Assessment of Bone Mineral. Part 1

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

Mayo Clinic and Mayo Foundation, Rochester, Minnesota

J Nucl Med: 1134–1141, 1984

There is a growing need for better understanding of bone loss with age, with osteoporosis, and with metabolic bone disease in general. The aging female population in the world is constantly increasing in number, and thus the number of subjects predisposed to an osteoporotic fracture syndrome (spine, hip, and radius). The impact of osteoporotic fractures on health-care resources is already significant and expected to increase even further. Therapeutic efforts to restore bone already lost have been unsuccessful, with the exception of sodium fluoride, and the emphasis is now directed toward finding measures to decelerate or if possible prevent this bone loss. During the past two decades, these investigations have been the stimulus for a growing interest in developing nontraumatic measurement techniques for bone mineral. As a result, several useful and well-tested clinically applicable procedures to assess bone mineral are now available to physicians concerned with the clinical diagnosis and treatment of bone disease. Instruments ranging from those requiring modest financial investments (single-photon absorptiometry) to heavy investments (x-ray computed tomography, neutron activation analysis) are offered by several commercial suppliers.

As different methods are applied to bone-mineral measurements, the complex behavior of mineral in the skeleton is gradually unraveled. It appears that not only do cortical and trabecular bone show different responses to physiological and abnormal stimuli, but variations in degree may be found even in individual bones or parts of a bone. This explains why there is no single technique applicable to all clinical questions regarding mineral status of the skeleton and why a certain familiarity with several techniques is necessary to select the most appropriate technique for a given clinical problem. It is often not a poor technique but rather the selection of an inappropriate method that is responsible for disappointing clinical information. The complexity seen today in interpreting results from bone-mineral measurements was not appreciated when the first procedures were developed, and still today it is probably the most important reason why even the more simple and inexpensive techniques are not used more widely. Because all nontraumatic bone-mineral techniques are based on the use of ionizing radiation (x-rays, emissions from radioactive sources), physicians in nuclear medicine and radiology are often being asked to participate in the decision as to which of the different methods would be most suitable for a specific clinical setting. Besides, radiation absorption is the basis for these techniques, and they have common technical problems and sources of error that are familiar to physicians in these specialties.

It is the purpose of this work to introduce the reader to newer observations of bone-mineral behavior under physiological and pathological conditions and to discuss several available procedures to measure bone mineral. Finally, it is the intent of this survey to help the physician select the most appropriate procedure for a given problem, i.e., the procedure that is least traumatic and least expensive, yet provides the most specific information. A position paper on radiological methods to evaluate bone-mineral content has recently been published by an expert panel from the American College of Physicians, and it addresses some of these questions (*1*). For additional information the reader is referred to recent proceedings from workshops and monographs on bone mineral, which give a state-of-the-art assessment of various techniques and their applications (*2–5*). Many of the technical details are in specialized journals or proceedings from meetings with limited editions, and may not be available in a general hospital library. In this paper we discuss first facts from the pathophysiology and biochemistry of the skeleton that pertain to the objective of this survey; followed by a detailed description of methods for bone mineral measurements with emphasis

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

on photon absorptiometry; and conclude with a short clinical summary.

BACKGROUND

The developing skeleton. Longitudinal growth of the skeleton continues, with intermittent spurts, for nearly two decades, but the maximum bone mass is reached only by the third decade. In this developmental period, longitudinal growth and bone mass may increase at different rates. In early adolescence, for example, rapid longitudinal growth is accompanied by only a modest increase in bone mineral, and a temporary cortical porosity occurs. Thus, bone density (g/cm^3) or bone mineral content (g/cm) change with age in the adolescent skeleton, and physiological decreases are observed when these measurement units are used. This very complex period of skeletal development is not the main concern of this paper, because the major application of bone-mineral measurements is in the adult patient after maximal bone mass has been reached. Bone mineral content by different methods, including total-body calcium, has been reported in the literature for ages ranging from premature babies to adolescents. From years 7 to 9 and from years 15 to 20, the mean values for estimated total-body calcium (from measurements on the distal radius) are significantly higher in boys than in girls. During childhood there is, in general, a slow increase in total-body calcium with age, followed by a sharp increase at the time of puberty (*6–10*). However, the range of variation in normal children overlaps the maturational delay of malnourished and diseased children, and so far none of the techniques has found wider application in clinical pediatric practice.

The adult skeleton: Maximum bone mass is reached at some time in the third decade. At this age, growth and modeling, the two processes by which bone achieves its adult proportions, have ceased. Bone mass, however, continues in a dynamic state throughout life. The function through which this is achieved is referred to as remodeling. The elements of remodeling are bone formation and bone resorption, which are coupled. Thus, bone loss in osteoporosis—as well as in metabolic bone disease in general—can be viewed as a disorder of bone remodeling. Repair of microscopic or macroscopic bone fracture is another more localized function that is also retained into adulthood.

Because of this physiological bone loss with age, peak bone mass achieved is the single most important factor that determines how much bone can be lost (with age or disease) before a critically low bone mass is reached and fractures occur. The factors that determine peak bone mass result from genetic, mechanical, nutritional, and hormonal forces. The latter three factors are probably important as modulators for the achievement of the maximum genetic potential. In a comprehensive review of this subject, Heaney (*11*) states that bone mass at any time after the age of about 40 yr is the resultant of (a) peak bone mass achieved, (b) average remodeling balance, (c) remodeling rate, and (d) time. The factors that modulate this bone loss with age are mechanical loading (exercise), nutritional status (particularly calcium intake), hormonal status (especially estrogen withdrawal at menopause, parathyroid hormone, somatotropin, calcitonin), and lastly accumulated structural errors during remodeling.

As previously stated, maintenance of bone mineral is accomplished by the complex process of bone remodeling, consisting of bone formation and resorption. Insight into this process can be obtained only at the cellular level from information obtained with iliac-crest biopsy and nondecalcified histologic sections. An understanding of this process is necessary for an appreciation of the different rates of remodeling that may occur in trabecular and cortical bone. This is important for the selection of the appropriate sample site for a bone-mineral test. A short overview follows: Bone formation is by intramembranous ossification from mesenchymal osteoblasts or by endochondral ossification from preexisting cartilage. Generally, both types of ossification take place in a given bone. The long bones grow in length by endochondral ossification. Ossification of the shaft is by membranous ossification. Bone is synthesized by the deposition of organic matrix (osteoid) and its subsequent mineralization by a number of defined sequences. In man this process normally takes about 23 days. The time for completing mineralization is referred to as mineralization lag time, and can be evaluated with a time-spaced double-tetracycline label. Abnormalities in osteoid formation or in osteoid mineralization can thus be identified. At any time, there are numerous foci of remodeling present in the skeleton.

Bone remodeling is performed by cells of the periosteal, the Haversian (intracortical pores), the endosteal, and the trabecular bone surfaces. These surfaces are referred to as envelopes. The envelope with the greatest surface area—and therefore the greatest metabolic activity in health and disease—is the endosteal envelope. Resorption at the endosteal envelope reduces trabecular size and transforms the trabecular network into short spicules. This results in a reduction of the total surface area of the envelope. In contrast, cortical bone resorption takes place by increasing the size of the Haversian canals (porosity) and the number of resorption cavities at the endosteal and periosteal surfaces. This results in an increase in the total surface area of the three envelopes of the cortex (Haversian, endosteal, periosteal). The importance of this change in active bone surface area from trabecular to more and more cortical bone with progressive net resorption lies in the potential for accumulation of irreversible changes that may accumulate over time and affect future bone responses to resorption

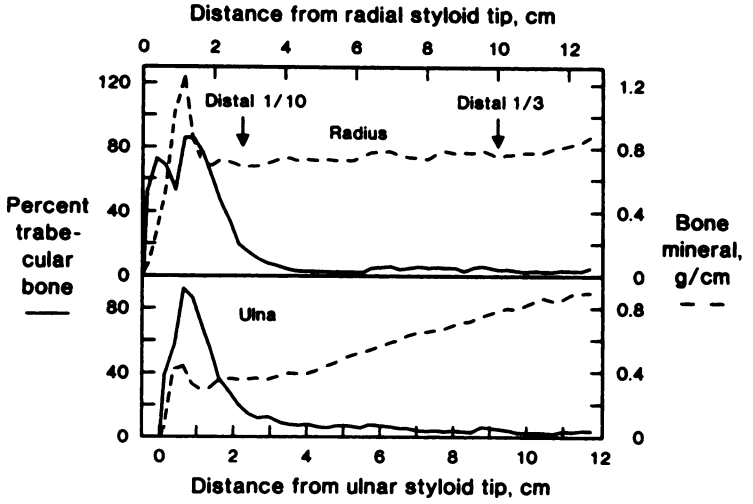

FIG. 1. Distributions of cortical and trabecular bone in forearm. Commonly used scanning sites are: (a) 0.8 cm below separation of radius and ulna (about 1 to 1.5 cm from the distal end, with both radius and ulna scanned; (b) distal radius at one tenth of its length; (c) at end of distal third of radius length; and (d) mid radius. Importance for exact relocation in longitudinal studies is apparent, particularly for distal measuring sites. Adapted from Schlenker et al: *Calc Tiss Res* 20:41–52, 1976, with permission.

stimuli. Thus, with progressive resorption, more trabecular and then gradually more cortical bone becomes involved. Since, as will be shown later, the trabecular-to-cortical bone ratio varies in different parts of the skeleton, net bone loss can be expected to differ in different parts of the skeleton and in different stages of a disease. This observation is supported by several studies obtained with different methods. A very attractive hypothesis to explain differential bone loss in different parts of the skeleton is discussed in more detail by Atkinson (*12*).

Mazess (*4*) speculates on other reasons for the apparently greater responsiveness of trabecular bone to loss in osteoporosis, such as the greater blood supply and the proximity of the trabecular bone surfaces to the bone marrow, which contains the progenitor cells for bone remodeling. Together these factors may also explain why vertebral sites of trabecular bone show preferential loss in osteoporosis when compared with other trabecular bone sites. With age, the balance between bone formation and resorption rates is disturbed, resulting in a gradual net decrease in bone mass. It appears that while formation remains constant, resorption increases. This results first in a predominant reduction of trabecular bone mass, then an increase in porosity of cortical bone, and finally a reduction in cortical thickness as well.

The appendicular skeleton. The long bones are predominantly cortical bone, which constitutes 80% of the skeleton. The contribution of trabecular bone to total mass in a bone varies significantly with the site and the bone itself. An example of the varying relationship between cortical and trabecular bone in the radius is given in Fig. 1. The site with the highest percentage of cortical bone is the mid diaphysis; the sites with the highest percentage of trabecular bone are the distal and the proximal metaphyses. Remodeling in cortical bone occurs at the endosteal, periosteal, and Haversian envelopes. With aging, the endosteal resorption is generally more pronounced than the periosteal, resulting in a progressive thinning of the cortex and enlargement of the medullary canal. A small increase in the bone diameter occurs (*13*). At the Haversian envelope, bone remodeling results in increased porosity. These changes in cortical bone occur with different rates in different parts of the skeleton, and within a given bone even in different parts of the bone. There is a gradient of porosity that progresses from endosteum to periosteum, is fairly constant in mature bone, and increases with aging (*14*). The gradient changes along the axis of the bone and appears to have a global spread from the metaphysis (*15*). These gradients of internal porosity appear to be similar in males and females. Even within a cross section of a long bone, anterior and posterior parts may have different remodeling rates and resulting densities (*16*).

Bone loss in the trabecular component of the long bones results in a reduction in thickness of the trabeculi. This, together with the increase in porosity at the endosteal surface of the cortical bone, makes it increasingly difficult to separate cortical from trabecular bone on special radiographs or even on excised specimens in the laboratory. In addition, with advancing age bone marrow is gradually replaced by fat, and fat fills the spaces made available by the receding trabeculi and cortex. As will be shown later, the increase in osseous fat is a significant factor that has to be considered in all x-ray absorptiometry methods, whether they use film, photon absorptiometry, or x-ray computed tomography.

The axial skeleton. The axial skeleton is predominantly trabecular bone and constitutes about 20% of the total bone mass. In its typical structure a vertebra has a small cortical sheet that surrounds the larger trabecular bone component. The axial bones most studied by bone-mineral techniques are the vertebrae, and by biopsy the iliac crest. Trabecular bone is not equal in a cross section through a vertebral body. The central area has less bone mineral per unit volume than the periphery, and there is a centrifugal extension of trabecular loss with age (*17*). Again, the spaces within the vertebrae contain

bone marrow, 75% of which is hematopoietic in the young adult. Later in life, fat replaces the marrow and the receding trabeculae. In older osteoporotic vertebrae, only 25% of the marrow may be hematopoietic. As in the long bones, the relationship between cortical and trabecular bone varies. The posterior elements of a vertebra have relatively more cortical bone than the vertebral body. About 50 to 60% of a vertebra is considered to be trabecular bone. With reduction in bone mineral, there is a predominant loss of horizontal trabeculae, and microfractures of predominantly vertical trabeculae near the end plates occur (*18–22*), especially in lumbar vertebrae. These microfractures lead to callus formation and local repair. Trabecular microcalluses are seen as nodular structures on special radiographs, and represent repair superimposed on the remodeling process. Whether this microcallus formation is impaired in accelerated osteoporosis has not been investigated. Perhaps the microcallus formation may contribute to the occasional increase in uptake of Tc-99m-labeled diphosphonates seen on bone scintigrams in cases of osteoporosis where the radiograph is normal or shows only osteopenia.

Morbidity resulting from bone loss is mainly due to fractures. Bone-mineral measurements are therefore of interest in predicting the fracture risk in a given patient. The relationship between bone mineral and compressive strength or breaking strength of vertebrae and long bones has been examined under laboratory conditions and with epidemiological and clinical studies (*23–25*). Compressive strength (lb/in^2) of the bodies of lumbar vertebrae is about equal in the lower cervical and upper thoracic vertebrae, then increases gradually to another plateau in the region of L2 to L4. The mass of a lumbar vertebra increases from L1 to L4, but its areal density (g/cm^2) remains unchanged. Peak strength of vertebrae is reached in the third decade, after which there is a loss of compressive strength with age, more pronounced in women. The rate of loss of compressive strength with age is faster in the vertebrae relative to the proximal tibia. Lindahl (*25*) has shown a relationship between vertebral bone density (g/cm^3) and compressive strength in excised vertebrae free of fat and bone marrow (CV, 0.7). Clinical and epidemiological studies have supported this relationship. A threshold of areal density in the spine of 0.96 g/cm^2, below which the risk of nontraumatic vertebral fractures increases, has been found with dual absorptiometry (*26*). All subjects with bone-mineral values below 0.62 g/cm^2 have been found in our laboratory to have two or more vertebral fractures.

DIAGNOSTIC PROCEDURES TO ASSESS BONE MASS

Routine radiographic evaluation of the skeleton. The standard radiograph shows low sensitivity for the detection of osteopenia before the presence of vertebral collapse. However, the radiograph helps to exclude focal bone disorders and it detects advanced diffuse disease. Therefore, standard radiographs should be the first test. A general approach to the detection of osteoporosis includes a lateral radiograph of the thoracic spine, biplanar views of the lumbar spine, and occasionally a radiograph of pelvis and hips with internal rotation of the feet. Spine and hips are searched first for signs of osteopenia—vertical striation, picture-frame appearance, visibility of iliac crest through L4 and L5 on lateral spine film, general density decrease (Smith Index)—and second for evidence of ballooning, wedging, or collapse. Next, the radiographs of the hips are inspected for trabecular changes in the femoral neck and head (Singh Index), and the thickness of the calcar femorale (cortical thickness above minor trochanter) is measured. This is often adequate to make the diagnosis of bone loss in advanced cases of osteoporosis when compression fractures have already occurred. If further evaluation is necessary, magnification free radiographs of the hands for radiogrammetry, or a more specific method for bone-mineral estimation, should be considered. These tests will now be discussed.

Photodensitometry (radiographic absorptiometry). The optical density of bone on x-ray films obtained under standardized conditions has been used as a quantitative indicator of bone mineral content for many years and probably is the oldest nontraumatic method of assessing bone mineral (*27*). As routinely obtained radiographs vary widely in density, a strict standardization of kilovoltage, exposure time, and film processing is essential for these measurements. The method is also very sensitive to changes in overlying tissue, and is therefore restricted to appendicular bones, particularly the phalanges, although radius, tibia, and less frequently other appendicular bones have been studied.

Radiographs performed without a simultaneously exposed standard have been analyzed by deriving a ratio of affected bone to unaffected bone, the soft-tissue cover being equal. This, however, provides only a crude estimate and is unacceptable at the present state of the art. In metabolic bone disease it is generally not possible.

Simultaneously exposed wedge or other types of reference standards have to be used to correct for differences due to changes in kilovoltage, film exposure, and film processing. The measurements on the film are made with a densitometer as spot measurements, or with a more sophisticated instrument as line or area measurements.

The interest in photodensitometry has declined in recent years and shifted to photodensitometry using radioactive sources (monoenergetic gamma emitters) and photomultiplier tubes instead of film. The only photodensitometry method currently acceptable immerses the hand in water for constant "soft-tissue thickness," and uses a microdensitometer and computer (*28*). This method has been used for the study of various

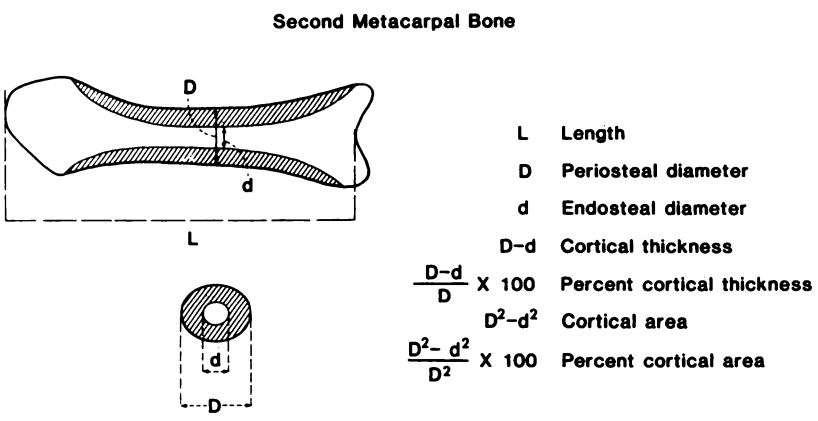

FIG. 2. Basic measurements made in radiogrammetry. Metacarpal bone length at mid axis is used here (Dequeker). Another approach used metaphysis length (Nordin, Horsman).

metabolic bone diseases and their responses to treatment (*29*). The data have been expressed as area densities in cross-sectional and longitudinal studies. Another approach uses analysis of absorption-curve profiles across the bone from multiple slices along its axis. Yet another approach proposes spot measurements in longitudinal studies at distal end and mid shaft of the bone, to study the relationship between the two sites. This is essentially a comparison of cortical bone (midshaft) with mixed trabecular and cortical bone (distal end). An obesity index has also been proposed, which analyzes the curve profile for bone and soft-tissue components. However, even under the best conditions the method has not reached the precision and accuracy that can be achieved with modern photon-absorptiometry procedures, as shown in a comparative study (*30*). The curve-profile approach has not been tested widely. For a more detailed review of the photodensitometry technique, the reader is referred to Ref. (*29*). A scanning-slit x-ray video absorptiometry method is under development at the University of Wisconsin (*31*).

Radiogrammetry. This was first introduced by Barnett and Nordin (*32*) and Virtama and Mahonen in 1960 (*33*), and expanded later by Garn et al. (*34*), Dequeker (*35*), and Horsman et al. (*36*), to name only a few reference sources. The method has been used extensively, and a vast literature is available on normal populations in different countries, races, and nutritional states, and from patient populations with various diseases (*37*).

Radiogrammetry is applicable only to bones of the appendicular skeleton. The most commonly used site is the second metacarpal of the nondominant hand, or several metacarpals from one or both hands. The radius, and less frequently humerus, femur, clavicle, and tibia, have also been used. The model on which quantification in radiogrammetry is based requires the optimal bone site (a) to be of cylindrical shape at outer and inner surfaces, (b) to show structural morphological uniformity of the cortex, (c) to be easy to relocate in exactly the same position for radiography, (d) to have little surrounding tissue, and (e) to show good correlation with skeletal bone mass. There is general agreement that the mid portion of the second metacarpal comes closest to these requirements.

To perform radiogrammetry, a high-quality posteroanterior radiograph is taken under standard conditions. For the hand, industrial fine-grain film is used, exposed to 52 kVp radiation for 0.04 sec at a tube current of 500 mA. Film-to-tube distance is 100 cm and the films are processed in an automatic developer. For data analysis the mid point of the second metacarpal is identified from measurements of its total length. At the mid portion of the metacarpal bone, and perpendicular to its long axis, the outer and inner diameters of the

TABLE 1. MEASUREMENTS (L,D,d, FIG. 2) AND INDICES FOR BONE MASS FOR 3 DIFFERENT LENGTHS (L) OF SECOND METACARPAL BONE AT MID POINT IN FEMALES IN AGE GROUP 25-34 yr*

L†	D	d	D − d	$\frac{D-d}{D}$ (%)	$D^2 - d^2$	$\frac{D^2-d^2}{D^2}$	$\frac{D^2-d^2}{DL}$
6.10	7.0	2.20	4.80	68.57	44.16	90.12	0.1034
6.30	8.0	2.80	5.20	65.00	56.16	87.75	0.1114
6.55	9.0	3.45	5.55	61.66	69.10	85.30	0.1172

* From Dequeker, J (Ref. *35*), with permission.
† L, D, d in nm.

TABLE 2. REMODELING AT ENDOSTEAL AND PERIOSTEAL SURFACES AND CORTICAL AREA AT MID PORTION OF SECOND METACARPAL BONE, AS OBTAINED BY RADIOGRAMMETRY, IN VARIOUS CLINICAL CONDITIONS.*

Diagnosis	Periosteal surface	Endosteal surface	Cortical area
Normal aging (adults)	Bone gain	Bone loss	Decrease
Osteoporosis	Bone loss (++)	Bone loss	Decrease (+++)
Hyperparathyroidism	Bone gain (+)	Bone loss (+)	Normal or decrease
Estrogen treatment	Bone gain	Bone loss (reduced)	Increase
Acromegaly	Bone gain (+)	Bone loss or gain	Increase
Hemiplegia	Bone gain (+)	Bone loss (+)	Decrease

* Adapted from Ref. (*37*), with permission.

cortex are measured to 0.1-mm accuracy using high-precision needle-tipped calipers (Fig. 2). An example of the results that can be expected is given in Table 1.

Normalization for variations in skeletal size is attempted by expressing cortical thickness relative to a parameter of skeletal size. A number of different indices have been introduced. These are listed in Fig. 2. Such normalization attempts are not altogether satisfactory. Longitudinal studies are best performed without correction for skeletal size. The Barnett-Nordin cortical-thickness index appears to be the best single parameter to separate normal from osteoporotic women (*38*).

Cortical thickness is then used to estimate bone mass in the total skeleton and sites of interest such as the spine or hip. The metacarpal index correlates moderately well with both regional and total skeletal osteopenia and with the number of compression fractures in the spine. Magnification radiogrammetry has been introduced to detect intracortical porosity that cannot be appreciated by the standard technique, and to improve recognition of changes on the endosteal and periosteal surfaces (*39*). In this technique, radiographs obtained with fine-grain industrial films (long exposure time) are inspected under a stereoscopic microscope or with a high-power magnifier. Magnifications up to ten times are possible with negligible effect of grain on fine details. Results with this technique have shown excessive intracortical resorptive changes in hand bones in thyrotoxicosis, hyperparathyroid disease, and acromegaly—all diseases with high bone turnover. By contrast, intracortical resorption was found to be minimal or absent, with bone loss occurring mainly at the endosteal surfaces, in osteoporosis and in Cushing's syndrome, both of which have low bone turnover. A combination of magnification radioscopy with measurements of cortical thickness based on the same film allows a detailed evaluation of the cortical bone. Trabecular bone is not accessible to this technique.

The method also allows description of endosteal and periosteal bone remodeling. The outer diameter gives information on periosteal bone remodeling, the inner diameter on endosteal. This was extensively used by Garn et al. (*34*) to study the behavior of tubular bones from birth to death with respect to endosteal and periosteal surface changes. Typical findings in different diseases are summarized in Table 2.

Precision for cortical thickness measurements (c. v.) is given as follows: within-observer, 1.2% for outer diameter, 4.8% for inner diameter; between-observer, 1.5% for outer diameter and 6.4% for inner diameter (Table 3). This can be slightly improved by using four or eight metacarpals from both hands. The inner diameter is particularly difficult to determine because of the adjacent trabecular bone, and this becomes progressively

TABLE 3. ERRORS IN ESTIMATES OF CORTICAL THICKNESS AT CENTER OF SECOND METACARPAL, AS MEASURED BY RADIOGRAMMETRY WITH VARIOUS TECHNIQUES

Reference	Error estimate: Intra-observer	Error estimate: Inter-observer	Subjects	Remarks
Dequeker (*42*)	3.1%	—	6 women 60–65 yr	X-ray caliper read out to 0.1 mm
Adams et al. (*40*)	8–10%	8–11%	86 subjects 55–64 yr	Caliper-ruler
Morgan et al. (*41*)	6.9%	9.2%	41 films	Transparent ruler read out to 0.25 mm

more difficult as bone loss occurs (*40–42*).

The method, even in the best laboratories, can detect changes of cortical thickness only in advanced stages of osteoporosis; it is not applicable for the detection of early disease or evaluation of risk factors for spinal compression fractures. It has been used mainly for epidemiological studies of advanced disease. There is a lower mean value of cortical thickness at the metacarpal bone with osteoporosis, but the overlap between the populations is significant. In some studies not more than 5% of the cases with osteoporosis lie beyond 2 s.d. from the normal mean. Cortical thickness is greater in men than in women at all bone sites. It decreases with age slowly in men, but more rapidly in women for 10 to 15 yr after the menopause.

The procedure is easy to perform, is applicable to all tubular bones, at least for longitudinal studies, and is the least expensive in terms of equipment and material required. Adequate measurements, however, require skilled personnel, and it is time-consuming. It assesses only cortical bone, and is the only nontraumatic procedure giving information on periosteal or endosteal remodeling. The results show a good correlation with densitometric measurements on the radius (*43*).

ACKNOWLEDGMENTS

We acknowledge the expertise of Ms. Judy Ashenmacher in typing the manuscript and Ms. Pat Griffen, Ms. Kim Beaupre, and Ms. Darla Jech in performing the laboratory studies.

REFERENCES

1. Health and Public Policy Committee, American College of Physicians. Radiological methods to evaluate bone mineral content. *Ann Int Med* 100:908–911, 1984
2. *Non-Invasive Bone Measurements: Methodological Problems.* Dequeker J, Johnson CC, Jr., eds. Proceedings Workshop on Non-invasive Bone Measurements, Knokke, Belgium, 1981, 250 pp
3. *Clinical Disorders of Bone and Mineral Metabolism*, Chapter 2. Frame B, Potts JT, Jr., eds. Proceedings of the Francis and Anthony D'Anne Memorial Symposium, 1983. Amsterdam, Excerpta Medica, 1983, pp 27–61
4. MAZESS R: Noninvasive methods for quantitating trabecular bone. In *The Osteoporotic Syndrome, Detection, Prevention and Treatment.* L.V. Avioli, ed. Grune & Stratton, New York, 1983, pp. 85–114.
5. JOHNSTON CC, JR: Noninvasive methods for quantitating appendicular bone mass. In *The Osteoporotic Syndrome, Detection, Prevention and Treatment*, Avioli LV, ed., New York, Grune & Stratton, 1983, pp 73–84
6. MAZESS RB, CAMERON JR: Skeletal growth in school children: Maturation and bone mass. *Am J Phys Anthrop* 35:399–408, 1971
7. MAZESS RB, CAMERON JR: Growth of bone in school children: Comparison of radiographic morphometry and photon absorptiometry. *Growth* 36:77–92, 1972
8. CHRISTIANSEN C, RÖDBRO P, THÖGER NIELSEN C: Bone mineral content and estimated total body calcium in normal children and adolescents. *Scand J Clin Lab Invest* 35:507–510, 1975
9. GREER FR, LANE J, WEINER S, et al: An accurate and reproduciable absorptiometric technique for determining bone mineral content in new born infants. *Pediatr Res* 17:259–262, 1983
10. MINTON SD, STEICHEN JJ, TSANG RC: Bone mineral content in term and preterm appropriate-for-gestational-age infants. *J Pediatr* 95:1037–1042, 1979
11. HEANEY RP: Prevention of age-related osteoporosis in women. In *The Osteoporotic Syndrome. Detection, Prevention and Treatment.* Avioli LV, ed. New York, Grune & Stratton, 1983, pp 123–144
12. ATKINSON PJ: Relevance of peripheral, axial or total skeletal mass measurements. In *Non-invasive Bone Measurements: Methodological Problems.* Dequeker J, Johnson CC, Jr., eds. Proc. Workshop on Non-Invasive Bone Measurements, Knokke, Belgium, 1981, pp 141–154
13. SMITH MW, WALKER RR: Femoral expansion in aging women: Implications for osteoporosis and fractures. *Science* 145:156–157, 1964
14. ATKINSON PJ: Changes in resorption spaces in femoral cortical bone with age. *J Pathol Bact* 89:173–178, 1965
15. DOYLE FH: Age-related bone changes in women. In *Progress in Methods of Bone Mineral Measurement Conference.* Bethesda, 1968, pp 115–135, 1970
16. ATKINSON PJ, WEATHERELL JA: Variation in the density of the femoral diaphysis with age. *J Bone Joint Surg* 49B: 781–788, 1967
17. COHEN J, HARRIS WH: The three-dimensional anatomy of Haversian systems. *J Bone Joint Surg* 40A:419–434, 1958
18. ATKINSON PJ: Variation in trabecular structure of vertebrae with age. *Calc Tiss Res* 1:24–32, 1967
19. BELL GH, DUNBAR O, BECK, JS: Variations in strength of vertebrae with age and their relation to osteoporosis. *Calc Tiss Res* 1:75–86, 1967
20. FROST HL: Presence of microscopic cracks in vivo in bone. *Henry Ford Hospital Med Bull* 8:25–35, 1960
21. HANSSON R, ROOS B: Microcalluses of the trabeculae in lumbar vertebrae and their relation to the bone mineral content. *Spine* 6:375–380, 1981
22. VERNON-ROBERTS B, PIRIE CJ: Healing trabecular microfractures in the bodies of lumbar vertebrae. *Ann Rheum Dis* 32:406–412, 1973
23. KAZARIAN L, GRAVES GA: Compressive strength characteristics of the human vertebral centrum. *Spine* 2:1–14, 1977
24. YAMADA H: Strength of biological materials. Baltimore, Williams and Wilkins, 1970
25. LINDAHL O: Mechanical properties of dried defatted spongy bone. *Acta Orthop Scand* 47:11–19, 1976
26. RIGGS BL, WAHNER HW, DUNN WL, et al: Differential changes in bone mineral density of the appendicular and axial skeleton with aging. *J Clin Invest* 67:328–335, 1981
27. OESER H, KROKOWSKI E: Quantitative analysis of inorganic substances in the body. A method using Xrays of different qualities. *Br J Radiol* 36:274–279, 1963
28. COLBERT C, SPRUIT JJ, DÁVILA, LR: Fels microdensitometer/computer for bone mineral determination from roentgenograms. *Crit Rev Radiol Sci* 1:459–471, 1970
29. COLBERT C, BACHTELL RS: Radiographic absorptiometry (photodensitometry). In *Non-Invasive Measurements of Bone Mass and Their Clinical Application.* Cohn SH, ed. CRC Press, Inc., 1981, pp 51–84
30. COLBERT C, MAZESS RB, SCHMIDT PB: Bone mineral determination in vitro by radiographic photodensitometry and direct photon absorptiometry. *Investigative Radiol* 5:336–340, 1970

31. DUBBINS JT, III, MAZESS RB, CAMERON JR: Scanning slit x-ray videoabsorptiometry for measurement of bone mineral content. *Med Phys* 8:563, 1981 (abst)
32. BARNETT E, NORDIN, BEC: The radiological diagnosis of osteoporosis. A new approach. *Clin Radiol* 11:166-174, 1960
33. VIRTAMA P, MAHONEN H: Thickness of cortical layer as an estimate of mineral content of human finger bones. *Br J Radiol* 33:60-62, 1960
34. GARN SM, ROHMANN CG, WAGNER B: Bone loss as a general phenomenon in man. *Fed Proc* 26:1729-1736, 1967
35. DEQUEKER J: Bone loss in normal and pathological conditions. Leuven, Leuven University Press, 1972, p 214
36. HORSMAN A, KIRBY PA: The geometric properties of the second metacarpal. *Calc Tiss Res* 10:289-301, 1972
37. DEQUEKER J: Clinical relevance of the radiogrammetric measurement of peripheral skeletal mass. In *Non-invasive Bone Measurements: Methodological Problems.* Dequeker J, Johnston CL, eds. Proceedings of the Workshop on Non-invasive Bone Measurements, the XVI European Symposium on Calcified Tissue Research, Knokke, Belgium. Oxford, IRL Press, 1982, pp 165-168
38. DEQUEKER J: Influence of sampling, sex, age, skeletal size on the variability of radiogrammatic bone mass values. In: *Non-invasive Bone Measurements: Methodological Problems*, Dequeker J, Johnston CL, eds. Proceedings of the Workshop on Non-invasive Bone Measurements, the XVI European Symposium on Calcified Tissue Research, Knokke, Belgium, Oxford, IRL Press, 1982, pp 107-113
39. MEEMA HE, SCHATZ DL: Simple radiologic demonstration of cortical bone loss in thyrotoxicosis. *Radiology* 97:9-15, 1970
40. ADAMS P, DAVIES GT, SWEETNAM PM: Observer error and measurements of the metacarpal. *Br J Radiol* 42:192-197, 1969
41. MORGAN DB, SPIERS FW, PULVERTAFT CN, et al: The amount of bone in the metacarpal and the phlanx according to age and sex. *Clin Radiol* 18:101-108, 1967
42. DEQUEKER J: Problems in measuring the amount of bone: reproducibility, variability, sequential evaluation. In *Bone Histomorphometry*, Mennier PJ, ed. Toulouse, Soc. Imprim. Fourme, 1977, pp 19-37
43. MEEMA HE, MEEMA S: Comparison of microradioscopic and morphometric findings in the hand bones with densitometric findings in the proximal radius in thyrotoxicosis and in renal osteodystrophy. *Invest Radiol* 7:88-96, 1972