on the breast and uterus (*14,15*).

Associated with the growing awareness of the significance of osteoporosis for public health and the development of new treatments for its prevention, in the past decade there has been a rapid evolution of new radiologic techniques for the noninvasive assessment of skeletal integrity (Table 1) (*16,17*). The technique most associated with the recent growth in bone densitometry is dual-energy x-ray absorptiometry (DXA) (*18*). DXA was developed in the mid-1980s from the earlier technique of dual photon absorptiometry (DPA) by replacing the ^{153}Gd radionuclide source with an x-ray tube. Because of the advantages of high precision, short scan times, low radiation dose, and stable calibration, DXA has proven to be appropriate in meeting the need for scanning equipment to assist in the diagnosis of osteoporosis and aid decisions about treatment.

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TABLE 1
Characteristics of Different Bone Densitometry Techniques

Technique	Regions of interest	Units reported	Precision (%CV)	Effective dose (μSv)
DXA	PA spine	BMD (g/cm^2)	1%	1–10
	Proximal femur		1%–2%	1–10
	Total body		1%	3
QCT	Spine	BMD (g/cm^3)	3%	50–500
pDXA	Forearm	BMD (g/cm^2)	1%–2%	0.1
	Calcaneus		1%–2%	0.1
pQCT	Forearm	BMD (g/cm^3)	1%–2%	1–3
RA	Phalanx	BMD (g/cm^2)	1%–2%	10
QUS	Calcaneus	BUA (dB/MHz)	2%–5%	None
	Calcaneus	SOS (m/s)	0.1%–1%	None
	Tibia	SOS (m/s)	1%–2%	None
	Multisite	SOS (m/s)	1%–2%	None

PA = posteroanterior; BUA = broadband ultrasonic attenuation; SOS = speed of sound.

THE DEFINITION OF OSTEOPOROSIS

The term ''osteoporosis'' is derived from the classical Greek word ''osteon,'' meaning bone, and ''poros,'' meaning a small passage or pore. Thus, the term is descriptive of the changes in bone tissue found in this generalized skeletal disease. The modern definition of osteoporosis is ''a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture'' (*19*). It should be noted that this definition does not necessitate that an individual sustain a fracture before a diagnosis of osteoporosis is made but introduces the concept of low bone mass and its relationship to increased fracture risk. Although it could be argued that it is wrong to define a disease on the basis of what is essentially a risk factor (i.e., low bone density), there is nevertheless some logic to this because fractures only occur late in the disease process when skeletal integrity is already severely compromised. Therefore, it is desirable to identify individuals at high risk for osteoporosis, with the goal for beginning treatment early enough to prevent fractures from occurring.

DEFINITION OF OSTEOPOROSIS USING BONE MINERAL DENSITY

In recent years, the widespread availability of bone densitometry systems has led to working definitions of osteoporosis that are increasingly based on measurements of bone mineral density (BMD). In particular, in 1994 a World Health Organization (WHO) study group recommended a definition of osteoporosis that was based on a BMD measurement of the spine, hip, or forearm expressed in SD units called T-scores (*20*,*21*). The WHO report also proposed creating an intermediate category characterized by low bone mass between the normal and osteoporotic states and referred to as ''osteopenia.''

The T-score is calculated by taking the difference between a patient's measured BMD and the mean BMD of healthy young adults, matched for gender and ethnic group, and expressing the difference relative to the young adult population SD:

$$\text{T-score} = \text{Measured BMD} - \text{young adult mean BMD/young adult SD.}$$

Therefore, a T-score result indicates the difference between the patient's BMD and the ideal peak bone mass achieved by a young adult.

The WHO definitions of osteoporosis and osteopenia are based on T-score values such that an individual with a T-score ≤ -2.5 at the spine, hip, or forearm is classified as having osteoporosis; a T-score between -2.5 and -1 is classified as osteopenia; and a T-score ≥ -1 is regarded as healthy. A fourth category of ''established osteoporosis'' was also proposed to denote osteoporosis as defined above but in the presence of 1 or more documented fragility fractures, usually of the wrist, spine, or hip.

The WHO study group definitions of osteoporosis, osteopenia, and healthy are intended to identify patients with high, intermediate, and low risk of fracture, respectively (Fig. 1). It is important to recognize that the WHO criteria refer only to BMD measurements of the spine, hip, or forearm. As is discussed later, these definitions cannot automatically be applied to other BMD measurement sites or to other technologies such as quantitative CT (QCT) or quantitative ultrasound (QUS) (Table 1).

The rationale for the WHO definition of osteoporosis is

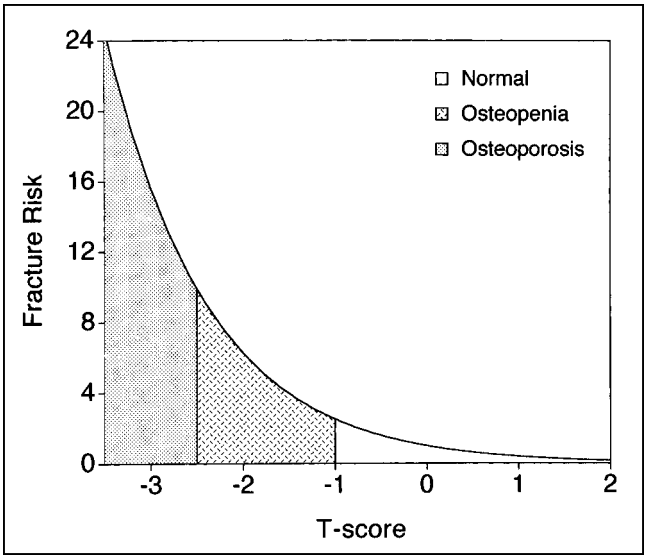

FIGURE 1. Gradient-of-risk relationship between bone density and fracture risk. Bone density is plotted in T-score units relative to mean and SD of healthy young adult population. WHO definitions of osteoporosis, osteopenia, and ''normal'' are intended to identify patients at high, intermediate, and low risks of fracture. In this figure, a decrease in T-score by 1 unit increases fracture risk by a factor of 2.5. This approximates to relationship between hip BMD and hip-fracture risk (see Figure 2).

that it captures approximately 30% of all white postmenopausal women (*1*). As explained above, this figure approximates to the lifetime risk of fracture for a 50-y-old woman. In comparison, it can be argued that the WHO definition of osteopenia captures too high a percentage of women to be clinically useful, and nowadays this term is being used less often, particularly in the context of therapeutic decision making. In contrast, the WHO definition of osteoporosis has had a major influence on clinical practice, to the extent that if the question is, ''Does this patient have osteoporosis, yes or no?'', this is now regarded as a T-score issue.

In addition to the T-score, another useful way of expressing BMD measurements is in Z-score units (*22*). Like the T-score, the Z-score is expressed in units of the population SD. However, instead of comparing the patient's BMD with the young adult mean, it is compared with the mean BMD expected for the patient's peers: For example, for a healthy subject matched for age, gender, and ethnic origin:

$$\text{Z-score} = \text{measured BMD} - \text{age-matched mean BMD/age-matched SD.}$$

Although they are not as widely used as T-scores, Z-scores nevertheless remain a useful concept because they express the patient's risk of sustaining an osteoporotic fracture relative to his or her peers. Epidemiologic studies of the relationship between BMD and fracture incidence are interpreted using a gradient-of-risk model in which fracture risk increases exponentially with decreasing BMD (Fig. 1) (*23*). The findings are expressed in terms of the relative risk (RR), which is the increased risk factor for each 1-SD decrease in BMD. Results for RR values by fracture site and BMD measurement site derived in a recent meta-analysis of prospective studies (*24*) are plotted in Figure 2. Typically, every reduction of 1 SD in BMD equates to a 1.5–2.5 increase in the likelihood of fracture. It follows that patients with a Z-score < -1 are at a substantially increased risk of fracture compared with their peers.

TECHNIQUES AVAILABLE FOR BONE DENSITOMETRY

Table 1 lists the methods currently available for the noninvasive assessment of the skeleton for the diagnosis of osteoporosis or the evaluation of an increased risk of fracture. These include DXA, QCT, peripheral DXA (pDXA), peripheral QCT (pQCT), radiographic absorptiometry (RA), and QUS. These techniques differ substantially in fundamental methodology, in clinical discrimination and use, and in general availability and cost. Each is reviewed briefly below. The reader can find further information about these techniques in several comprehensive reviews (*16,17,25,26*).

DXA

Over the past decade, DXA has established itself as the most widely used method of measuring BMD because of its advantages of high precision, short scan times and stable calibration in clinical use. DXA equipment (Fig. 3A) allows scanning of the spine and hip (Fig. 3B and 3C), which are usually regarded as the most important measurement sites because they are frequent sites of fractures that cause substantial impairment of quality of life and increased morbidity and mortality. A measurement of hip BMD has been shown to be the most reliable way of evaluating the risk of hip fracture (Fig. 2) (*24,27*). Also, because of the metabolically active trabecular bone in the vertebral bodies, the spine is regarded as the optimum site for monitoring response to treatment (*28*).

The fundamental principle behind DXA is the measurement of the transmission through the body of x-rays of 2 different photon energy levels (*18*). Because of the dependence of the attenuation coefficient on atomic number and photon energy, measurement of the transmission factors at 2

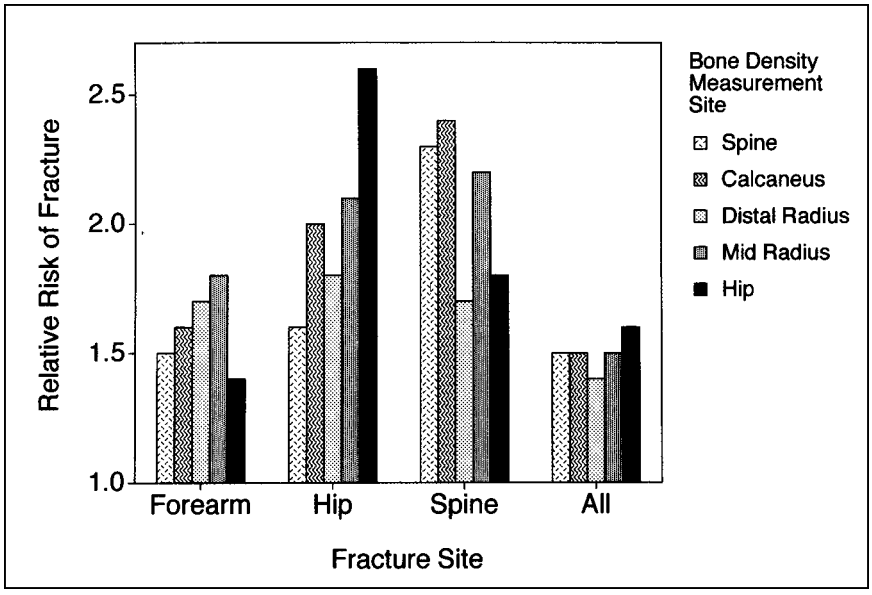

FIGURE 2. RR values for fractures at different skeletal sites for bone density measurements in spine, calcaneus, distal radius, midradius, and hip. RR is defined as increased risk of fracture for a 1-SD decrease in BMD. Data are taken from meta-analysis of prospective studies collated by Marshall et al. (*24*).

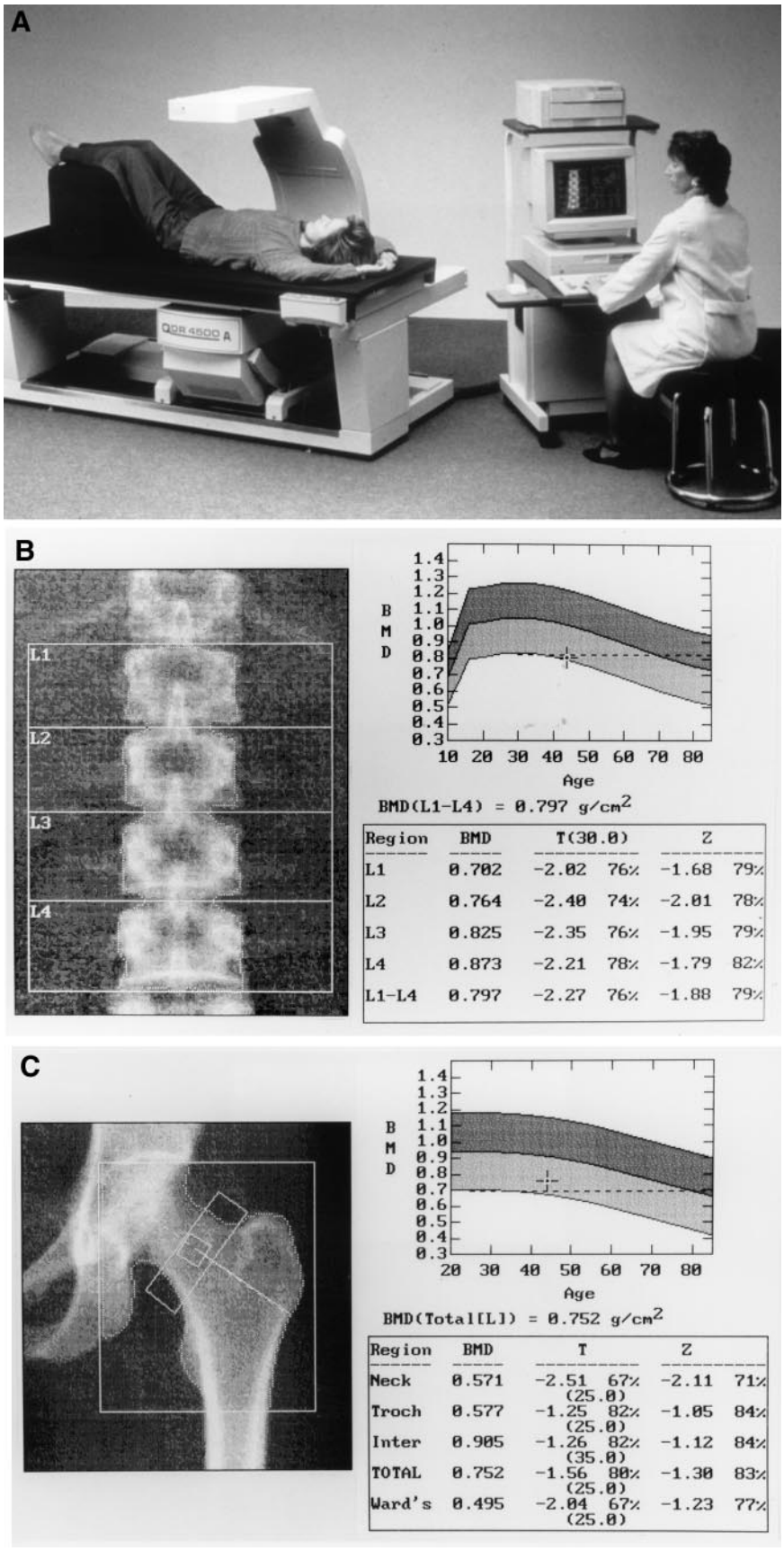

FIGURE 3. (A) QDR4500 fanbeam DXA scanner (Hologic, Bedford, MA). Densitometers such as this are most frequently used for measuring spine and hip BMD but can also be used for total body, forearm, and lateral projection studies of the spine. (B) Portion of computer printout from DXA scan of the spine. Printout shows (clockwise from left): scan image of lumbar spine; patient's age and BMD plotted with respect to the reference range; and BMD figures for individual vertebrae and total spine (L1–L4) with interpretation in terms of T-scores and Z-scores. (C) Portion of computer printout from a DXA scan of the hip. Printout shows (clockwise from left): scan image of proximal femur; patient's age and BMD for the total femur ROI plotted with respect to the NHANES III reference range; and BMD figures for 5 ROIs in hip (femoral neck, greater trochanter, intertrochanteric, total femur, and Ward's triangle) together with interpretation in terms of T-scores and Z-scores using the NHANES III reference range.

energy levels enables the areal densities (i.e., the mass per unit projected area) of 2 different types of tissue to be inferred. In DXA scans, these are taken to be bone mineral (hydroxyapatite) and soft tissue, respectively. Radiation dose to the patient is very low (1–10 μSv) (*29*) and is comparable with the average daily dose from natural background radiation of 7 μSv.

It is widely recognized that the accuracy of DXA scans is limited by the variable composition of soft tissue. Because of its higher hydrogen content, the attenuation coefficient of fat is different from that of lean tissue. Differences in the soft tissue composition in the path of the x-ray beam through bone compared with the adjacent soft tissue reference area cause errors in the BMD measurements, according to the results of several studies (*30*,*31*). Svendsen et al. reported on a cadaver study in which the effect of fat inhomogeneity on the random accuracy errors for BMD measurements in the spine, hip, and forearm were examined (*31*). The root mean square accuracy errors were reported to be 3% for forearm, 5% for spine, and 6% for femoral neck and total hip BMD.

The first generation of DXA scanners used a pinhole collimator, which produced a pencil beam coupled to a single scintillation detector in the scanning arm. Since then, the most significant development has been the introduction of new systems that use a slit collimator to generate a fanbeam coupled to a linear array of solid state detectors. As a result, image resolution has improved, and scan times have shortened from around 5–10 min for the early pencil beam models to 10–30 s for the latest fanbeam systems. Radiation dose to patients is higher for fanbeam systems compared with pencil beam, and the resulting increased scatter dose to technologists may require more active precautions to limit exposure (*32*).

QCT

QCT has the advantage of determining the true 3-dimensional (i.e., volumetric) bone density (units: mg/cm^3) compared with the 2-dimensional areal density measured by DXA. QCT is usually applied to measure the trabecular bone in the vertebral bodies (Fig. 4) (*33*). The measurement can be performed on any clinical CT scanner, provided the patient is scanned with an external reference phantom to calibrate the CT numbers to bone equivalent values. Most CT manufacturers provide a software package to automate the placement of the regions of interest (ROIs) within the vertebral bodies. Patient dose is much lower than for standard CT scans, provided the examination is performed correctly (*34*). QCT studies are generally performed using a single kV setting (single-energy QCT), when the principal source of error is the variable composition of the bone marrow. However, a dual-kV scan (dual-energy QCT) is also possible. This reduces the accuracy errors but at the price of poorer precision and higher radiation dose. The advantage of spinal QCT is the high responsiveness of the vertebral trabecular bone to aging and disease (*17*,*33*). The principal disadvantage is the cost of the equipment.

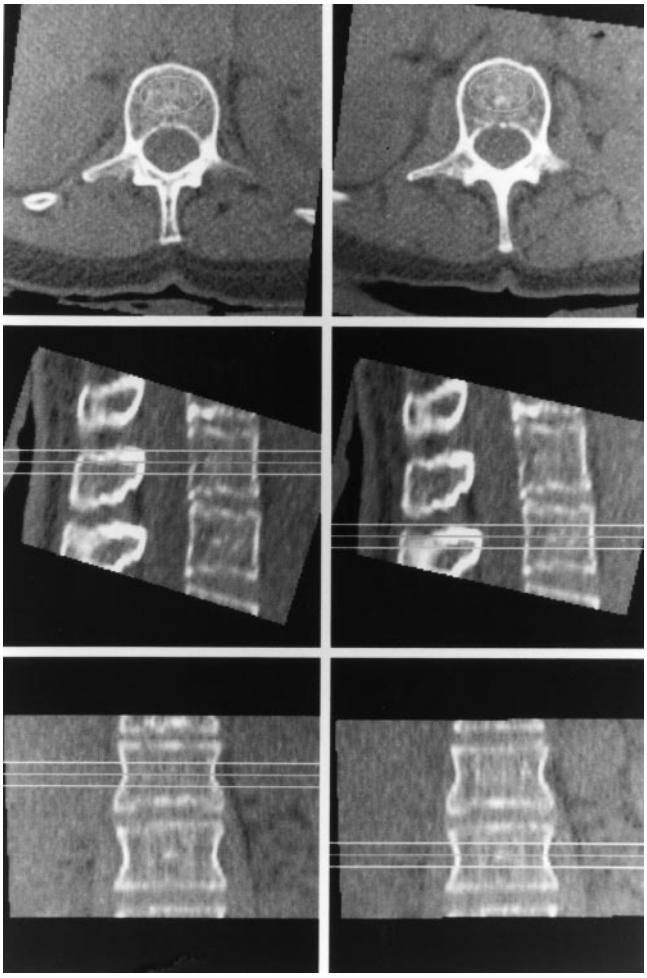

FIGURE 4. Portion of computer printout from spinal QCT scan showing transverse, sagittal, and coronal images of 2 lumbar vertebrae. The study was analyzed using commercially available QCT software package (Mindways Software, San Francisco, CA).

pDXA, pQCT, and RA

Despite the widespread popularity of spine and hip DXA, there is continuing interest in the development of new devices for assessing the peripheral skeleton (*35*). The first bone densitometers were forearm scanners that used the technique of single photon absorptiometry (SPA) that was based on a ^{125}I radionuclide source (*36*). A 25-y follow-up period of patients after SPA studies has shown that forearm bone density measurements can predict fracture risk (*37*). In recent years, the technology has been updated by replacing the radionuclide source with a low-voltage x-ray tube (40–60 kV_p) and using the principles of DXA to perform BMD scans of the distal radius (Fig. 5) and the calcaneus. The advantages of pDXA systems include the small footprint of the devices, relatively low cost, and extremely low radiation dose (0.1 μSv (*38*)).

Just as pDXA devices were developed as an alternative to DXA scanning of the central skeleton, small dedicated pQCT systems are also available for measuring the forearm (*35*). These devices have the advantage of separating the

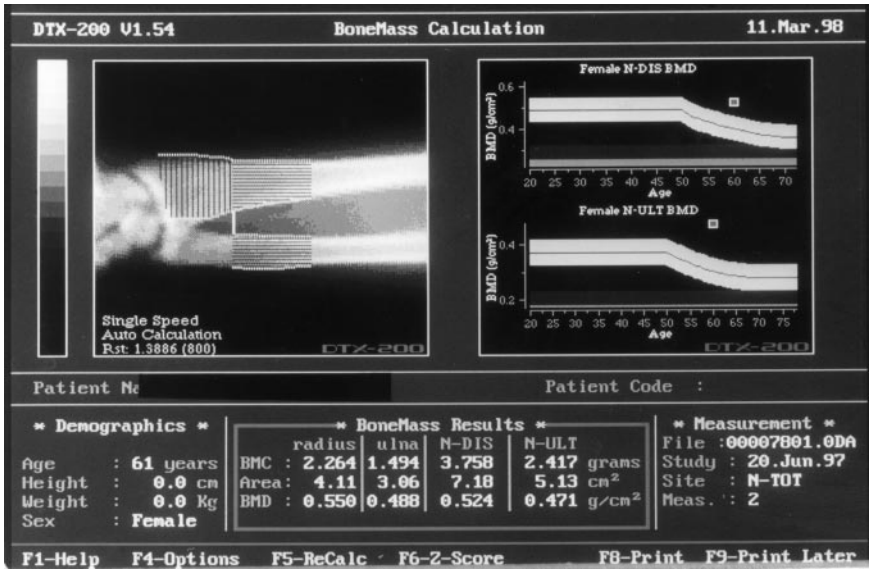

FIGURE 5. Computer printout from pDXA scan of distal forearm. Scan was performed on DTX-200 system (Osteometer Meditech, Hawthorne, CA).

trabecular and cortical bone of the ultradistal radius and of reporting volumetric density. Although widely used in some countries in Europe, they have been primarily limited to research studies in the United States.

RA is a technique that was developed many years ago for assessing bone density in the hand, but the technique has recently attracted renewed interest (*35*). It has the advantage of using conventional x-ray equipment, usually with the addition of a small aluminum wedge in the image field for calibration. The radiographic image is captured on a personal computer and then processed automatically using a specially developed software application to measure BMD in the phalanges. The main advantage of RA is its potential for general use on the basis of the widespread availability of conventional film radiography.

Peripheral x-ray absorptiometry methods such as those described above have obvious advantages when selecting bone densitometry methodologies suitable for use in physicians' offices or in primary care. However, epidemiologic studies have shown that the discriminatory ability of peripheral BMD measurements to predict spine and hip fractures is probably lower than when spine and hip BMD measurements are used (Fig. 2) (*24,27*). In addition, changes in forearm BMD in response to HRT, bisphosphonates, and SERMs are relatively small, making such measurements less suitable than spine BMD for monitoring response to treatment (*39,40*). Finally, although the radiation doses to patient and operator are both extremely small, pDXA and pQCT devices are subject to government regulatory requirements controlling the use of x-ray equipment, including the training of technologists and physicians in the principles of radiation safety.

QUS

QUS is a technique for measuring the peripheral skeleton that has raised considerable interest in recent years (*26,35,41*). There is a wide variety of equipment available, with most devices using the heel as the measurement site (Fig. 6). The calcaneus is chosen because it encompasses a large volume of trabecular bone between relatively flat faces and is readily accessible for transmission measurements. The physical principles of QUS measurements are outlined in Figure 7. A sonographic pulse passing through bone is strongly attenuated as the signal is scattered and absorbed by trabeculae. Attenuation (measured in decibels) increases linearly with frequency, and the slope of the relationship is referred to as the broadband ultrasonic attenuation (BUA; units: dB/MHz) (Fig. 7C). BUA is reduced in patients with osteoporosis, because there are fewer trabeculae in the calcaneus to attenuate the signal. In addition to BUA, most QUS systems also measure the speed of sound (SOS) in the heel by dividing the distance between the sonographic transducers by the propagation time (units: m/s) (Fig. 7A). SOS values are reduced in patients with osteoporosis because, with the

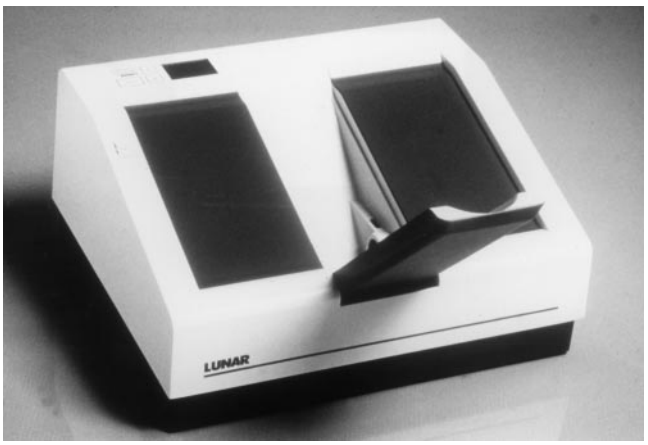

FIGURE 6. Achilles system for performing QUS measurements in the heel (Lunar Corp., Madison, WI). Devices such as this measure BUA and SOS in calcaneus. The 2 measurements are combined into 1 index ("Stiffness"), which is supposed to improve discrimination compared with BUA or SOS alone.

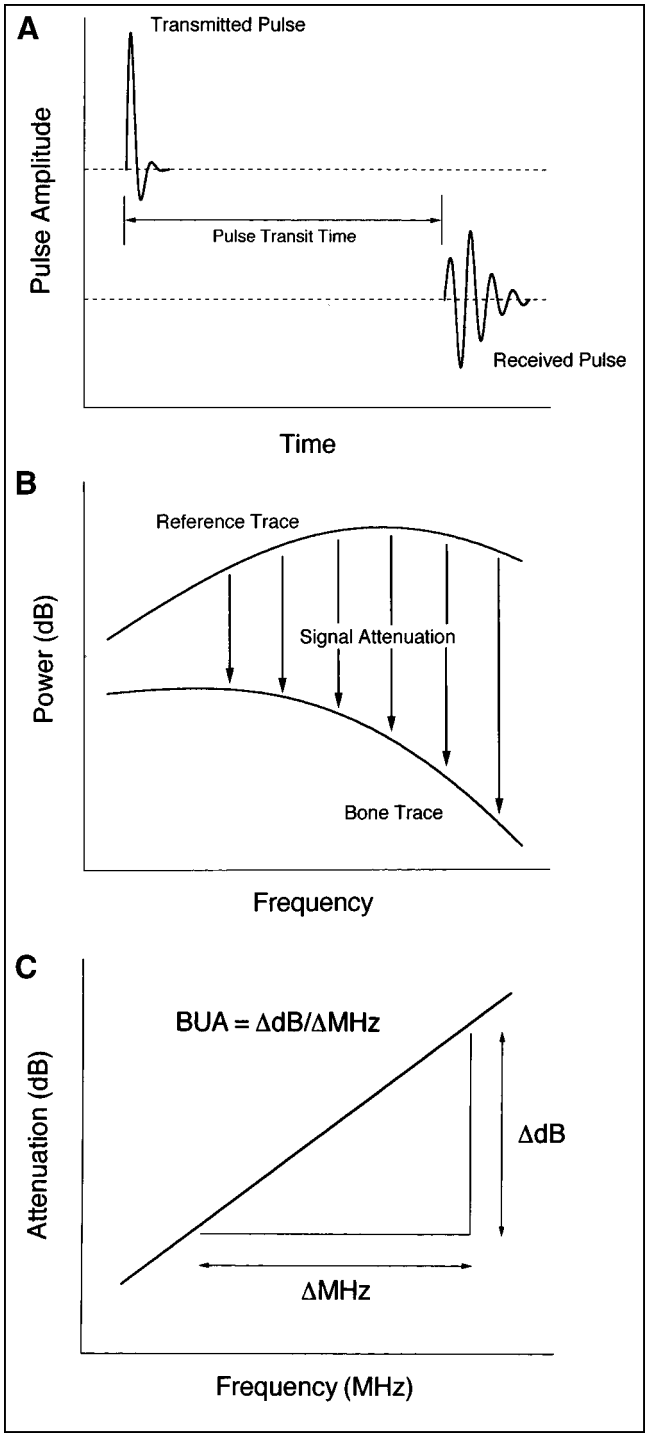

FIGURE 7. Physical principles behind measurement of BUA and SOS. (A) Received pulse is digitized, and fourier analysis used to determine the power spectrum. Pulse transit time is used for SOS measurement. (B) Power spectrum of signal transmitted through patient's heel is compared with reference trace from signal transmitted through water. Difference between the 2 traces represents attenuation from patient's heel. (C) When attenuation through patient's heel is plotted against frequency, linear relationship is found at frequencies less than 1 MHz. BUA is defined as slope of regression line and is measured in units of dB/MHz.

loss of mineralized bone, the elastic modulus of the bone is decreased. Some manufacturers combine the BUA and SOS values into a single parameter referred to as ''stiffness'' or the Quantitative Ultrasound Index (QUI). These combinations have no particular physical meaning but may improve precision and discrimination by averaging out errors such as those caused by temperature variations (*42*). With most early-generation QUS devices, the patient's foot was placed in a water bath to couple the sonographic signal to the heel. However, most recent devices are dry contact systems in which rubber pads covered with sonographic gel are pressed against the patient's heel.

A major attraction of bone sonography devices is that they do not use ionizing radiation and, therefore, avoid the regulatory requirements for x-ray systems mentioned above. In addition, the instrumentation is relatively inexpensive and several devices, especially among the dry systems, are designed to be portable. Therefore, sonography could be more widely used than conventional DXA scanners, which are largely restricted to hospital-based osteoporosis clinics. Moreover, recent evidence from several large prospective studies confirms that RR values for QUS measurements predicting hip-fracture risk are comparable with DXA (*43–45*).

There remain, however, several limitations to QUS measurements. In general, the fracture studies mentioned above were conducted in elderly populations who were older than 70 y, examined only hip-fracture risk, and used the earlier generation of water-based calcaneal QUS systems. Thus, the success of QUS in predicting fracture risk in younger patients remains uncertain. Another difficulty with QUS measurements is that they are not readily encompassed within the WHO definitions of osteoporosis and osteopenia, which, as emphasized above, should be applied only to BMD measurements at the spine, hip, or forearm (*46,47*). Recently, Kanis and Glüer proposed a more inclusive paradigm in which a measurement of hip BMD would be regarded as the gold standard for the definition of osteoporosis (*48*). For the peripheral methodologies such as QUS, intervention thresholds would be developed so that measurements could be interpreted in terms of a fracture-risk equivalent to that defined for hip DXA.

There are also several technical limitations to QUS. Many devices use a foot support that positions the patient's heel between fixed transducers. Thus, the measurement site is not readily adapted to different sizes and shapes of the calcaneus, and the exact anatomic site of the measurement varies from patient to patient. Furthermore, as a measurement site, the calcaneus has the disadvantage of being particularly sensitive to the amount of exercise the patient takes. The former problem is avoided by imaging QUS systems that perform a raster scan of the heel and ensure a more consistent placement of the measurement site (*49*). Finally, it is generally agreed that the relatively poor precision of QUS measurements makes many devices unsuitable for monitoring patients' response to treatment (*50*). In part, this is

because QUS technology is inherently less stable than DXA, but in some devices this problem is compounded by a lack of suitable anthropomorphic phantoms for adequate instrument quality control.

RELATIONSHIP BETWEEN BONE MEASUREMENT SITES

The spine and femur are generally regarded as the most important BMD measurement sites because they are the sites of the osteoporotic fractures that cause the greatest impairment of quality of life, morbidity, and mortality. Many would still consider spine BMD the optimum measurement because of its sensitivity to the changes associated with aging, disease, and therapy. However, spine BMD has the disadvantage that, with advancing age, measurements are often affected by the presence of degenerative changes that lead to the artificial elevation of BMD values. This becomes an increasing problem after the age of 70 y but can occur earlier. Other clinicians would argue that hip BMD is the most useful measurement, because it is the most predictive of hip fracture (*24*,*27*), which is clinically the most important fracture. In the research community, a consensus is developing that the total femur should be the gold standard for bone densitometry measurements (*48*). In practice, when DXA measurements are performed, spine and hip BMD are usually both available for evaluation.

Because osteoporosis is common and is a primary-care disease, there is a need for a more simple evaluation of BMD than DXA, which is generally found only in large hospitals. There is therefore considerable interest in pDXA and QUS devices, because such systems are smaller and cheaper than DXA. Because osteoporosis is a systemic disease, bone loss is not limited to the axial skeleton. However, correlation coefficients between BMD measurements at different skeletal sites are typically around 0.6 to 0.7, and thus a measurement at 1 site is far from being a perfect predictor of that at any other. Furthermore, whatever intervention threshold is chosen as the basis for initiating treatment, somewhat different groups of patients are selected depending on the measurement site.

The meta-analysis of prospective fracture studies published by Marshall et al. (*24*) provides a basis for evaluating the relative merits of different measurement sites for the assessment of fracture risk (Fig. 2). The data show that, although there is a strong indication that hip BMD measurements are best at predicting hip fracture, the degree to which spine BMD best predicts vertebral fracture or radius BMD forearm fracture is weaker and less conclusive. Furthermore, when assessed by the ability to predict fractures occurring at any site, the RR values are closely comparable for the different measurement sites. Thus, on the basis of the present knowledge, and with the probable exception of hip fracture, the differences between the various BMD measurement sites for predicting future osteoporotic fractures are relatively slight. As discussed above, recent studies now extend this conclusion to include QUS measurements of the calcaneus (*43–45*). In addition to BMD, the statistical models used to analyze fracture studies also incorporate age as an independent risk factor. In general, these studies show that, after adjustment for BMD, each decade of age is associated with a doubling of hip-fracture risk (*27*).

The fact that different patients may be selected for treatment depending on the methodology used is conceptually more difficult, but it should be kept in mind that there is no absolute fracture threshold (Fig. 1). There will always be substantial overlap between measurements from fracture and nonfracture patients, and absolute discrimination between these groups is not possible using any type of BMD measurement. Bone densitometry studies provide a measure of fracture risk that is analogous to assessment of blood pressure with regard to the risk of stroke, or measurement of cholesterol with regard to the risk of developing ischemic heart disease. It is important to distinguish the concepts of risk as applied to an individual and to a population. BMD measurements are well suited to the study of populations, where they are effective in identifying patients who have a higher than average risk of fracture but are less accurate in identifying those individuals who will later sustain a fracture. This is at least partially explained by the fact that although BMD may be the most important single risk factor for fracture, osteoporotic fractures are nevertheless multifactorial and, in addition to low bone density, depend on other issues such as accidents and the propensity to fall.

REFERENCE RANGES

If the WHO criterion of a T-score ≤ -2.5 is used to define osteoporosis, then it is apparent that any errors in the mean BMD or population SD of the reference group might lead to significant differences in the apparent incidence of osteoporosis when applied to other populations. The great majority of centers that have a scanning service use reference ranges provided by the equipment manufacturers, and issues over the accuracy of these ranges have caused controversy in the past (*51*). This continues to be a problematic area in view of the large number of new devices that are being introduced for the assessment of the skeleton. However, for DXA the problem is now largely resolved after a report by the International Committee for Standards in Bone Measurement (ICSBM) (*52*), which recommended that hip BMD measurements should be interpreted using the total femur ROI and the hip BMD reference ranges derived from the U.S. NHANES III study (*53*). The NHANES III project studied a nationally representative sample of over 14,000 men and women with approximately equal numbers of non-Hispanic white, non-Hispanic black, and Mexican Americans. Data were gathered using Hologic QDR1000 densitometers operated from trailers so that subjects from all regions of the United States could be included. The ICSBM report recommends use of the total femur ROI instead of the previously widely used femoral neck site because of its improved precision and the fact that it is the hip region most readily implemented on all manufacturers' systems.

Many centers have already acted on these recommendations, and they are increasingly being used for scan reporting. It is important to note that these changes affect the percentage of patients who are diagnosed as having osteoporosis at the hip. Using the total femur ROI and the NHANES III reference range, fewer patients will be diagnosed as having osteoporosis than using the femoral neck ROI and the manufacturer's reference range (*54*). There is no definite right or wrong answer in this situation. What is more important is to have a consistent approach, and it is certainly highly desirable to have universally accepted DXA BMD criteria for the diagnosis of osteoporosis.

One advantage of presenting bone densitometry results in terms of T- and Z-scores is that they avoid the confusion caused by the raw BMD figures that differ for different manufacturers' equipment (*55*). The ICSBM Committee has addressed this issue by publishing equations that allow each manufacturer to express their BMD values on a consistent scale in standardized units (sBMD: units mg/cm^2) (*52,56*). Their report also included figures for the NHANES III total femur reference data converted into sBMD values.

CLINICAL DECISION MAKING

With the development of new treatments for preventing osteoporosis and the wider availability of bone densitometry equipment, much debate has centered on the issue of the clinical indications for the diagnostic use of bone densitometry and recommendations for the initiation of treatment on the basis of the findings. In the United States, an influential report was published by the National Osteoporosis Foundation (NOF) (*57*). In Europe, similar reports have been issued by the European Foundation for Osteoporosis (EFFO) (*1*), and in the United Kingdom by the Royal College of Physicians (RCP) (*58*).

The NOF report (*57*) included a sophisticated set of guidelines for therapeutic intervention. Various nomograms were developed that incorporate age, BMD, and 4 other risk factors for osteoporosis (Table 2). An interesting aspect of the NOF approach is that the calculations for therapeutic intervention are based on the concept of a quality-adjusted life year, which is approximated to be $30,000. This is a relatively high value and one that would not be considered appropriate for application in Europe. This implies that there may have to be different BMD criteria for therapeutic intervention in different countries. It also follows from the NOF approach that there will be different thresholds for intervention depending on the cost of treatment. Although the NOF report is an extremely important document, with an extensive review of the relevant background information, it is nevertheless complex, and it is unlikely that primary care physicians will instigate treatment on the basis of such a scheme. The NOF subsequently published a physicians' handbook with simplified recommendations that included the availability of BMD measurements for all women over the age of 65 y and in all postmenopausal women under the age of 65 y in whom clinical risk factors are present (*59*). Even if desirable, such a recommendation is simply not feasible in Europe at the present time.

TABLE 2
Risk Factors for Osteoporosis, Additional to Age and BMD, Incorporated in the NOF Guidelines for Therapeutic Intervention

- History of fracture after age 40.
- History of hip, wrist, or vertebral fracture in a first-degree relative.
- Being in lowest quartile for body weight (≤57.8 kg [127 lb]).
- Current cigarette smoking habit.

Data from NOF guidelines (*57,59*).

Clinical guidelines for the prevention and treatment of osteoporosis in the United Kingdom were recently published by the RCP (*58*). The authors concluded that at present, there is no consensus for a policy of population screening using BMD scans. Instead, a case-finding strategy is recommended for referring patients for bone densitometry on the basis of a list of widely accepted clinical risk factors (Table 3). The list is identical to that published in the EFFO report (*1*). The RCP report also recommended a T-score of ≤ -2.5 as the basis for instigating therapy.

It is important to emphasize that the WHO definition of osteopenia ($-2.5 < T < -1$) is not useful in isolation with regard to decisions about treatment, because it captures too high a percentage of postmenopausal women and, in fairness, was never intended to be used in this way. A considerable body of evidence indicates that it is the patients with the most severe disease who benefit most from antiresorptive therapies such as bisphosphonates (*60*). Thus, there seems to be a consensus supporting the use of a T-score of ≤ -2.5 as the appropriate intervention threshold for instigating treatment in white women. However, it is important to take all the other relevant clinical factors into account such as those listed in Tables 2 and 3. In particular, the age of the patient and whether there is a history of previous fragility fractures are important independent predictors of future fracture risk.

No consensus has yet emerged on what intervention thresholds are appropriate in men and other ethnic groups. However, the revised guidelines recently published by Kanis and Glüer (*48*) recommend that the same absolute BMD thresholds applied to white women should also apply to these other groups. There are also difficulties in applying the WHO criterion in elderly persons, because, on the basis of a T-score of -2.5, the majority of women will have osteoporosis. It may be more appropriate to use Z-scores in elderly persons, but at present there is no consensus on how this can best be achieved.

SUMMARY AND CONCLUSION

In the 1990s, large international clinical trials proved the effectiveness of several new treatments for the prevention of osteoporosis, such as bisphosphonates and SERMs. In addition to these developments, the pace of technologic

TABLE 3
Risk Factors Providing Indications for the Diagnostic Use of Bone Densitometry

Category	Risk factor
Presence of strong risk factors	Estrogen deficiency Premature menopause (age <45 y) Prolonged secondary amenorrhea (>1 y) Primary hypogonadism Corticosteroid therapy Prednisolone >7.5 mg/day for 1 y or more Maternal family history of hip fracture Low body mass index (<19 kg/m^2) Other disorders associated with osteoporosis Anorexia nervosa Malabsorption syndrome Primary hyperparathyroidism Post-transplantation Chronic renal failure Hyperthyroidism Prolonged immobilization Cushing's syndrome
Radiographic evidence of osteopenia or vertebral deformity	
Previous fragility fracture, especially of the hip, spine, or wrist	
Loss of height, thoracic kyphosis (after radiographic confirmation of vertebral deformities)	

Data from RCP guidelines (*58*).

innovation was rapid, with the introduction of new radiologic methods for the noninvasive assessment of patients' bone density status. DXA scanning of the hip and spine remains the gold standard, although there is now a wider appreciation of the need for smaller, cheaper devices for scanning the peripheral skeleton if the many millions of women most at risk of a fragility fracture are to be identified and treated. Several sets of guidelines for the clinical use of bone densitometry have been published, and most have included recommendations for intervention thresholds for initiating treatment in white women. The WHO criterion of a T-score ≤ -2.5 has been especially influential, although it cannot automatically be applied to the newer peripheral techniques such as QUS, or in men and patients from other ethnic groups.

At the present time, most experts do not advocate mass screening of the population for osteoporosis, and instead the guidelines recommend a case-finding strategy that is based on identifying patients with generally accepted clinical risk factors. However, with the widespread availability of QUS systems, this view may change. The advantages of QUS outlined above mean that it may have a role in many specialist departments and primary care facilities. However, in view of the large number of commercial devices available, there are concerns about whether all the reference ranges are accurate and appropriate. As emphasized above, the WHO definition of a T-score of ≤ -2.5 cannot automatically be applied to QUS, and there is a consensus emerging toward defining intervention thresholds for peripheral devices on the basis of estimates of absolute fracture risk. It seems premature to advocate the routine use of QUS until these issues have been resolved and appropriate clinical strategies have been agreed on. Nevertheless, it is probable that sonography will be widely used for the assessment of the skeleton within the next 5 to 10 y, and at that point there would effectively be screening for osteoporosis.

REFERENCES

1. Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D, on behalf of the European Foundation for Osteoporosis and Bone Disease. Guidelines for diagnosis and treatment of osteoporosis. *Osteoporosis Int.* 1997;7:390–406.
2. Ray NF, Chan JK, Thamer M, Melton LJ. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. *J Bone Miner Res.* 1997;12:24–35.
3. Chrischilles E, Shireman T, Wallace R. Costs and health effects of osteoporotic fractures. *Bone.* 1994;15:377–386.
4. Jacobsen SJ, Goldberg J, Miles TP, et al. Race and sex differences in mortality following fracture of the hip. *Am J Public Health*. 1992;82:1147–1150.
5. Koval KJ, Skovron ML, Ahanonoff GB, Meadows SE, Zuckerman JD. Ambulatory ability after hip fracture: a prospective study in geriatric patients. *Clin Orthop*. 1995;310:150–159.
6. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D_3 and calcium to prevent fractures in elderly women. *N Engl J Med.* 1992;327:1637–1642.
7. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of the effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet*. 1996;348:1535–1541.
8. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA*. 1999;282:637–645.
9. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med*. 1992;117:1016–1037.
10. Collaborative group on hormonal factors in breast cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet.* 1997;350:1047–1059.
11. Lin JH. Bisphosphonates: a review of their pharmacokinetic properties. *Bone*. 1996;18:75–85.
12. Liberman UA, Weiss SR, Bröll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med.* 1995;333:1437–1443.
13. Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston CC. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. *J Clin Endocrinol Metab*. 1998;83:396–402.
14. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifine on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med.* 1997;337:1641–1647.
15. Lufkin EG, Whitaker MD, Nickelsen T, et al. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. *J Bone Miner Res*. 1998;13:1747–1754.
16. Genant HK, Engelke K, Fuerst T, et al. Noninvasive assessment of bone mineral and structure: state of the art. *J Bone Miner Res*. 1996;11:707–730.
17. Grampp S, Genant HK, Mathur A, et al. Comparisons of non-invasive bone mineral measurements in assessing age-related loss, fracture discrimination and diagnostic classification. *J Bone Miner Res*. 1997;12:697–711.
18. Blake GM, Fogelman I. Technical principles of dual energy x-ray absorptiometry. *Semin Nucl Med.* 1997;27:210–228.
19. Consensus Development Conference. Diagnosis, prophylaxis and treatment of osteoporosis. *Am J Med*. 1993;94:646–650.

20. World Health Organization. WHO Technical Report Series 843. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva, Switzerland: World Health Organization, 1994.
21. Kanis JA, Melton LJ, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. *J Bone Miner Res*. 1994;9:1137–1141.
22. Blake GM, Fogelman I. Interpretation of bone densitometry studies. *Semin Nucl Med*. 1997;27:248–260.
23. Jergas M, Glüer C-C. Assessment of fracture risk by bone density measurements. *Semin Nucl Med*. 1997;27:261–275.
24. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *Br Med J*. 1996;312: 1254–1259.
25. Blake GM, Wahner HW, Fogelman I. *The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry and Ultrasound in Clinical Practice*. 2nd ed. London, England: Martin Dunitz, 1999.
26. Njeh CF, Hans D, Fuerst T, Glüer C-C, Genant HK. *Quantitative Ultrasound: Assessment of Osteoporosis and Bone Status*. London, England: Martin Dunitz, 1999.
27. Cummings SR, Black DM, Nevitt MC, et al. Bone density at various sites for prediction of hip fractures. *Lancet*. 1993;341:72–75.
28. Eastell R. Treatment of postmenopausal osteoporosis. *N Engl J Med*. 1998;338: 736–746.
29. Njeh CF, Fuerst T, Hans D, Blake GM, Genant HK. Radiation exposure in bone mineral assessment. *Appl Rad Isotope*. 1999;50:215–236.
30. Tothill P, Pye DW. Errors due to non-uniform distribution of fat in dual x-ray absorptiometry of the lumbar spine. *Br J Radiol*. 1992;65:807–813.
31. Svendsen OL, Hassager C, Skodt V, Christiansen C. Impact of soft tissue on in-vivo accuracy of bone mineral measurements in the spine, hip, and forearm: a human cadaver study. *J Bone Miner Res*. 1995;10:868–873.
32. Patel R, Blake GM, Batchelor S, Fogelman I. Occupational dose to the radiographer in dual x-ray absorptiometry: a comparison of pencil-beam and fan-beam systems. *Br J Radiol*. 1996;69:539–543.
33. Cann CE. Quantitative CT for determination of bone mineral density: a review. *Radiology*. 1988;166:509–522.
34. Kalender WA. Effective dose values in bone mineral measurements by photon absorptiometry and computed tomography. *Osteoporosis Int*. 1992;2:82–87.
35. Glüer C-C, Jergas M, Hans D. Peripheral measurement techniques for the assessment of osteoporosis. *Semin Nucl Med*. 1997;27:229–247.
36. Cameron JR, Sorensen JA. Measurement of bone mineral in vivo: an improved method. *Science*. 1963;142:230–232.
37. Düppe H, Gärdsell P, Nilsson B, Johnell O. A single bone density measurement can predict fractures over 25 years. *Calcif Tissue Int.* 1997;60:171–174.
38. Patel R, Blake GM, Fogelman I. Radiation dose to the patient and operator from a peripheral dual x-ray absorptiometry system. *J Clin Densitom*. 1999;2:397–401.
39. Faulkner KG. Bone densitometry: choosing the proper skeletal site to measure. *J Clin Densitom.* 1998;1:279–285.
40. Hoskings D, Chilvers CE, Christiansen C, et al. Prevention of bone loss in postmenopausal women under 60 years of age. Early postmenopausal intervention cohort study group. *N Engl J Med.* 1998;338:485–492.
41. Njeh CF, Boivin CM, Langton CM. The role of ultrasound in the assessment of osteoporosis: a review. *Osteoporosis Int*. 1997;7:7–22.
42. Nicholson PH, Bouxsein ML. Influence of temperature on ultrasonic properties of the calcaneus in situ [abstract]. *J Bone Miner Res*. 1999;14(suppl 1):S498.
43. Hans D, Dargent-Molina P, Schott AM, et al. Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. *Lancet*. 1996;348:511–514.
44. Bauer DC, Glüer C-C, Cauley JA, et al. Broadband ultrasonic attenuation predicts fractures strongly and independently of densitometry in older women. *Arch Intern Med.* 1997;157:629–634.
45. Pluijm SMF, Graafmans WC, Bouter LM, Lips P. Ultrasound measurements for the prediction of osteoporotic fractures in elderly people. *Osteoporosis Int*. 1999;9:550–556.
46. Faulkner KG, VonStetton E, Miller P. Discordance in patient classification using T-scores. *J Clin Densitom.* 1999;2:343–350.
47. Delmas PD. Do we need to change the WHO definition of osteoporosis? *Osteoporosis Int*. 2000;11:189–191.
48. Kanis JA, Glüer C-C. An update on the diagnosis and assessment of osteoporosis with densitometry. *Osteoporosis Int*. 2000;11:192–202.
49. Fournier B, Chappard C, Roux C, Berger G, Laugier P. Quantitative ultrasound imaging at the calcaneus using an automatic region of interest. *Osteoporosis Int*. 1997;7:363–369.
50. Glüer C-C. Quantitative ultrasound techniques for the assessment of osteoporosis—expert agreement on current status. *J Bone Miner Res.* 1997;12:1280–1288.
51. Faulkner KG, Roberts LA, McClung MR. Discrepancies in normative data between Lunar and Hologic DXA systems. *Osteoporosis Int*. 1996;6:432–436.
52. Hanson J. Standardization of femur BMD [letter to the editor]. *J Bone Miner Res*. 1997;12:1316–1317.
53. Looker AC, Wahner HW, Dunn WL, et al. Updated data on proximal femur bone mineral levels of US adults. *Osteoporosis Int*. 1998;8:468–489.
54. Chen Z, Maricic M, Lund P, Tesser J, Gluck O. How the new Hologic hip reference values affect the densitometric diagnosis of osteoporosis. *Osteoporosis Int.* 1998;8:423–427.
55. Genant HK, Grampp S, Glüer C-C, et al. Universal standardization for dual x-ray absorptiometry: patient and phantom cross-calibration results. *J Bone Miner Res*. 1994;9:1503–1514.
56. Steiger P. Standardization of spine BMD measurements [letter to the editor]. *J Bone Miner Res.* 1995;10:1602–1603.
57. National Osteoporosis Foundation. Osteoporosis: review of the evidence for prevention, diagnosis, and treatment and cost-effectiveness analysis. *Osteoporosis Int*. 1998;8(suppl 4):S7–S80.
58. Royal College of Physicians. *Osteoporosis: Clinical Guidelines for Prevention and Treatment*. London, England: Royal College of Physicians, 1999.
59. National Osteoporosis Foundation. *Physicians Guide to Prevention and Treatment of Osteoporosis*. Washington, DC: National Osteoporosis Foundation, 1998.
60. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fracture: results from the Fracture Intervention Trial. *JAMA.* 1998;280:2077–2082.