Assessment of Bone Mineral. Part 2

Heinz W. Wahner, William L. Dunn, B. Lawrence Riggs

Mayo Clinic, Rochester, Minnesota

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DIAGNOSTIC PROCEDURES TO ASSESS BONE MASS (CONTINUED)

Single photon absorptiometry. Single photon absorptiometry (SPA) was first described by Cameron and Sorensen in 1963 (*44*) and was developed in an attempt to circumvent some of the problems inherent in the use of film and radiographs in radiogrammetry and radiometry methods. Like radiogrammetry, SPA is applicable only to appendicular bones because tissue composition surrounding the bone has to be uniform and minimal. As in radiometric techniques (and in contrast to radiogrammetry), cortical and trabecular bone components are not separated, and the entire bone at a cross-section is assayed. Information as to whether bone loss occurs on the endosteal or periosteal bone envelope is not available from this method. Changes in the Haversian envelope (porosity), however, are reflected in this measurement but cannot be recognized as such. The unit of measurement, Bone mineral content (BMC), is grams of ashed bone per centimeter of axial length (Fig. 3). Initially bones of the hands were measured, or the humerus, femur, tibia, mandible, and calcaneus, but the greatest experience has been collected with the forearm bones as scanning sites. Because of easy access to the forearm, better reproducibility is achievable there than at most other sites. The method is also used in veterinary practice.

For reprints contact: H. W. Wahner, MD, Section of Diagnostic Nuclear Medicine, Mayo Clinic, 200 First St. SW Rochester, MN 55905.

Figure 1 (see *J Nucl Med* 25: 1136, 1984) shows the distributions of cortical and trabecular bone along the radius. Frequently used sites on the radius are distal portion (10% of the total length from styloid process of the ulna), distal third of radius, and mid radius. Measurements on ulna and radius together at the distal end of the radius are also used by some investigators (*45*). The very distal end of the radius is predominantly trabecular bone (*46*) but is difficult to reposition, and this site may be influenced by changes in the joint such as synovitis. The very distal end of the radius is attractive as a measuring site because its cortical-to-trabecular bone ratio is similar to that of the spine, but for the above reasons it has not been used to predict spinal bone mineral.

Instrumentation. The typical measuring device used for SPA consists of a Na(Tl) scintillation detector and a 200-mCi I-125 source, held rigidly in parallel opposed geometry and is motor-driven in a direction across the longitudinal axis of the radius.

Figure 4 is a schematic drawing of the complete system. Several different instruments of good quality are available from commercial sources.

Principle of measurements. The thickness of bone mineral (T_b) in the path of the photon beam is given by the following equation:

$$T_b = [\ln(I_o^*/I]/(\mu_b\rho_b - \mu_s\rho_s)$$

By convention I_o is the beam intensity in air and I_o^* is the intensity after passage through tissue. I is the beam intensity after passage through bone and tissue. The

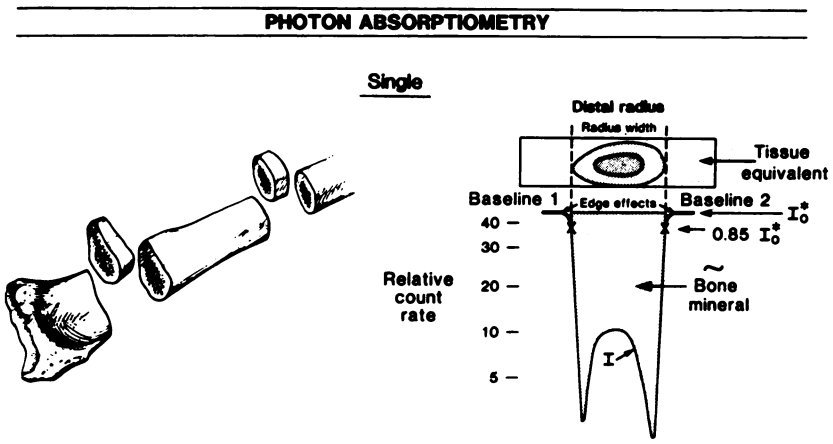

FIG. 3. Left panel: unit of measurement is gram of ashed bone per 1 cm of axial length. Right panel: Logarithm of count rate is plotted on graph paper by analog recorder. Area of logarithmic plot is proportional to bone mineral content in scanning path. This can be expressed in computer units or converted to bone mineral content (g/cm) by an experimentally obtained factor. Calculation of bone mineral content and bone diameter can be performed graphically with planimeter or by programmed small desk computer. All commercial instruments have automatic readout device that relieves investigator of all calculations. See text for explanation of terms.

mass absorption coefficients of bone mineral and tissue are μ_b and μ_s, and the densities of bone mineral and tissue are ρ_b and ρ_s, respectively. These values are constants and do not change in bone disease. A plot of I as a function of position across the bones gives a profile through the radius, as shown in Fig. 3. The integration of this curve between the limits defined by I and corrected for edge effect, as shown in Fig. 3, yields a value proportional to the cross-sectional area of the radius and to the amount of bone mineral in the section of the radius scanned. The factor 0.85 corrects for an edge effect when the beam passes from tissue to bone, and depends on beam size and photon energy. The mineral content is determined from a calibration of the system with 1 cm thick ashed pieces of human radius with known bone mineral content, surrounded by tissue-equivalent material. Details of the calibration procedure and description of a typical instrument are in Ref. *47*.

Instrument performance. The precision in clinical studies with the instrument as originally designed (one path through radius) is about 5%, even when ashed bones are scanned under water (*48,49*). The greatest problem in improving reproducibility is the difficulty of accurate repositioning of the bone site for repeated measurements. Five percent precision is not sufficient for clinical or research applications, particularly when a treatment effect is under investigation. To improve this reproducibility, modifications on the original design have been introduced in different instruments, such as multiple paths about 1 mm apart, with data averaging; a light or laser beam and a water bath (instead of a plastic tissue equivalent material) for better positioning of the scanning beam; or an automated positioning algorithm based on the distance between radius and ulna. These modifications have resulted in a CV of 1 or 2% in the study of subjects. This is achievable with most commercial instruments under strictly controlled conditions.

Clinical relevance. Accuracy can be considered at three different levels. First, accuracy of measuring bone mineral at the scanning site can be determined by

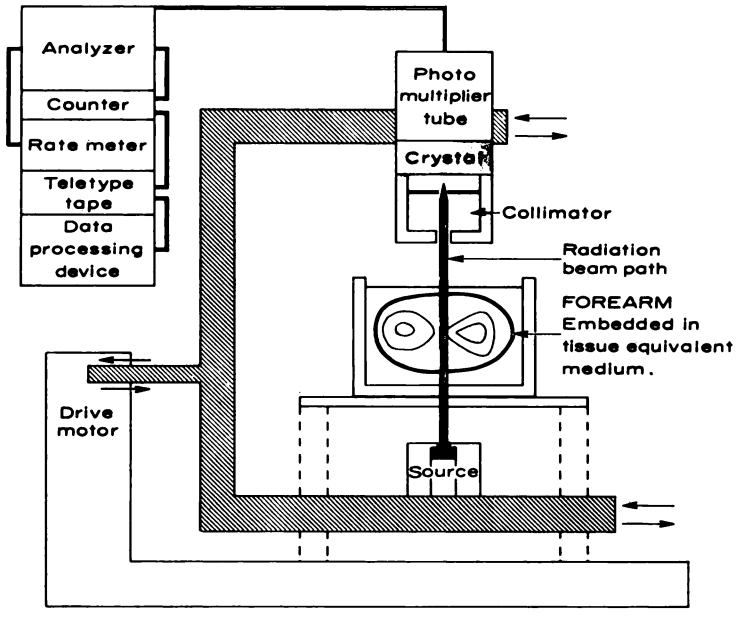

FIG. 4. Schematic of single-photon absorptiometry instrument for forearm measurements. Typical instrument can be used for several measuring sites along forearm and bones of hand. If humerus, femur, or tibia are used, an americium source should be used instead of I-125. Water-filled bag, plastic tissue-equivalent material, or waterbath are used to surround extremity to simulate constant thickness in soft tissue. From Riggs BL, Jowsey J, Kelly PJ, Wahner HW: *Med Clin North Am* 54: 1061, 1970. By permission of W. B. Saunders Co.

TABLE 4. COEFFICIENTS OF CORRELATION BETWEEN TOTAL WEIGHT OF SKELETON AND BONE MINERAL CONTENT (BMC), MEASURED IN 23 NORMAL SKELETONS

Location of BMC measurement	r	s.e.e. (%)*
Radius (distal part)	0.86	12.6
Radius (proximal part)	0.76	16.2
Ulna (distal part)	0.78	15.7
Ulna (proximal part)	0.84	13.7
Femur (distal part)	0.90	10.7
Femur (proximal part)	0.89	11.6
Humerus (distal part)	0.82	14.5
Humerus (proximal part)	0.88	12.0
Tibia (distal part)	0.82	14.5
Tibia (proximal part)	0.84	13.8
Calcaneus	0.59	20.3
Radius + ulna (distal parts)	0.85	13.1
Radius + ulna (proximal parts)	0.87	12.6

* Mean standard error of estimate (s.e.e.). From Christiansen C, Rodbro P: Estimation of total body calcium from the bone mineral content of the forearm. *Scand J Clin Lab Invest* 35:425–431, 1975.

scanning excised radius bones and relating the results to the ashed bone weight of the piece actually scanned (Fig. 4). Second, accuracy is measured in predicting bone mineral at different skeletal sites. For this, bone-mineral results from the scanning site are correlated with the ash weights of different parts of the skeleton, such as other long bones or the vertebrae. Third, accuracy in predicting total body calcium is determined by correlation of BMC with results from total-body neutron activation analysis. The most critical factor affecting accuracy is tissue fat which, because of its absorption properties, will indicate too little bone mineral.

A number of studies performed on excised bones and in vivo have shown that in the normal population bone-mineral measurements made at the radius are highly correlated ($r = 0.9$) with BMC at sites in other long bones and with the total skeletal weight or total body calcium (*50–54*). This would be expected, since 80% of the skeleton is cortical bone. Prediction of total skeletal calcium from the BMC of the distal radius in a single patient incurs a minimum error of about ±200 g Ca (*55*). A list of several appendicular bone sites, with the correlations between their BMCs and total skeletal weight in a normal population, is given in Table 4. Normalized radius measurements also correlate highly ($r = 0.95$) with the density of samples from the iliac crest (*56*). Correlations between BMC at long-bone sites and the femoral neck are lower (15% s.e.e., Ref. *57*), and are worse for the spine, with 20% to 25% error (*58,59*).

Clinical application. As in radiogrammetry, the value of BMC measurements is greatly enhanced by studying well-defined samples from more than one subject. The study of treatment effect on loss of bone mineral usually requires measurements every 4 to 6 mo over a period of 2 yr when individuals or small numbers of patients are being used. The method has been used successfully to demonstrate reduction of total skeletal calcium in patients taking drugs known to reduce bone mineral, to show that total skeletal calcium can be increased with small doses of vitamin D, and has been applied to various metabolic bone diseases. If appendicular skeletal sites are measured in cases of preferential trabecular bone loss, such as in osteoporosis, this leads to an overestimation of total skeletal calcium and spinal bone mass. The chronically poor performance of bone-mineral measurements on the forearm for detection of osteoporosis can thus be explained. Localized cortical and trabecular bone loss at the distal radius in patients under steroid treatment for rheumatoid arthritis has led to underestimation of total body calcium and spinal bone mass (*59*). If the radius is used for screening, it should be realized that low radius bone mineral indicates a high probability for concomitant low total skeletal calcium and low spinal bone mineral, but a normal value does not exclude spinal osteoporosis. Radius BMC may be of more value in predicting bone loss at the hip than in the spine. It seems doubtful whether forearm BMC can be used reliably enough to diagnose and quantify early bone loss in osteoporosis or most of the other metabolic bone diseases.

Well-defined normal ranges for the two radius sites have been reported for different populations. Qualitatively, all appendicular bone sites measured have behaved in a similar manner, but the magnitudes of the changes vary with the specific bone site and are probably influenced by the contribution of trabecular bone to the total measurement (*60*). Bone mineral, measured as BMC, increases with age in infancy, and there is no sex

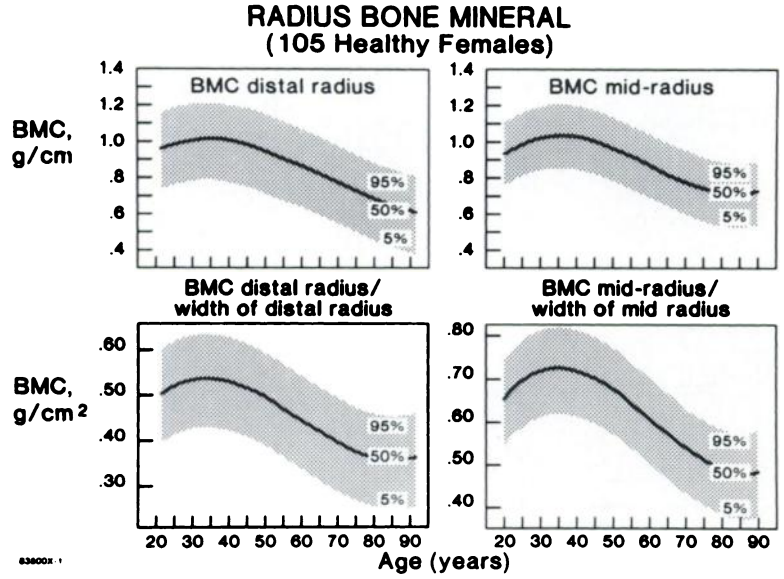

FIG. 5. Normal BMC at distal tenth of radius length and at mid radius, in women at varying ages, from cross-sectional study performed in our laboratory. Data are expressed as g/cm (BMC) and normalized (g/cm^2).

difference. With puberty a marked increase of BMC can be recognized in males. For both sexes the maximum BMC is reached about 30 to 35 yr of age, with males having a higher bone mineral content. After that age BMC declines gradually in males, but more rapidly in females. The highest rate of loss occurs around the menopause, with lesser loss after about 65 years of age. This bone loss is slightly more pronounced at the distal radius site where there is more trabecular bone. From age 51 to 65 yr bone mineral diminishes at rates of 0.0118 and 0.0108 g/cm per year, respectively, at the distal and mid-radius sites. The age-related bone loss at old age from maximal values in young adult life is about 30% for the mid radius and 39% for the distal radius. In men, where the decline in BMC with age is linear, the annual loss is 0.0032 g/cm per year for the distal radius, and is insignificant for the mid radius (*61*). Data for bone loss of similar magnitude have been obtained in other studies. Attempts to reduce this variation by normalization based on height, weight, surface area, body potassium, or creatinine excretion, have not been satisfactory (*62*). A normalization based on the width of the radius at the measuring site (BMC/width, g/cm^2) is probably the best approach to correct for differences in skeletal size. In longitudinal studies on the same patient or in the study of large populations, such a correction is not necessary. Results from a typical population study are given in Fig. 5. Dosimetry measurements were conducted to measure patient radiation dose from single photon absorptiometry of the radius utilizing I-125 and four passes 1 mm apart. In this study, the dosimetry was determined with LiF thermoLuminescent chips

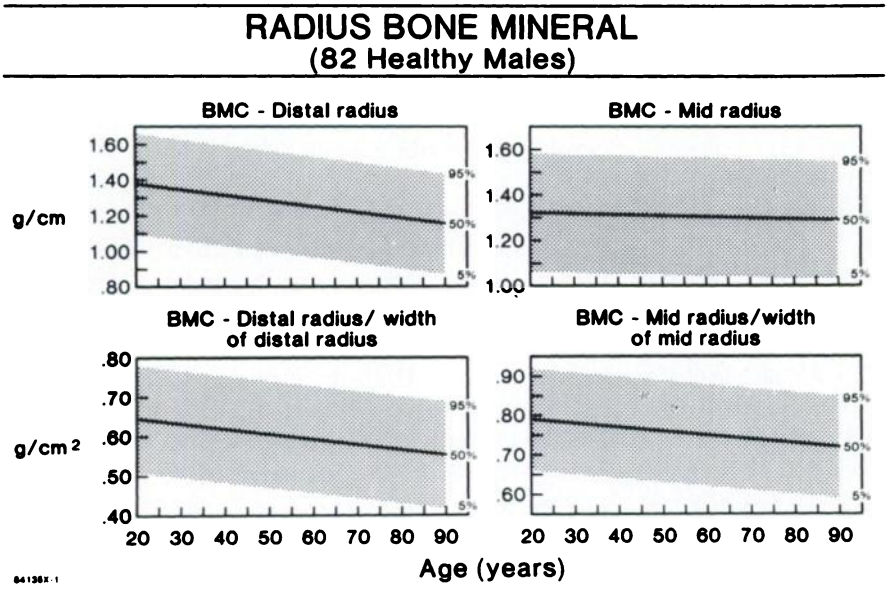

FIG. 6. Normal BMC at distal tenth of radius length and at mid radius for men. See Fig. 5 for more details.

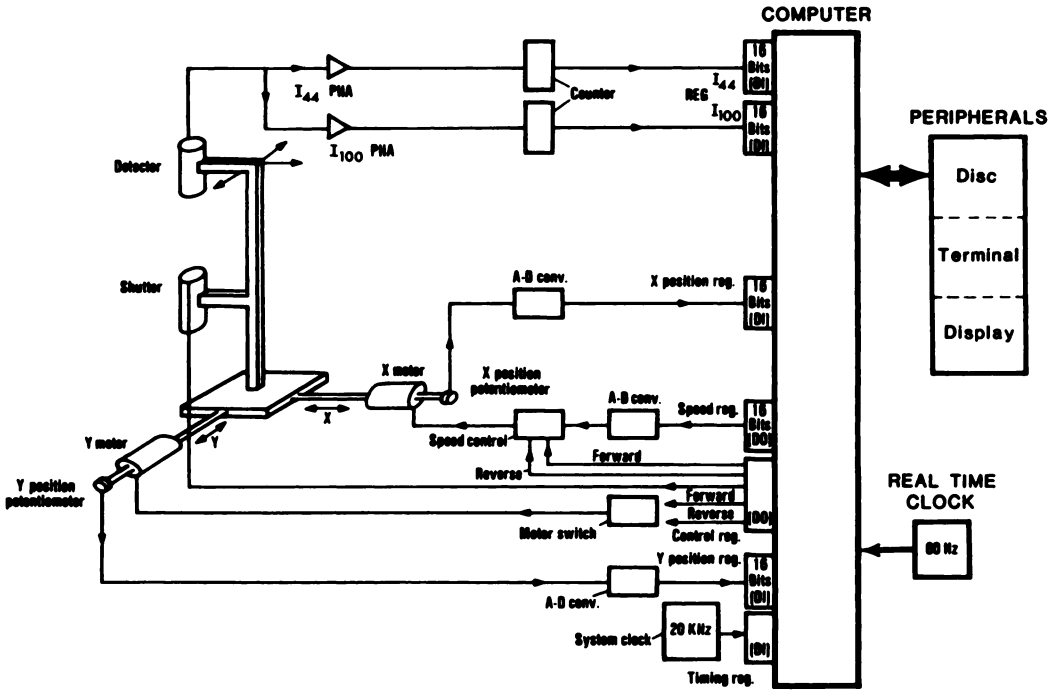

FIG. 7. Schematic of typical instrument for dual-photon absorptiometry. PHA = pulse-height analyzers. (From Dunn, W. L., Wahner, H. W., and Riggs, B. L.: Measurement of bone mineral content in human vertebrae and hip by dual-photon absorptiometry. *Radiology* 136:485, 1980). By permission of the Radiological Society of North America.

(TDL-100) and read with a Harshaw model 2000-A analyzer. Peak skin dose with background measured at both eye and gonad sites was 13 mrad.

Dual-photon absorptiometry (DPA). This technique, developed by Reed (*63*), Roos (*64,65*), and Mazess (*66*), was adapted for total body calcium and lumbar spine measurements by Wilson and Madsen (*67*), and Madsen, Peppler, and Mazess (*61*), and for the hip by Dunn, Wahner, and Riggs (*69*). Its principal effectiveness is to eliminate the effect of soft tissue on the absorption measurements, and its main application has been to measure bone mineral in lumbar spine and hip, and total skeletal calcium. From total skeletal measurements, specific regions of interest can be defined for any desired part of the skeleton.

Instrumentation. A typical dual-photon bone-mineral analyzer consists of a whole-body scanner frame, a 1.5-Ci Gadolinium-153 source, and a NaI(Tl) detector. The system is interfaced to a computer. Several such instruments are available commercially. A block diagram of the instrument constructed in our laboratory is given in Fig. 7 (*69*). Pulses from the NaI(Tl) scintillation detector are amplified and conveyed to two pulse-height analyzers, one set for 44 keV and the other for 100 keV. En route to the computer the output of each analyzer passes through a digital counter that accumulates the number of transmitted photons detected in each second of scanning. This number is recorded on disk for subsequent calculation of a point M_{bm} value. Corrections are made for resolving time (2.3 μsec) and for spillover from the 100-keV channel to the 44-keV channel (5%). In the one second during which data for a point M_{bm} value are obtained, a distance of ~1.2 mm is scanned. Because of high counting rates in air and pulse pile-up problems, the I_0 values are extrapolated from measurements made in water.

The mechanical scanning system was constructed from a dual-probe scanner. The current device includes only the table, yoke assembly, and drive mechanism of the original system. The lower detector was removed and replaced with a shielded holder for the gadolinium-153 source. This holder includes the collimator and a beam shutter that can be activated by hand or by computer. The upper detector was replaced with a collimated 2.5 cm diam × 1 mm thick NaI(Tl) detector. The source-detector separation is 40 cm. The bores of the source and detector collimators are both 6 mm in diameter.

A constant-speed stepping motor controls the cephlocaudad movement (y direction) of both the source and the detector. The lateral motion (x direction) of the assembly is controlled by a variable-speed stepping motor. Both motors are driven by computer-generated signals during the scan. High-resolution potentiometers are linked mechanically to each motor, and provide x and y positional information to the computer. The desired scanning speed in the x direction is entered into the computer and stored in the x speed register. The digitized x speed is converted to an analog voltage signal by a digital-to-analog converter, and this signal is directed

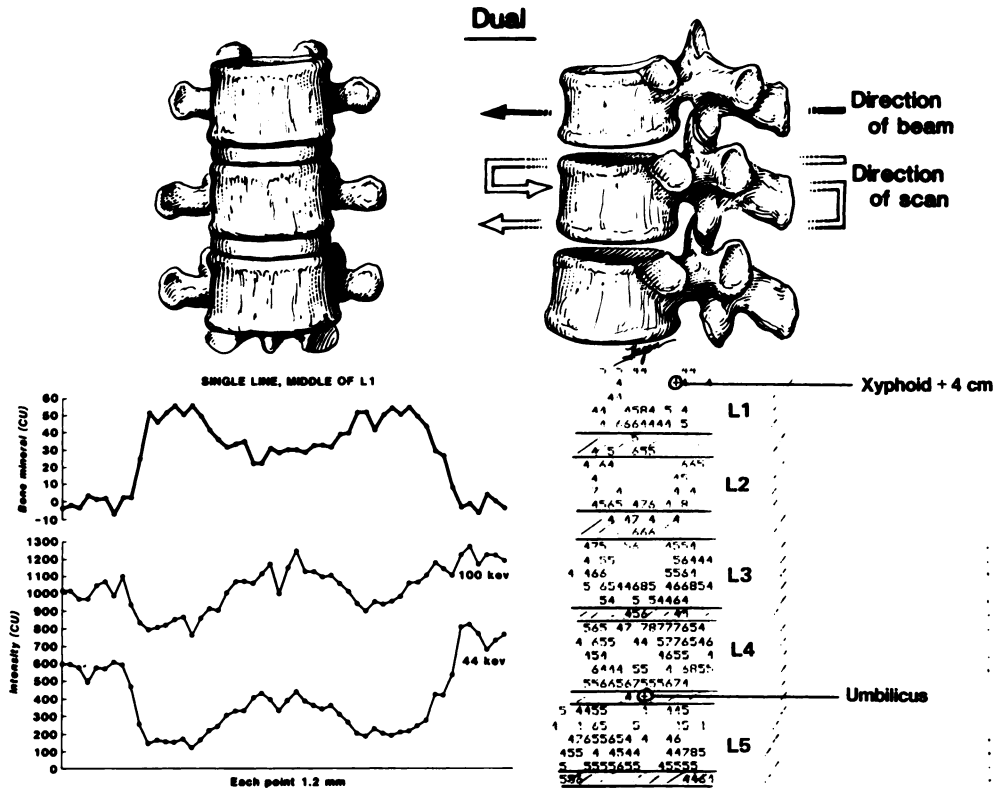

FIG. 8. Dual-photon absorptiometry. Posteroanterior (sagittal) direction of photon beam is indicated. Values are expressed as g per cm^2 area of bone scanned projected onto anterior surface. Records for each of two energies, for one pass across vertebra, are shown at lower left, with thick line representing calculated bone mineral for each point. At lower right is character plot for final bone-mineral data.

to the variable-speed control unit in order to set the desired x speed. Because the accuracy and reproducibility of the bone-mineral measurement depend on the constancy of the scanning speed, it is necessary to monitor the speed continuously. The output of the x-position potentiometer is fed through an analog-to-digital converter to the x-position register. This digitized positional information is compared with the elapsed time and the desired x speed, to determine whether the true scanning speed is in error. If the scanning speed is not correct, an "error" message is printed at the computer keyboard. The step between scanning lines is adjustable. For the studies reported here this was fixed at 4.5 mm.

The 44-keV channel output is directed to a logarithmic amplifier and displayed on a cathode-ray tube (CRT) with storage capability. This display of the 44-keV count rate is helpful in positioning the patient, locating bone edges, and identifying technical artifacts during scanning.

The data on bone-mineral content acquired during scanning can be displayed either as a numerical printout with a character plot, or as an intensity-modulated image (Fig. 8).

Principle of measurements. The method is based on measurements of the transmission of two separate photon energies through a medium consisting primarily of two materials, bone and soft tissue. With a Na(Tl) detector, the gadolinium-153 energy spectrum has photoelectric peaks at approximately 44 and 100 keV (europium K x-rays, 42 and 48 keV; gammas at 97 and 103 keV, Fig. 9).

Equations 1 and 2 describe the transmission of each photon energy through a medium composed of bone and soft tissue.

$$I^{44}x,y = I_o^{44} \exp[-(\mu/\rho)_{st}^{44} \cdot M_{st} - (\mu/\rho)_{bm}^{44} \cdot M_{bm}] \quad (1)$$

$$I^{100}x,y = I_o^{100} \exp[-(\mu/\rho)_{st}^{100} \cdot M_{st} - (\mu/\rho)_{bm}^{100} \cdot M_{bm}] \quad (2)$$

$I_{x,y}^{44}$ and $I_{x,y}^{100}$ refer to the transmitted radiation intensity at a point x,y for 44 keV x-rays and 100 keV gamma photon energies, respectively. I_o^{44} and I_o^{100} are the unattenuated photon intensities. The mass attenuation coefficients for soft tissue (st) and bone mineral (bm) at energy A are represented by (μ/ρ)st and (μ/ρ)bm, re-

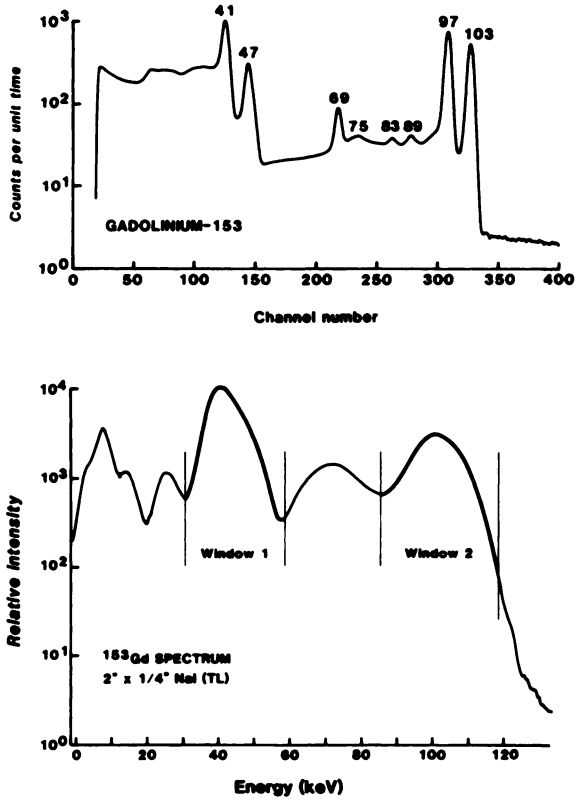

FIG. 9. Pulse-height spectra for gadolinium-153 in air. Above: With Ge(Li) detector, and below with NaI(Tl).

spectively. The masses per unit area (g/cm^2) for tissue and bone mineral are indicated by M_{st} and M_{bm}. Solving these two equations simultaneously yields the following equation for bone mineral:

$$M_{bm} = \frac{RST(\ln I^{100}x,y/I_o^{100}) - (\ln I^{44}x,y/I_o^{44})}{(\mu/\rho)_{bm}^{44} - RST(\mu/\rho)_{bm}^{100}} \quad (3)$$

where $RST = (\mu/\rho)_{st}^{44}/(\mu/\rho)_{st}^{100}$ (For explanation see later in text.)

In the measurement of bone mineral, the anatomic region of interest is scanned, and a point-by-point determination of bone mineral is made. The total bone mass is determined by summing the individual M_{bm} point values. The RST value is averaged over all of the extraosseous area scanned, and the average RST is used to calculate M_{bm}.

The actual absorption coefficients for soft tissue do not need to be determined. The RST is calculated from the measured radiation intensities, as shown here:

$$\left.\begin{aligned} I^{44}x,y &= I_0^{44}\exp[-(\mu/\rho)_{st}^{44}\cdot M_{st}] \\ I^{100}x,y &= I_o^{100}\exp[-(\mu/\rho)_{st}^{100}\cdot M_{st}] \end{aligned}\right\} \text{In tissue only}$$

$$\ln(I_o^{44}/I^{44}x,y) = (\mu/\rho)_{st}^{44}\cdot M_{st}$$

$$\ln(I_o^{100}/I^{100}x,y) = (\mu/\rho)_{st}^{100}\cdot M_{st}$$

$$(\mu/\rho)_{st}^{44}/(\mu/\rho)_{st}^{100} = \ln(I_o^{44}/I^{44}x,y)/\ln(I_o^{100}/I^{100}x,y) = RST$$

If bone-edge detection is not effective, intensites obtained within the bone may erroneously affect the calculated RST. For this reason it is necessary to have an effective routine for bone-edge detection. The bone's surface area and edge limits are defined by an edge-detection routine based on the change in the magnitude of M_{bm}.

Instrument performance. Long-term stability of instruments for DPA has been established. In our laboratory repeated measurements on standard phantoms performed over 9 mo show a coefficient of variation of 1.8%. Precision of measurements tested on patients or volunteers is about 2-3% (CV) in different laboratories, for both spine and hip. Studies on accuracy of DPA for total body calcium have been performed with total-body neutron activation analysis (*69*), and showed a coefficient of variation of 0.99%. A standard error of 3% has been reported for studies imaging DPA of excised lumbar spine vertebrae and measuring their ash weight (*67*).

The instruments are available from several commercial vendors with similar specifications. The capabilities of these instruments range from measurements of total skeletal calcium by DPA, to instruments for spine and hip, to instruments for spine alone.

Clinical applications. DPA of the spine or hip can be performed without specific preparation on any patient able to remain supine for about 30 min. There are a few relative contraindications that need special attention during data interpretation. There are patients with severe deformities, prior spinal surgery, severe spinal degenerative disease, or focal spinal disease such as Paget's or metastasis and in these patients the spinal bone mineral is a reflection of their local disease, and general statements regarding normality and fracture risk are not applicable. Metallic orthopedic devices or metallic objects on clothing my result in uninterpretable scans. This is generally quite apparent from the scan pattern. Recent barium contrast radiographs of the gastrointestional tract or radionuclide tests may interfere with the study.

Patterns of bone loss in the axial skeleton (spine and hip) with aging and in osteoporosis have been studied and compared with that of cortical bone in the radius (*61*). In normal women mineral loss from the vertebrae begins at about 30 to 35 yr, and is linear. When examined in cross-sectional studies, however, a slight increase in rate of loss at the time of menopause has been found by several investigators and by us in a longitudinal study. Overall bone diminution throughout life was 47% for the lumbar vertebrae (Fig. 10). In normal men, age-linked bone diminution in the spine was minimal. Similar observations have been made for the hips (Fig. 11). In women, overall decrease during life was 58% in the femoral neck, 53% in the intertrochanteric region. For

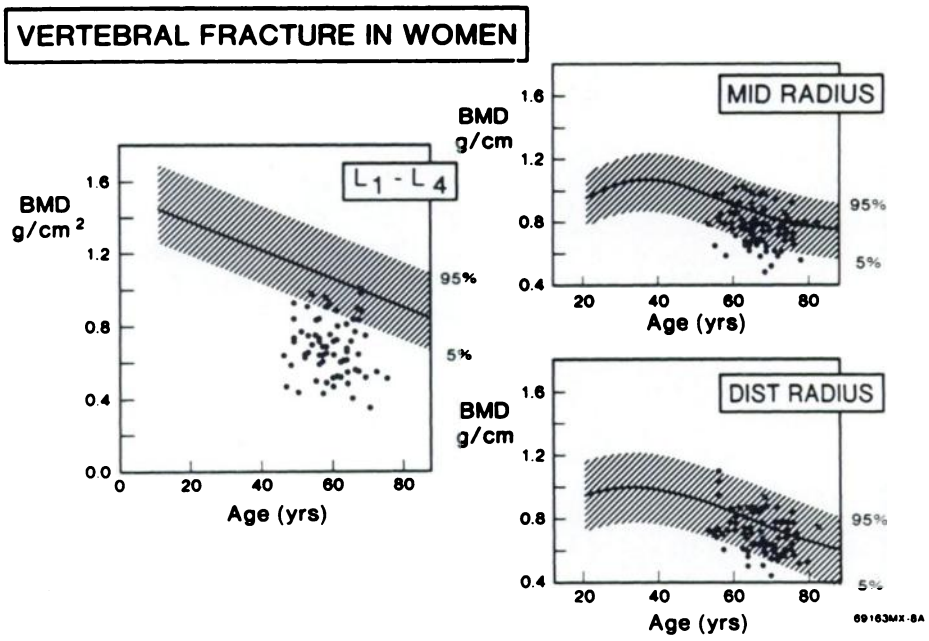

FIG. 10. Bone mineral content in spine by dual-photon absorptiometry: in normal subjects (shaded area) and women with osteoporosis (dots). Spinal data have been normalized to correct for loss of vertebral height occurring with lumbar fracture. Bone mineral in radius for comparison. Data from population published in Ref. (*61*).

normal men the age regression was also linear, but the decrease during life was only two thirds of that in women (*70*).

Studies of patients with osteoporosis have shown a significantly better separation of these patients from the normal range by lumbar spine than by radius bone mineral. This has been alluded to in the preceding section on single-photon absorptiometry.

The studies also allow definition of a threshold for spinal compression fractures. The 90th percentile for vertebral bone mineral of all patients studied who had nontraumatic compression fractures was 0.98 g/cm^2. We have chosen this value as the point below which the risk for compression fractures significantly increases. Thus data on spinal bone mineral should be expressed (a) relative to the normal range and corrected for age and sex, and (b) in terms of relationship to the fracture threshold as an index for fracture risk, and if it is a repeated measurement (c) in terms of rate of bone loss per year. Bone mineral measurements with dual-photon absorptiometry techniques in different endocrine dysfunctions have been reported (*60*). In hypoparathyroidism several studies have shown significant bone loss at sites of predominantly trabecular bone, whereas sites of predominantly cortical bone (measured by SPA) showed less changes. These observations are supported by increased occurrence of vertebral fractures in hyperparathyroidism, particularly in postmenopausal women. In contrast, patients with secondary hyperparathyroidism complicating renal failure do not show this decrease in trabecular bone and the cortical bone sites vary: normal, increased or decreased values have been reported. Hypercortisolism causes severe and disproportinate loss of trabecular bone, with little or no loss of cortical bone. Increase in trabecular bone mineral of the spine has been shown in acromegaly and surgical hypoparathyroidism. Our data show that bone mineral content of the axial and appendicular skeleton changes differentially in response to endocrine function and that induced alterations in BMC are both site and disease specific. In fluoride-treated patients bone mineral of the spine increases whereas no change or even a decrease in cortical bone has been reported (*71*). Decrease in rate of trabecular bone loss in patients with osteoporosis under treatment with calcium, estrogen, and vitamin D supplements have been recorded with SPA and are now beginning to appear in the literature for DPA (*71*). Exercise-induced increase in BMC of the spine has been observed in normal subjects (*72*). A seasonal change in bone mineral of the spine with increase in summer has been reported for a normal population from Denmark (*73*). We could not find such a difference for a population in Minnesota. There is little information on children.

Dosimetry measurements performed in our laboratory showed that a dual-photon scan of the lumbar spine 1.5Ci^{153}Gd source and performed on the Mayo instrument gave a peak skin dose 18 mrad with scatter dose to the eyes of 5 mrad and to gonads of 8 mrad. In this study the dosimetry was determined with LiF thermoLuminescent chips (TDL-100) and read with a Harshaw model 2000-A analyzer.

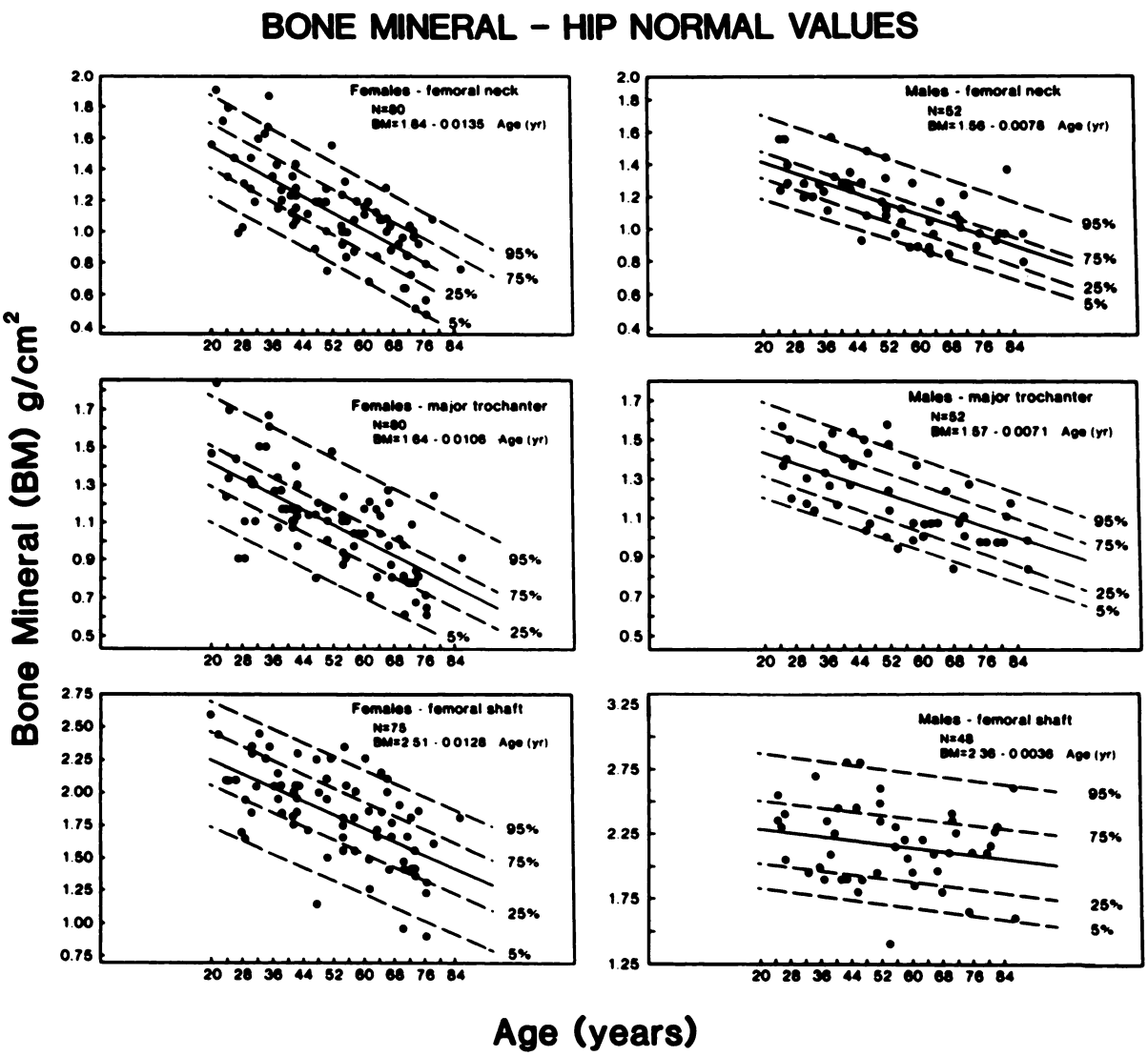

FIG. 11. Bone mineral content at three sites in proximal femur in normal subjects, obtained with dual-photon absorptiometry.

Neutron activation analysis. This technique is currently restricted to a few specialized laboratories mainly because of the equipment requirements and technical expertise needed for low-level counting of Ca-49 and the manipulation of the neutron source. There are available a number of different techniques that use different neutron sources and are applicable to different portions of the skeleton, or designed for total-body calcium measurements. The financial investment ranges from relatively inexpensive (hand counter) to very expensive (total skeletal calcium).

The techniques best adapted to clinical applications include measurement of total calcium in the hand (*74,75*), forearm (*76*), the lower spine (*76,77*), torso (*78*), and seven techniques for the measurement of total body calcium (*79*).

The first biological study that used a controlled dose of neutron radiation to measure total body calcium and sodium dates back to 1964 (*80*). To date, absolute values of Ca, Na, Cl, and P can be determined in the living organism. Since 99% of the total body calcium is in the bone, measurement of total body calcium constitutes a direct measurement of bone mineral. The technique is an analytical one, based on nuclear reactions rather than chemical reaction. Briefly, a neutron source supplies the neutron flux (thermal energy range) to which the total skeleton or bones are exposed. Neutron bombardment converts the Ca-48, one of the stable isotopes of natural calcium (abundance 0.18 percent) into radioactive Ca-49, and sodium, chlorine, and phosphorus into Na-24, Cl-38, and P-32, respectively. The beta emitter P-32 is not recognizable due to soft-tissue absorption; the other three are short-lived gamma emitters. The gamma energy spectrum is then analyzed and the Ca-49 quantitated. A weak neutron flux is adequate to induce measurable amounts of radioactivity, about 5 μCi in the trunk measurements. This should be compared with about 100 μCi of natural K-40 in the body. Data are

TABLE 5. PRECISION AND ACCURACY OF NEUTRON ACTIVATION ANALYSIS IN DIFFERENT MEASURING TECHNIQUES.*

Site	Precision		Accuracy		CV of normal range after normalization
	Patients or cadavers	Phantoms, bones	Patients or cadavers	Phantoms, bones	
Hand	2.4%	2.4–5%		3.2%	9–14%
Forearm	2.6%				12%
Spine	3–5%	2–4%			
Torso	6.4%	4.8%			10–13%
Total body	2%	1–3.5%	5.2%	4–4.5%	6.5–7%

* Adapted from Ref. (*79*).

Precision or reproducibility is expressed as the coefficient of variation (CV) of repeated measurements. Accuracy is the difference between actual and measured calcium expressed as a coefficient of variation. Values are given for in vivo studies on patients or cadavers and for studies on excised bones or bone equivalent phantoms.

expressed in grams of calcium normalized to parameters of body size. The efforts to find appropriate parameters for normalization have been extensive. For the hand technique the volume of the hand is used, whereas measurements in the forearm, torso, and total skeletal calcium use the height cubed as a normalization factor. Because of the necessity to normalize the Ca values obtained for accuracy measurements, the spread in the normal range (coefficient of variation after normalization) is an important parameter to consider. This and other quality-control data are given in Table 5 for the most commonly used methods.

The technique of neutron activation analysis has been used in normal populations and in patients with metabolic bone disease. Precision and accuracy are equal to the best procedures previously discussed. Total-body calcium measurements are used as reference standards for other techniques such as dual-photon absorptiometry of the total skeleton. From the preceding discussion, however, it is questionable whether a total-body calcium measurement, for example, is the most specific approach to osteoporosis, since only 20% of the total skeleton is trabecular bone. Measurements of the trunk include the spine and hip, which may have different rates of bone loss in osteoporosis (*70*). The hand and forearm as sampling sites do not seem to offer much above and beyond the methods previously discussed. For total body calcium the dual absorptiometry procedure is a serious alternative.

For an in-depth review of this method, the reader is referred to Refs. (*79*) and (*81*). The radiation dose from these techniques is given in Table 6.

Quantitative computed tomography. Considerable effort has been expended in the last years on developing the potential for quantitative computed tomography (CT). Bone mineral measurements with CT have been of particular interest and are the most advanced in this field at present. The output from such measurements is a cross-sectional slice; the quantitative data reflect attenuation coefficients. Thus the technique permits both display of anatomy and determination of bone mineral at any location in the transverse section. The method has been applied mostly to trabecular bone mineral at the distal radius and lumbar spine, but total vertebral bone mineral and trabecular bone of the femoral neck have also been measured.

The technique has been developed for bone mineral

TABLE 6. RADIATION ABSORBED DOSE FROM NEUTRON ACTIVATION TECHNIQUES.*

Site	Radiation dose
Hand	2–15 rem (hand)
Forearm	6 rem (skin) 1.7 rem (bone)
Spine	6 rem (skin) 0.7 rem (bone)
Total body	0.3–2.1 rem

* Adapted from Ref. (*75*).

along three different concepts. A specially constructed CT instrument for forearm trabecular bone measurements was devised by Ruegsegger et al., (*82*), It uses a I-125 source and a computer-assisted reconstruction algorithm. Long-term precision of 0.6% (CV) has been reported for trabecular bone measurements of the distal radius. There is also a good correlation (r = 0.9) of trabecular bone from the radius sites with vertebral bone mass obtained from ashed specimens. Clinical studies have been performed with this method in patients with metabolic bone disease, including osteoporosis, and in studying fracture healing and immobilization. Separation between normal and osteoporotic populations appears to be superior to that performed with single photon absorptiometry of the radius, but studies on the same population are not available. Since only trabecular bone is measured, it is conceivable that CT of the radius is a more sensitive test for the early detection of osteoporosis than single-photon absorptiometry, which measures cortical and trabecular bone.

The second principal approach is the adaptation of a commercial CT head scanner for quantification of bone mineral (*83*). This is an attractive concept. Quality-control requirements are significantly more strict, particularly with respect to short- and long-term stability of the instruments. Initial problems with absolute standardization have been improved and special phantoms have been developed. Exact repositioning (to 1-mm accuracy) for repeated measurements is very critical. The mid portion of the second or third lumbar vertebrae are generally selected as optimal measuring sites for spinal bone mineral. Repositioning has further been improved by using volume reconstruction of the vertebra of interest from multiple axial slices (*83*).

The third approach uses dual-energy CT technology, directed particularly to reduce the effects of tissue and intraosseous fat on the measurements (*84*). This is particularly important, since the mid portion of the vertebral body experiences significant changes in fat content with age, as previously described. Early studies have shown that acceptable accuracy but less acceptable precision can be achieved with this approach. The method has not been applied to a routine clinical test.

SUMMARY

A number of different techniques are available to study bone mineral. Those based on radiographs are helpful as an initial approach to the symptomatic patient with advanced disease, but they do not have the sensitivity to detect early bone loss, to assist in the estimation of fracture risk, or to monitor effects of treatment in controlled drug studies. A radiograph of the spine and hip, however, should be the first step before other tests are ordered.

Photon absorptiometry methods or CT-based tests are currently most attractive as second-line approaches. Of these, photon absorptiometry is more widely tested clinically and allows studies of predominantly cortical or trabecular bone sites and total skeletal calcium. Although all of this cannot be done reliably with one instrument under routine laboratory conditions at present, it may well become possible in the near future. Of the CT-based procedures, the forearm scanner is very attractive because of its high precision and accuracy and the fact that it allows measurement of trabecular bone only. The technique is restricted to the forearm and may not be versatile enough for modern clinical requirements. A similar comment may be applicable to neutron-activation techniques of the hand, forearm, or spine. Low-level counting and the handling of neutron sources are not widely known techniques in many laboratories, and this will restrict their use in clinical practice.

At this time there is no optimal technique available for mass screening for early osteoporosis. Dual-photon absorptiometry of the spine has been in use in our institution as the method of choice in selected patients for early detection of osteoporosis. However, for screening purposes the radius is still a very attractive bone to measure. At the currently used measuring sites, however, it does not have the sensitivity required to indicate spinal bone loss. Perhaps measurements closer to the distal end, where the trabecular-to-cortical bone ratios approach that in the spine, could be more sensitive. The difficulty of relocating the arm for photon absorptiometry can perhaps be solved for photon absorptiometry, or may be resolved by CT of the forearm. Correlation of the extreme distal radius with the spine is necessary to answer this question.

Clinical relevance. In general there is little specific information on the cause of bone loss obtainable from bone mineral measurements. Clinical examination, laboratory tests, radiographs, and biopsy are the tools for making the specific diagnosis of metabolic bone disease. Other than that, important clinically useful information can be obtained from single and from repeated measurements of bone mineral. If possible, the data should be expressed relative to the normal range (corrected for age and sex) and in terms of fracture risk and in case of repeated measurements in terms of rate of bone loss. Each of these approaches has its own merit.

Data from single measurements compared with the normal range reflect whether mineral content of the total skeleton, or of a particular portion of it, is normal or low. If low, this could be part of the patient's present disease or the result of one or more previous insults to the skeleton from which the patient has not completely recovered. In the latter case there may be no relationship of the osteopenia to the patient's present disease. When the same is expressed in terms of fracture risk, however, a single measurement helps to define the severity of the osteopenia with respect to risk of complications. With

this information it is possible to weigh the benefit-to-risk ratio of a given treatment regimen against the fracture risk of the patient.

Repeated measurements give information on rate of bone loss in the total skeleton or portion of it, and allow assessment of the activity of the disease or the effects of a treatment regimen.

Not all of this information is available from most any one of the methods described. Particularly with respect to fracture threshold and fracture risk data and estimation of rate of bone loss, the greatest clinical experience is with dual-photon absorptiometry of the spine. Similar data for the hip should be available in the near future.

FOOTNOTE

* Bicron model IXM040/2B x-ray detector, Bicron Corp., Newbury, OH.

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