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Bone Density Determination

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Bone mineral density determination is an integral part of the diagnosis, therapeutic planning, and monitoring of a patient with osteoporosis. Although the utility of measuring bone density seems intuitive, decisions must be made regarding whom to test, when to test, which technique to use, and which body site to evaluate. Once a determination has been made, consideration has to be given to what to do with the results. Each patient must be individually considered, incorporating genetic, nutritional, lifestyle, pharmacologic, and endocrine risk factors. Other diseases that may be associated with a reduced bone mass must be excluded.
[Key words: bone mineral density, dual-energy x-ray absorptiometry, osteoporosis] **Spine 1997;22:49S–57S**

■ Definition of Terms

Osteoporosis has been defined as a ". . . disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk."[10] In histologic study, the proportion of bone mineral to bone matrix (osteoid) is normal. It is, therefore, a condition in which the bone is qualitatively normal, but quantitatively abnormal. Osteopenia is a term usually applied to the radiographic finding of reduced bone density.[36] Although osteoporosis is the most common cause of radiographic osteopenia, a number of other pathologic conditions may be responsible for this finding[36] (Figure 1).

In the strict sense of the word, "density" refers to mass per unit volume. Bone densitometry, however, is a term applied to a wide variety of techniques used to measure the mineral content of bone, expressed in grams. The term "bone mineral density" (BMD) as used in clinical practice may thus reflect a surface area (expressed in grams per square centimeter, and areal density) or a true volume (expressed in grams per cubic centimeter).[27]

■ Whom to Test, When to Test

Although mass screening for osteoporosis is not warranted,[43] select patients will benefit from a one-time study to establish the diagnosis of osteoporosis. The largest group encompasses perimenopausal women, especially those with several identifiable risk factors. Younger premenopausal women with prolonged amenorrhea (of more than 6 months' duration) should also be evaluated. Patients who have metabolic diseases or are taking medications that affect the skeletal system may benefit from bone density determination. Finally, a single bone density determination may be useful in premenopausal women with a high number of risk factors, especially if a low value will assist in lifestyle changes that will reduce their risk of fracture in later years.

Once the diagnosis of osteoporosis has been established, subsequent measurements are not indicated unless intervention has been undertaken and periodic reassessment will determine the efficacy of therapy. Because changes in bone density with passing time are slow, it is probably not reasonable to expect a significant change in less than 1 year.[40]

■ Methods

During the past two decades, there has been an explosion in technology designed to assess bone density. A variety of techniques have been used in clinical practice, including nuclear scans, computed tomography, radiography, and ultrasound. When choosing an assessment method, it should be remembered that the site that will be studied is chosen simultaneously. This will determine whether primarily trabecular bone (for example, the calcaneus), cortical bone (the mid radius) or a mixture of both (the spine) is to be evaluated. Reported precision for the different methods overlap (Table 1).

Nuclear Scanning

Nuclear techniques were among the earliest used for measuring bone mineral density in clinical practice. These methods required a long scanning time, and spatial resolution was poor. Nuclear scanning has therefore been largely replaced by other methods.

Single-Photon Absorptiometry. Developed in the 1960s, single-photon absorptiometry uses iodine-125 as a gamma ray source. This method is limited to areas with minimal soft tissues, including the radius (usually the nondominant forearm) and the calcaneus. To correct for overlying soft tissues, the area to be studied is placed in a water bath or surrounded by a material that can be molded around the extremity. Scanning is accomplished in a rectilinear manner.

Dual-Photon Absorptiometry. Dual-photon absorptiometry was developed in the 1970s. It uses an isotope source

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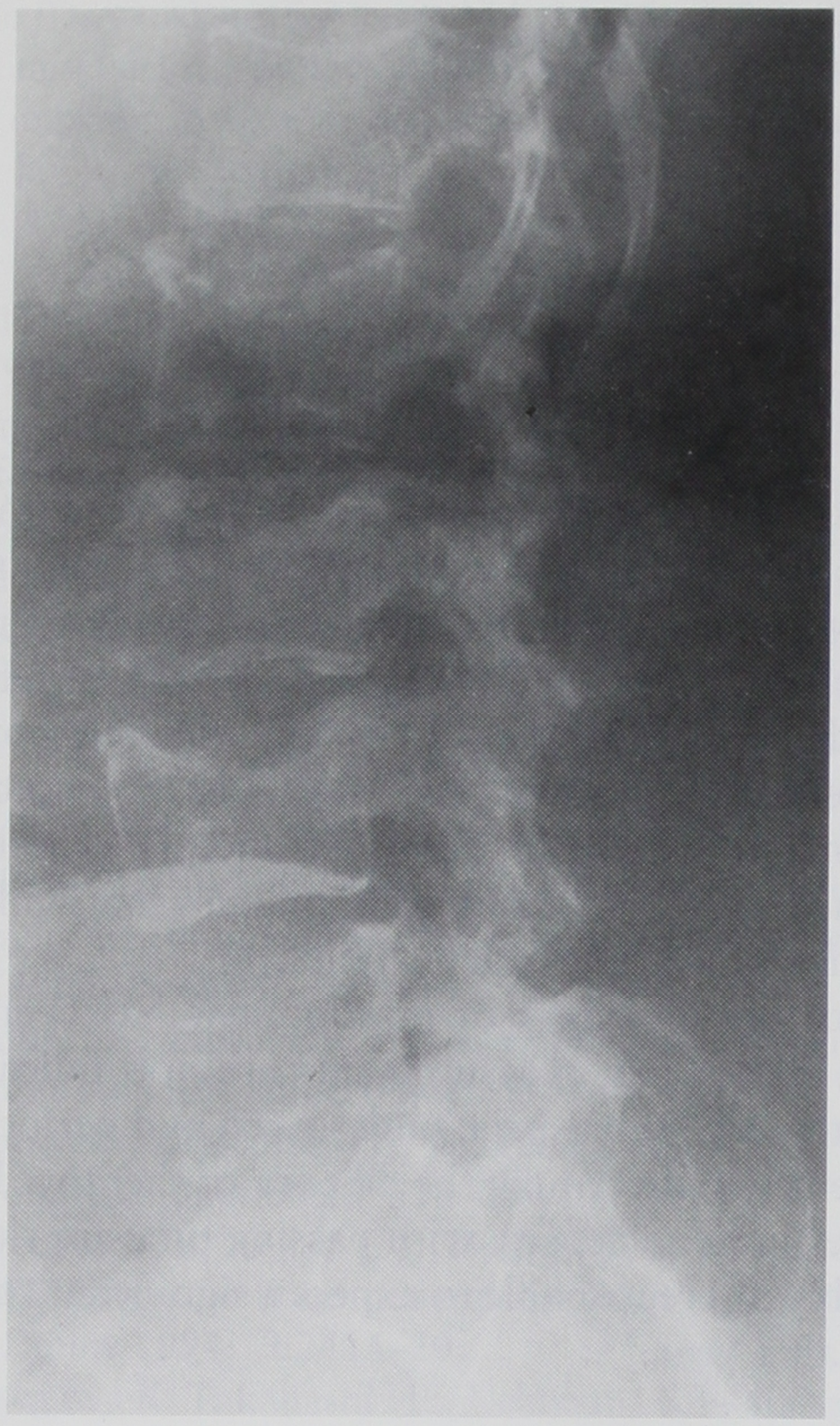


Figure 1. Multiple myeloma. Fifty-two year old woman who had back pain caused by multiple fractures. The lateral lumbar spine radiograph shows profoundly reduced bone density. The diagnosis of osteoporosis is, however, inaccurate.

that emits two discrete energy photons (usually gadolinium[153]). The absorption at each energy level is measured, allowing correction for overlying soft tissues. Attenuation caused by bone tissue is thus calculated without the use of a water bath. Although single-photon absorptiometry is restricted to peripheral BMD measurements, dual-photon absorptiometry can be used to analyze central areas with large or irregular soft tissues, including the spine and hip. A disadvantage of dual-photon absorptiometry compared with single-photon absorptiometry is lower precision because of aging of the source.[44] Source replacement, recommended every 6 to 12 months and mandatory every 18 months, is expensive.[48]

Radiography

Radiographic methods for measuring bone density rely on an x-ray source for photons. With the exception of plain radiography, these methods use a low-dose source.

Plain Radiography. Plain radiography has been used to determine the presence of osteopenia. This method carries a very low sensitivity, in that substantial demineralization must have taken place before it will be evident on radiographs.

The index of Singh et al[49] has been widely used to evaluate osteoporosis in the clinical setting and in research endeavors. This technique evaluates the compressive and tensile trabecular structure of the proximal femur, using an anteroposterior radiograph. Despite its popularity, results of recent studies have shown no correlation between the Singh index and dual-energy x-ray absorptiometry (DXA) measurements.[32]

Radiogrammetry uses a caliper to measure the cortical thickness of a bone on standard radiographs. The metacarpal shafts and phalanges of the hand are most commonly used for measurement.

Radiographic Absorptiometry. Radiographic absorptiometry is used for bone mineral assessment of the second through fourth metacarpal bones. Radiographs of the hand are taken, with an aluminum reference wedge, and cortical and trabecular bone are analyzed. Arguing that this method provides high precision and accuracy, some believe that radiographic absorptiometry should be used when more sophisticated equipment is not available.[59]

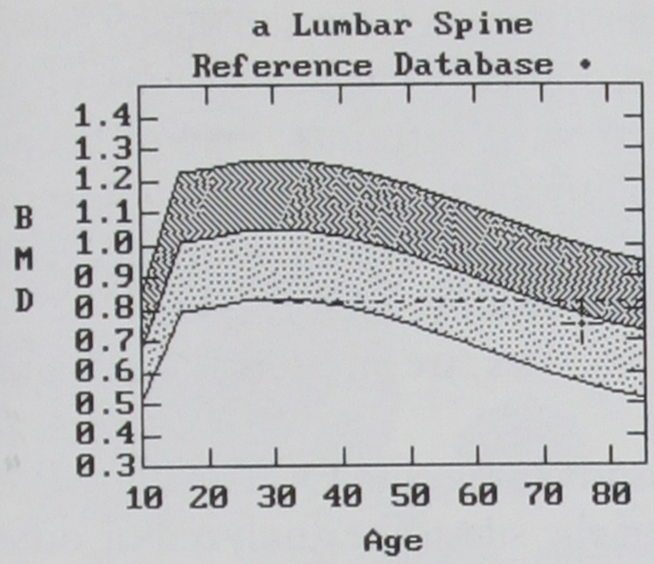
Single-Energy X-Ray Absorptiometry. Like single-photon absorptiometry, single-energy x-ray absorptiometry uses a water bath to correct for overlying soft tissues. The distal radius is usually studied, although the calcaneus can also be used for determination.

Dual-Energy X-Ray Absorptiometry. Introduced into clinical practice in 1987, DXA has largely replaced other methods. Precision and spatial resolution are improved, and scan time is reduced in comparison with that of dual-photon absorptiometry.[17] This technique is usually employed to study the hip and the lumbar spine, but software packages are also available for analysis of the calcaneus and distal radius. Analysis by DXA of the calcaneus has not been a useful adjunct to DXA of the spine[58] but may be used when spine measurements are inaccurate because of severe deformity[57] or prior surgery.

Standard spine DXA analysis includes values obtained in the posteroanterior plane for each lumbar vertebra from L1 to L4 and a total value for the four sites combined. For each site and for the total, the area analyzed (expressed in square centimeters), bone mineral content (expressed in grams), and BMD (expressed in grams per square centimeters) are reported. In the normal person, the area, bone mineral content, and BMD should progressively increase from L1 to L4. Sites that do not follow this orderly progression should probably be eliminated from the analysis (Figure 2), however the use

Table 1. Precision for Various Densitometry Modalities, Expressed as a Coefficient of Variation (%)[54,55]

Radiogrammetry	1–3
Radiographic absorptiometry	1–2
Single photon absorptiometry	1–2
Dual photon absorptiometry	2–5
Dual energy x-ray absorptiometry	1–3
Quantitative computed tomography	2–4
Quantitative ultrasound	1–3

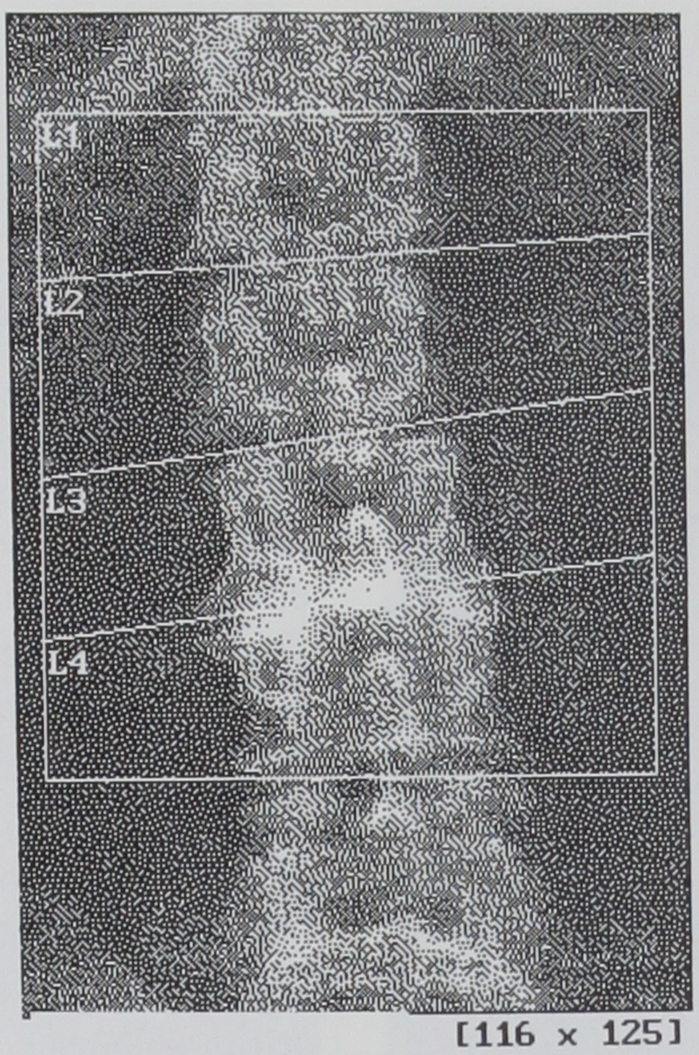


BMD(L1-L4) = 0.742 g/cm^2

Region	BMD	T(30.0)		Z	
L1	0.520	-3.68	56%	-1.50	76%
L2	0.622	-3.69	60%	-1.27	82%
L3	0.839	-2.23	77%	+0.32	104%
L4	0.891	-2.04	80%	+0.58	108%
L1-L4	0.742	-2.77	71%	-0.32	95%

• Age and sex matched
T = peak bone mass
Z = age matched

A



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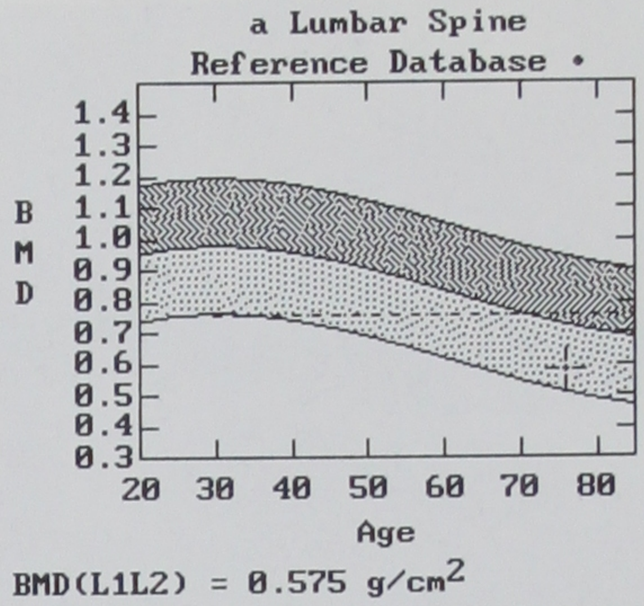
B



BMD(L1L2) = 0.575 g/cm^2

Region	BMD	T(30.0)		Z	
L1	0.520	-3.68	56%	-1.50	76%
L2	0.622	-3.69	60%	-1.27	82%
N/A					
N/A					
L1L2	0.575	-3.67	59%	-1.37	79%

• Age and sex matched
T = peak bone mass
Z = age matched

C

Figure 2. Discogenic sclerosis. **A,** Using L1–L4 for analysis, the *T* score is 2.77 standard deviations below normal. The values for L3 and L4 are substantially higher than those for L1 and L2. **B,** The digital image shows severe end-plate sclerosis at L3–L4. **C,** Reanalysis omitting these two sites further lowers the *T* score to 3.67 standard deviations below normal.

of only one or two sites will reduce the accuracy of the test.[3] It is important that identical sites be used for serial examinations.

Scanning of the hip by DXA evaluates the BMD of the femoral neck, greater trochanter, intertrochanteric region, and the total femur. In addition, a BMD value is reported for Ward's triangle, a region that reflects the cancellous bone found between the stress trabeculae in the femoral neck. Initially believed to reflect the earliest changes in BMD, Ward's triangle is disregarded by most clinicians in their decision making. Until recently, the femoral neck was used for reporting the BMD of the hip. Consensus among manufacturers of the equipment that produces DXA has now led to the use of the total femur, based on the National Health and Nutritional Examination Survey hip reference database.[35]

For each area examined, the BMD is compared with values for sex- and age-matched control subjects (the *Z* score) and to normal, healthy young control subjects at peak bone mass (the *T* score). Although the *Z* score analysis is important in evaluating the younger patient to determine the presence of osteopenia, the *T* score is the value used for clinical decision making in the older population. If the *Z* score were used in the postmenopausal population, a patient might appear relatively "normal" when compared with their peers, and the incidence of osteoporosis would not rise with increasing age, despite decreasing bone mass and an increased incidence of fractures.

Traditionally, evaluation of the spine with DXA has been done in the posteroanterior direction. The measurement thus includes all tissues anterior and posterior to the vertebral bodies, and several artifacts can be introduced. Prevertebral vascular calcifications, discogenic sclerosis from degenerative disc disease, and osteophyte formation from facet osteoarthritis will all falsely raise the measured bone density (Figure 3). Compression fractures may be inapparent on the digital image. Transitional vertebrae are often difficult to identify, rendering identification of vertebral site difficult. Prior surgical procedures will also alter results: previous laminectomy will lower the value, and prior lumbar fusion will raise the value. These latter situations can be avoided through careful screening of the patient before performing the scan. False values for measurements of the hip generally reflect improper positioning or congenital or developmental deformities of the proximal femur.

In an effort to improve the accuracy of DXA in the spine, lateral scanning techniques have been developed. These are performed with the patient supine (not in the lateral decubitus position), rotating the C-arm 90° to the side of the patient. Analysis thus excludes prevertebral vascular calcifications, endplate osteophytic spurs, and the posterior elements. Although attractive, this technique is associated with inherent errors. In the patient with scoliosis, differentiation between vertebrae may be impossible. There is an overlap of the iliac wing with L4 in 14% of patients,[22] and the ribs overlap the L2 body in essentially all patients.[46] It could be argued that this will reduce the precision of the test.

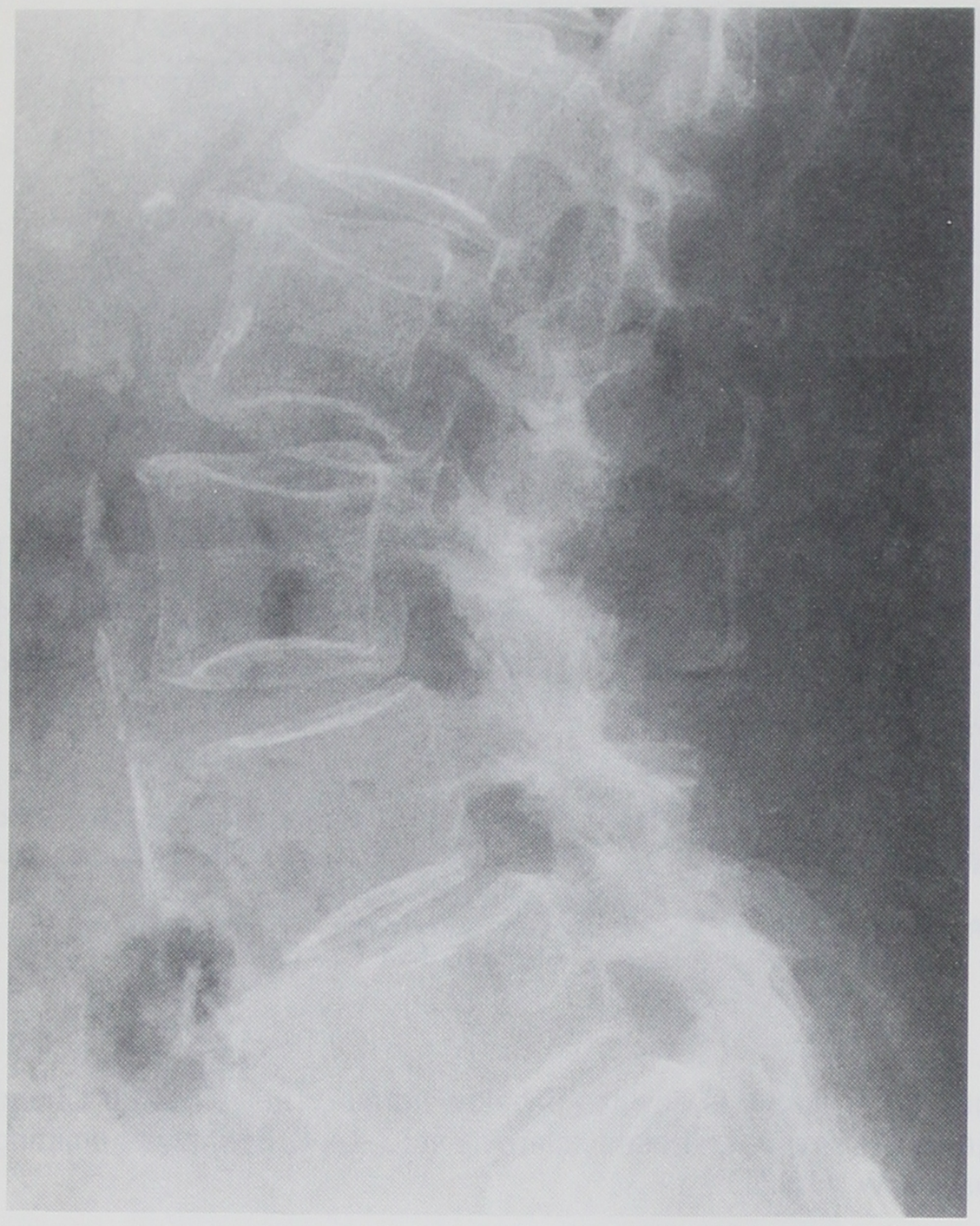


Figure 3. Lateral radiograph of the spine. The vertebral bodies are severely osteopenic. The aortic calcification anteriorly and severe osteoarthritis of the facet joints posteriorly would significantly elevate a bone density measurement done in the posteroanterior projection.

In addition to providing information regarding bone mineral density, DXA may be used to determine total body composition including lean body mass, fat body mass, and total body bone mineral.[50] These determinations are now primarily used for research purposes only. Although it is possible to derive BMD measurements of specific body sites from whole body analysis, these measurements have been shown to be inaccurate and should not replace site-specific measurements for documentation of regional osteopenia.[14]

Computed Tomography

Before the introduction of DXA, quantitative computed tomography (QCT) was the mainstay for clinical determination of BMD. It has been used for central (spine and hip) and peripheral (radius and proximal tibia) sites, and can be performed using single- or dual-energy techniques.[38] Dual energy reduces the error resulting from a high fatty marrow content in elderly patients,[34] but at the price of reduced precision and an increased radiation dose. Single-energy scanning is sufficient for clinical work.

Advantages to QCT include a three-dimensional volumetric analysis, representing a true density measurement. Some consider it to be an advantage that QCT measures only trabecular bone. Although this feature excludes extraneous mineralization from the analysis (vascular calcification, osteophytic spur formation), it has not yet been confirmed with certainty that trabecular bone measurements are more accurate than determinations of cortical and trabecular bone simultaneously. The vertebrae at T12–L3 are usually used for analysis, but some feel that only two sites are needed for adequate precision.[51]

There are several disadvantages to QCT. Minor alterations in localization of the site to be analyzed or differences in placement of the region of interest will significantly reduce precision[30] (Figure 4). This is a critical concept in serial examinations. In a partial attempt to reduce this potential source of error, automated slice selection and placement of the region of interest has been described.[29] This technique is not, however, in routine clinical use. The radiation dose in QCT is substantially higher than that used in DXA, an important consideration when evaluating younger patients who may need serial studies during a prolonged period.

More recently, peripheral QTC has been shown to provide high spatial resolution in high-precision measurements of the forearm.[42] With this method, trabecular and cortical bone can be analyzed independently. In results of a recent comparison study, however, QCT of spine trabecular bone was superior to trabecular and cortical peripheral QCT of the radius in assessment of age-related bone loss and discrimination of osteoporotic vertebral fractures.[20] Widely used in Europe and Asia, this method has not gained substantial popularity in the United States.

Ultrasound

Quantitative ultrasound is a method that has only recently begun to receive widespread attention in the United States. This method usually evaluates the calcaneus, incorporating two ultrasound transducers that are positioned opposite each other. Measurements include the speed of sound, ultrasound velocity through bone, and the broadband ultrasound attenuation of the sound beam. Broadband ultrasound attenuation, the calculation most widely used in clinical practice, is expressed in decibels per megahertz. Measurements can also be made of the tibia cortex, finger phalanges, patella, and ulna.

In contrast with radiographic methods that determine bone density, broadband ultrasound attenuation reflects trabecular orientation and correlates with trabecular structure.[18,39] Broadband ultrasound attenuation has been shown to be comparable to DXA in discriminating between patients who are normal and those who have sustained a fracture,[2,16] and results correlate with vertebral and femoral neck density measured by DXA,[15] single-photon absorptiometry of the distal forearm, and QCT of the lumbar spine.[41] Because broadband ultrasound attenuation measurements appear to be partly independent from bone density, they may be useful in combination with BMD studies.[16]

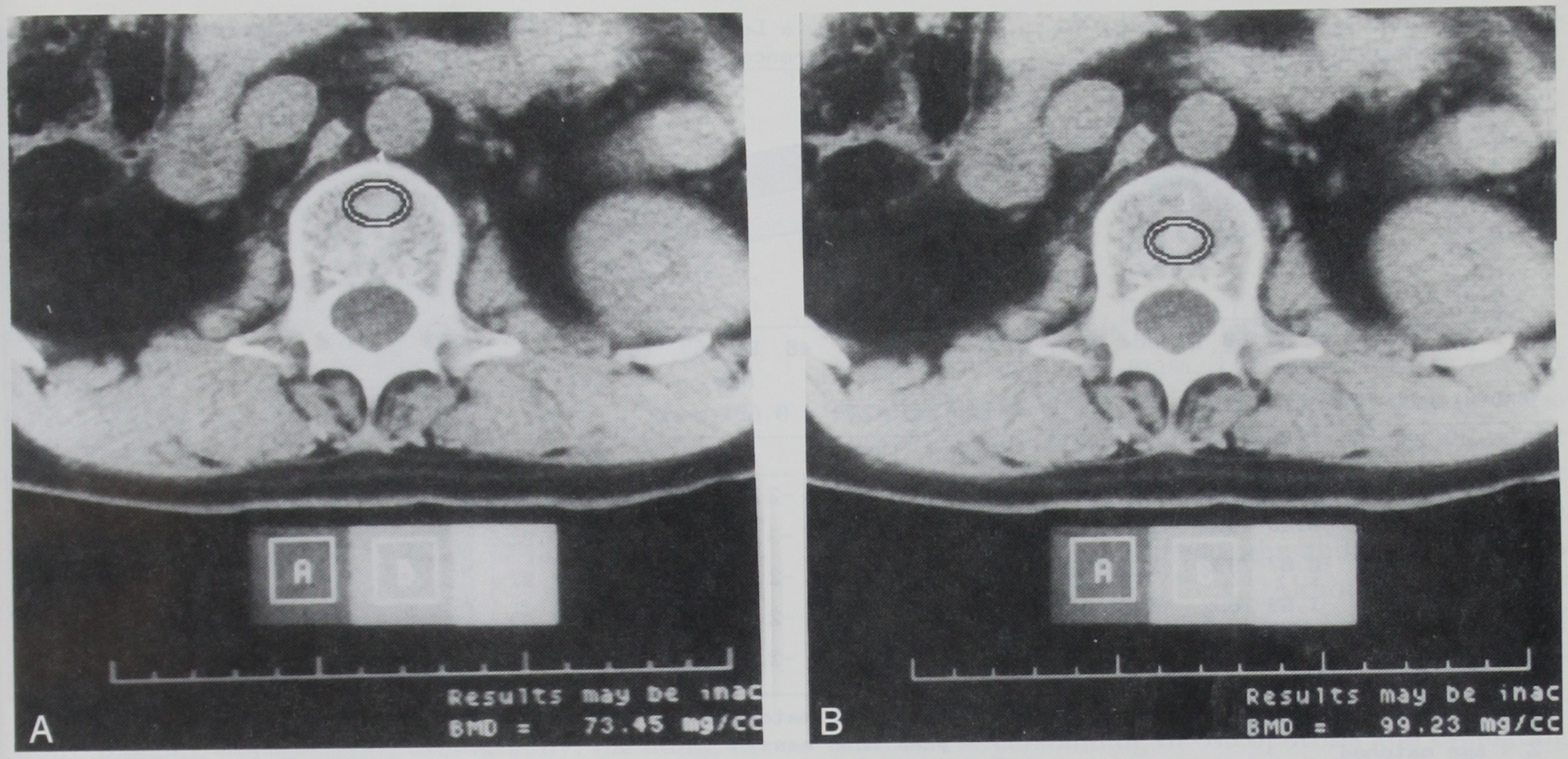


Figure 4. Quantitative computed tomographic scan. Placing the region of interest in the anterior (**A**) *versus* the posterior (**B**) aspect of the vertebral body results in a density difference of 73.45 mg/ml *versus* 99.23 mg/ml.

■ What Test to Use

The decision about which method to use is often one of practicality, depending on equipment availability. In the United States, DXA is widely available and is usually the preferred method. In Asia and Europe, quantitative ultrasound equipment is more widely available and thus used more widely.

Regardless of the method chosen, it should be kept in mind that differences in what is considered "normal" exist between different methods, and between different machines within one method. A measurement with one method therefore cannot be transferred to another and used for comparison.[6] Even less intuitively, a measurement from one machine cannot transfer to another of the same method or even the same manufacturer,[8,9] and reference phantoms for QCT are not interchangeable.[53] It is thus extremely important that sequential studies in a patient be carried out on the same equipment in the same laboratory. Consensus between DXA manufacturers has recently led to the agreement to standardize normal values for DXA, but this is not yet in clinical use.

■ Which Site to Test

The site tested will be a function of the method chosen. One of the more controversial issues regarding which test to use reflects the debate between central *versus* peripheral testing, rather than the specific method used. This controversy has been an important factor in ongoing debates among scientists and manufacturers, and significant research has been undertaken to prove or disprove a relation among different sites. Although it may be true that in a population as a whole one site reflects another,[5] this is probably not true within a person. Many, therefore, feel that the site of greatest interest should be measured (site-specific assessment).[33] In the clinical setting, this may imply that the hip should be the target of the measurement, because hip fractures are associated with higher morbidity and mortality rates than fractures elsewhere. A reasonable second site might be the spine, because vertebral fractures are the most frequent clinical manifestation of osteoporosis. If peripheral testing is done, it appears measurements of the calcaneus, distal radius, and proximal radius are equal in accurately predicting hip fracture.[11] Occasionally, central measurements are impossible to perform or are highly inaccurate. This situation may be encountered in a patient with advanced degenerative disease or multisite compression fractures of the spine and bilateral hip arthroplasty. In this instance, the argument of testing central *versus* peripheral sites is moot, and peripheral measurements should be used.

Contrary to this approach, it could be argued that the accuracy of the test result is the most important factor to consider when making the diagnosis of osteoporosis, whereas precision is of paramount importance in serial testing. Because results from one method cannot be transferred to another, accuracy and precision must be considered when determining which test to use in a patient. In addition, loss of cortical *versus* trabecular bone has been shown to vary depending on the cause of osteoporosis, including the perimenopausal state, the postmenopausal state with establish osteoporosis, anorexia nervosa, corticosteroid use, and hyperparathyroidism.[45] The appropriate choice of method (and thus site) should therefore reflect the underlying cause of bone loss.

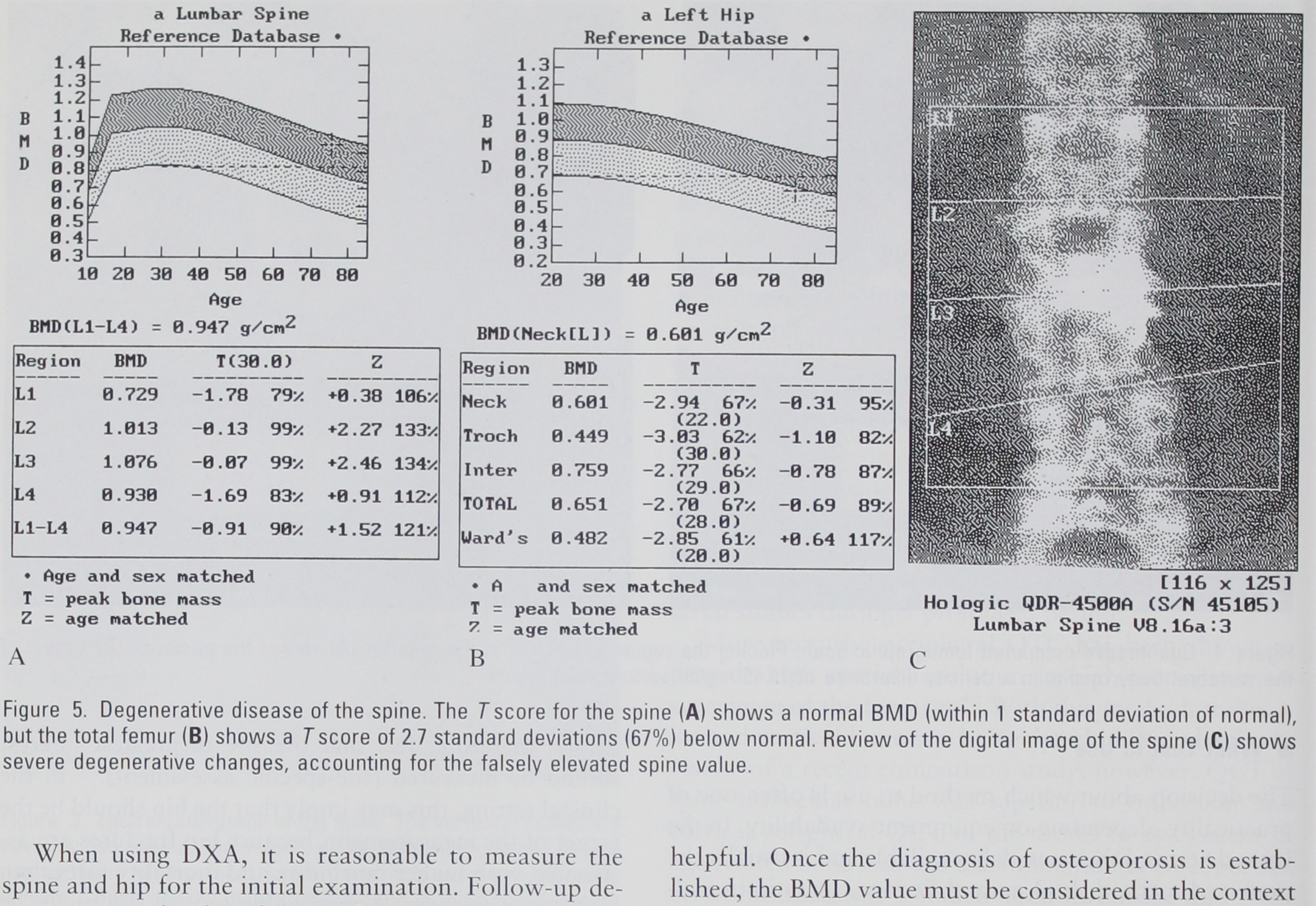


Figure 5. Degenerative disease of the spine. The *T* score for the spine (**A**) shows a normal BMD (within 1 standard deviation of normal), but the total femur (**B**) shows a *T* score of 2.7 standard deviations (67%) below normal. Review of the digital image of the spine (**C**) shows severe degenerative changes, accounting for the falsely elevated spine value.

When using DXA, it is reasonable to measure the spine and hip for the initial examination. Follow-up determinations should reflect the findings of the initial examination. If results of the spine study show advanced degenerative changes or a value that is disproportionately high when compared with that of the hip (Figure 5), follow-up studies are best restricted to the hip measurement. If values for the spine and hip are concordant, measuring both sites will increase the clinical utility of the examination. When evaluating the hip for serial examinations, it is critical to study the same side for all measurements. Although it has been reported that density values for the proximal femur show bilateral symmetry,[4] other investigators have found that density in one hip cannot be used to predict the density of the contralateral side.[1]

■ What To Do With Results

Once a bone mineral density determination has been made, the clinician must decide what to do with the results. Critical to patient treatment, the clinician must establish that low bone mineral content is caused by osteoporosis and not another, perhaps more ominous, process. This is especially important in the younger patient or premenopausal woman in whom a *T* score of more than 1 standard deviation below normal requires a full investigation to determine the cause. Although unusual, multiple myeloma or a previously undiagnosed metabolic disorder may manifest only as low bone density and fracture. Correlation with biochemical markers may be helpful. Once the diagnosis of osteoporosis is established, the BMD value must be considered in the context of the presence and number of risk factors; more aggressive treatment may be indicated in the younger patient who has several contributing risk factors.

In contrast with many common laboratory tests in which a range of normal in the results is established, a continuum exists between reduced bone mineral density and fracture risk, and there is no such thing as a clearly defined "fracture threshold." Defining a strict BMD level for the diagnosis of osteoporosis is thus inappropriate for use in clinical decision making.

Nonetheless, the World Health Organization has established definitions for DXA analysis that are in wide clinical use[31] (Table 2). In this system, a *T* score within 1 standard deviation of normal is considered normal, between 1 and 2.5 standard deviations below normal is considered to represent osteopenia, more than 2.5 standard deviations below normal is assigned osteoporosis, and more than 2.5 standard deviations below normal

Table 2. Standard Criteria for Interpreting Bone Densitometry[31]

Within 1 SD: normal
−1.0 and −2.5: osteopenia
>−2.5: osteoporosis
>−2.5 plus one or more fragility fracture: severe osteoporosis

SD = standard deviation.
Note: The T score (comparison to normal young adults at peak bone mass) is used.

Table 3. Alternative Scheme for Reporting Densitometry Studies

1.0–1.5 SD below: borderline osteopenia
1.6–2.0 SD below: mild osteopenia
2.1–2.5 SD below: moderate osteopenia
>2.5 SD below: severe osteopenia

SD = standard deviation.
Note: The T score (comparison to normal young adults at peak bone mass) is used. This method emphasized the fact that reduced bone density represents a spectrum. It also avoids potential litigation issues that may result from inappropriately assigning the diagnosis of osteoporosis to all individuals with reduced bone density.

with one or more fractures is considered severe or established osteoporosis. Although this set of definitions has served well to bring the magnitude of the issue of osteoporosis to the attention of the public and legislators, it is impractical for use in daily clinical practice. In addition, the definition of a "fracture," at least in the spine, has not been established.[37] Documentation of a fracture may require imaging beyond plain radiography, including radionuclide bone scanning[47] or magnetic resonance imaging (MRI).

When the individual responsible for reporting bone density results does not have access to the clinical profile of the patient under analysis, it is best to refer to a reduced bone mineral density regardless of severity as "osteopenia," to avoid potential litigation issues if the diagnosis of "osteoporosis" is assigned to a patient who has another disorder that is associated with reduced BMD. Some prefer to report a reduced bone density value along a spectrum. For example, a BMD *T* score (either spine or total hip) that is between 1 and 1.5 standard deviations below normal could be considered borderline; between 1.6 and 2 standard deviations below normal, mild; between 2.1 and 2.5 standard deviations below normal, moderate; and more than 2.5 standard deviations below normal, severe (Table 3).

Just as assigning the presence or absence and severity of a disease to the baseline BMD value is arbitrary, assessing the significance of a change in BMD between results of two serial tests also lacks scientific basis. Guidelines have not been established, and values for each patient must be considered in the context of the presence and intensity of intervening therapy. Comparing the percentage of change per year to the standard error for rate of change, a difference of less than 1.5 standard deviations between two examinations is probably not significant. Between 1.5 and 2 standard deviations may be of significance ("borderline significant"), whereas a change of more than 2 standard deviations is probably clinically significant.

In the spine, an increase in BMD may not be caused by intervening therapy. As a person ages, degenerative disc disease and facet osteoarthritis are likely to progress, leading in turn to an increase in the measured BMD when in fact, vertebral body density may be stable or decreasing. For this reason the importance of evaluating the values of the hip and spine simultaneously must be stressed. If consecutive values are discordant (hip decreasing, spine increasing), it is not safe to assume that the increase in the spine is caused by the positive effects of therapy.

■ The Future

Most of the commonly used methods to diagnose osteoporosis measure bone mass. There are, however, other factors that are likely to influence the propensity of a bone to fracture. Structural considerations, including the size and shape of the bone, ratio of cortical to trabecular bone, compensatory remodeling, and trabecular width and interspacing will influence the ability of a bone to withstand stress.[3,7,12,13,23–25,55] Although preliminary work has been undertaken in these areas, this type of analysis is not used in the clinical setting. It seems likely that those attempting to achieve significant future advances in understanding of osteoporosis and evaluating the efficacy of treatment will have to consider other factors in addition to measurement of bone mass.

Quantitative MRI has recently been used to evaluate trabecular structure of bone. Although significant effort has been put into the development of this technique, it remains experimental. Differing magnetic properties of trabecular bone and bone marrow produce inhomogeneities in the magnetic field. As such, transverse relaxation time is altered. This property is especially evident on gradient echo images and is thought to relate to the density of the trabecular network and its spatial geometry.[13] This indirect structural information may reflect bone strength. Quantitative MRI can differentiate between healthy patients and those with osteoporotic fractures,[55] and correlates with BMD as measured with DXA.[56] In results of a recent study evaluating the distal radius with DXA, peripheral QCT, and MRI, healthy postmenopausal and osteoporotic women could only be distinguished with peripheral QCT and DXA, but healthy pre- and postmenopausal women could only be distinguished with MRI.[21]

High-resolution MRI has also been used to depict trabecular bone microstructure (magnetic resonance microscopy).[26] This experimental technique provides high-resolution images of small body parts, showing individual trabeculae and demonstrating their orientation through consecutive images.

Morphometric evaluation of vertebral body shape is also under investigation. Both QCT-and DXA-based morphometry have been developed (morphometric x-ray absorptiometry), providing morphometric and densitometric information from results of the same study. Despite the apparent convenience of this method, conventional film-based morphometric radiography has been shown to have a higher reproducibility and lower error rate than morphometric x-ray absorptiometry.[19,52] Attempts to employ computer processing for morphomet-

ric x-ray absorptiometry image analysis have not proven successful, making the technique labor intensive.[28]

In the more immediate future, there is a need to standardize bone density studies not only among different methods and equipment manufacturers, but also among all races and between the sexes. These will not be small undertakings, but they are essential for individualized patient care.

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