# Why, When and How To Measure Bone Mass:

# A Guide for the Beginning User

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Technological advances in the past 10 years have provided a number of new capabilities for diagnosis and treatment of metabolic bone disease. Biochemical tests such as region-specific parathyroid hormone assays, nephrogenous cyclic AMP, vitamin D metabolite levels, osteocalcin (bone GLA protein) and skeletal isoenzymes of alkaline phosphatase as indicators of bone turnover, promise better characterization of disease processes. Automated procedures have made quantitative analysis of tetracycline-labeled bone biopsies semi-routine, and new or improved radiologic procedures have provided the clinician the capability to measure the mass or density of virtually any bone in the body. The concurrent emergence of this diagnostic armamentarium and cost-control measures in medicine has created a dilemma for the clinician—a decision must often be made whether to order one or several tests, and to choose those which will prove most efficacious in the diagnosis or monitoring of his or her patient. These decisions are made based on available knowledge; it is the purpose of this paper to discuss the current status of widely available bone mass measurements and to try to provide the clinician (both internist and orthopedist) and the medical physicist who must develop and support any technique a guide by which these decisions may be made in an effective manner based on clinical indication, cost, patient acceptance and diagnostic return. Because of this clinical orientation, several techniques in use at research centers (Compton scattering, neutron activation analysis, radiographic photodensitometry) will not be discussed thoroughly but instead I will concentrate on those methods which a clinician can reasonably assume may be available to his or her practice. The term "bone mass" will generally be used recognizing that most measurements are actually an index of bone mass or density rather than its actual determination. In the same manner, this is not a highly technical review and cross-comparison of techniques; rather, each measurement technique will be considered on its own merits as though all were equally available. The uses of these techniques in various clinical situations will be related to current concepts of basic bone physiology to show how the results of bone mass measurement can be optimally used.

## The Clinical Indication for Bone Mass Measurement

Perhaps the most important result of a bone mass measurement is whether the test is done at all. For the general internist, the decision whether or not to order a test will be based on a variety of factors, and those factors may change as new technology or new interpretation of measurements become available. The use of bone mass measurements in patient management can be divided into two basic applications: 1) diagnosis of bone disease, osteopenia (low bone mass) or osteoporosis (low bone mass with presence of minimally traumatic fracture), and 2) follow up of patients for progression of disease or response to therapy. As would be expected, these two are related; an internist may not generally treat the patient with normal bone mass nor would a patient with low bone mass be left without follow up. The technical requirements for a given methodology will be different for optimization of these two uses of bone mass measurements, but most available techniques will be used in the clinical sphere for both even if they are only suited for one or the other. Thus, the clinician must understand both the limitations as well as the strengths of each methodology and be prepared to tailor the method to the patient population studied.

Who should be a candidate for the measurement of bone mass? If this question is approached from the most general perspective, current research results and theories about the gain and loss of bone throughout life argue that a high peak bone mass is one of the most important protective factors against the development of osteoporosis. Thus, we might consider screening a large portion of the population to obtain this information both for epidemiologic purposes and to provide a known measure for each individual. This measurement and its relationship to osteoporosis might be likened to blood pressure measurements and hypertension. However, such a screening program is not inexpensive, at a cost of somewhere between $50 and $100 per person with the techniques that would provide the most useful information. There is also the risk, however small, of exposing a large part of the population to the small radiation dose necessary for these studies. The cost of this type of screening program would be borne by national health care, national research agencies or private insurers; one would not expect the patients to pay. The feasibility of such a program has not been explored, however; if we were to screen 75 persons per day per center with either a computed tomography (CT) scan or a hand film (the fastest methods available), 2 full

days per week on all available CT scanners in the US, it would take us over 10 years to screen the whole population. Thus, while a justification could be made on scientific and public health grounds that this information would be valuable, it is probably not feasible to consider answering these basic scientific questions for the population as a whole at the present time.

If only those groups at risk for the development of osteoporosis, are considered, we immediately cut our population roughly in half by considering only women and patients with other contributing diseases. Bone is lost with aging in both men and women; the accelerated loss occurring at the time of menopause in women is probably the major factor disposing many women to the development of osteoporosis. Osteoporosis is normally defined as a condition of low bone mass with the presence of at least one minimally-traumatic vertebral, wrist or hip fracture; the prevalence increases from approximately 15% of all women in the sixth decade to 35% and 61% in the seventh and eighth decades (1). Thus, age is a significant risk factor, especially age past menopause. However, while the risk of fracture as a function of age increases monotonically, it is not clear that it is linear. If the number of women per year developing osteoporosis is expressed as a function of the number of women with whom they passed age 50, the number of women alive and with vertebral fractures increases from 8 to 14% of the initial group from age 60 to 70 but by age 80 is only 18%. Thus, it appears that if a woman has reached age 65-70 without fractures the development of vertebral compressions subsequently may be more related to longevity than to any pathologic process (Figure 1). Whether or not a woman has fractures at age 80 may be due to the heterogeneity of bone mass at age 50; a woman with higher peak bone mass may lose the same amount as a woman with lower peak bone mass and be left with more bone at age 60 or later. Evidence from longitudinal studies in chemically menopausal women suggests little if any correlation between absolute bone loss and initial bone mass (Figure 2). Other investigators have found no decrease in the variance of measured bone mass as a function of age for population studies, again arguing against a proportional loss of bone (2).

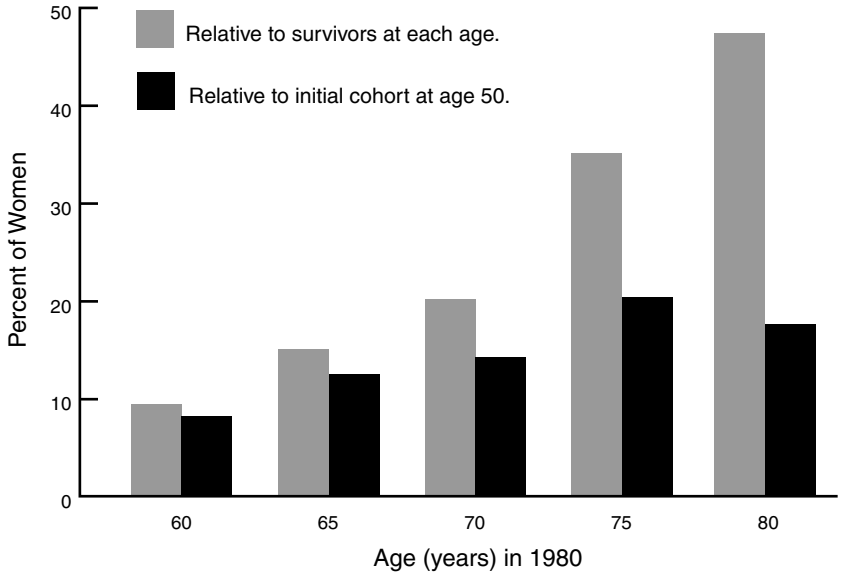



***Figure 1*** *Fraction of women who develop osteoporosis. The darker bar represents those women who are alive and have a vertebral fracture relative to their age cohort at age 50.*

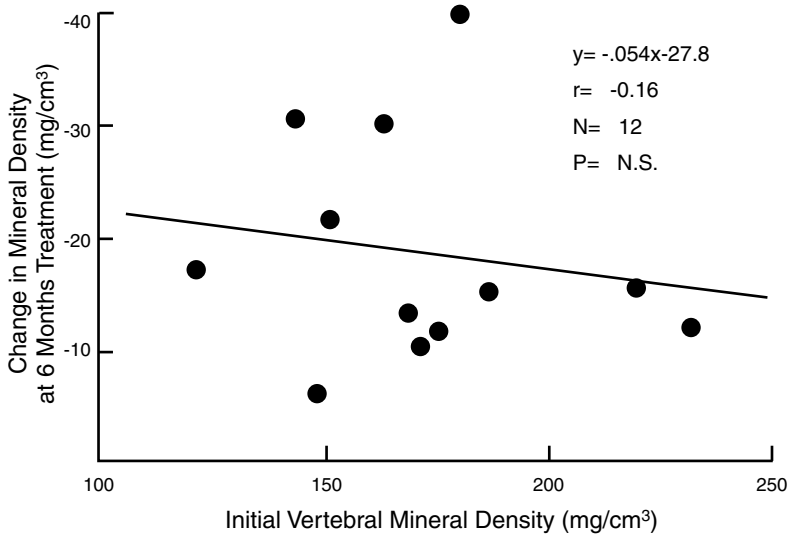



***Figure 2*** *Rate of bone loss in chemically oophorectomized women treated for endometriosis. There is no correlation between absolute rate of bone loss (mg/cm3/yr) and bone mass at beginning of treatment. This suggests that women with higher peak bone do not lose bone faster than others, and will take longer to reach a level of bone mass permissive of fracture.*

Should all women be screened as they approach menopause to determine an absolute level of bone mass? The logistics argue against it but not quite as severely; at 100 subjects per week per center 3 million women per year could be screened. The cost in this case may well be borne at least partially by the patient for the screening exam.

By the time a women has aged well past the menopause (8-10 years) most of the rapid phase of bone loss due to the endocrine stimulus of estrogen deficiency is over, and the rate of bone loss will decrease. Screening this population (60-80 year old women) may be useful in some cases, but the majority of these women are already below the bone mass threshold for fracture; therefore, if they do not have a fracture already, other factors such as frequency of falls (3) may have more importance in determination of future fracture risk than a simple measure of bone mass. Simple screening by bone mass measurement is not indicated in this group; rather a case by case evaluation is indicated.

If we use the result of a screening exam to decide if or how to monitor the patient, and if we expect to see the patient for a repeat exam in the future, the present state of bone mineral measurement technology can limit our ability to use the measurement as a baseline value against which we can compare follow up studies. To do this, we may need to remeasure the patient using a more sophisticated version of our simple screening procedure, thereby more than doubling the initial cost and also increasing the radiation exposure. This is a point generally not recognized by the referring physician (i.e. that the screening exam may not be the same quality as one normally used if the patient is to be followed), and one that must be considered for all bone mass measurements.

Several other indications exist for measurement of bone mass as an adjunct to diagnosis. Alcoholics are at high risk for bone disease (4) as are patients treated with significant doses of exogenous steroids (5). Rheumatoid patients and people with chronic mobility problems may be at risk due to disuse. Surgical menopause is an indication not only for diagnosis but for treatment (6). History or presence of prolonged amenorrhea in premenopausal women leads to decreased bone mass (7); it is not known if bone mass can be increased in this group or whether they will lose more bone at the time of a normal menopause.

Patients with any history of metabolic bone disease such as hyperparathyroidism, Cushings disease or chronic renal failure are candidates for diagnostic skeletal testing.

Conversely, indications exist against screening an individual. The primary contraindication is the woman who has been treated continuously with estrogen since the time of menopause. It is clear from recent case-control studies that these women have significantly more bone and fewer fractures than women who did not receive estrogen (8). However, the intermittent or interrupted therapy may only delay bone loss or prolong the period over which at occurs. The black population in general is not very susceptible to osteoporosis, and thus need not be screened. Once a patient has been determined to have low bone mass (diagnosis), the indication for serial follow up is high. We now know that sufficient and prolonged estrogen use in either naturally or surgically menopausal women can prevent bone loss in most but not all individuals (6, 9, 10). Additionally, some bone previously lost due to the lack of estrogen may be replaced if estrogen therapy is instituted soon enough. A single follow up study in 2–3 years should indicate if treatment is working for each individual, and later testing can be restricted to 4–6 year intervals or anytime treatment is stopped. Other therapeutic regimens to prevent postmenopausal bone loss are not fully effective (10, 11), and more frequent measurement to determine the response of each individual to treatment should be used. In many cases, women are not interested in any long term treatment, especially the use of estrogens. For this group, an initial measurement may determine if either follow up or treatment is indicated. A woman with relatively high bone mass at the time of menopause may only need a single repeat study at 2 years as in the estrogen-treated group to determine if bone mass is decreasing rapidly; if so, treatment can be initiated with some expectation of replacing at least some of the bone which has been lost and maintaining bone mass above the fracture threshold. On the other hand, a person with low bone mass and refusing treatment should be carefully monitored.

What are the other clinical situations in which serial bone measurements are indicated? An important consideration in defining those situations in which serial studies should be done is whether the bone measurements will change the course of treatment for the patient. For example, a patient with mild primary hyperparathyroidism who desires non-surgical management may be at risk for bone loss, and the rate of change of bone mass may influence the decision whether or not to recommend surgery to remove the adenoma. This is especially true in the older postmenopausal population in whom the surgical risk may outweigh the risks of mild osteoporosis. On the other hand, a patient with severe asthma may be treated with high dose glucocorticoids irrespective of their effect on bone. The clinical course of the disease will define the treatment, and bone measurements are only an adjunct to document the effects on the skeleton. Hyperprolactinemia induces bone loss in women due to hypoestrogenemia (7, 12). Management with bromocriptine or surgery can produce slight increases in bone density in some women, but not back to control levels. Whether it will be necessary to monitor hyperprolactinemic women will depend upon the reproductive endocrinologist's decision whether or not to treat this disorder. Women treated with GnRH analogs for endometrosis or leiomyoma lose significant spinal trabecular bone without losing cortical bone, but the bone lost is rapidly replaced in most women when treatment is stopped and estrogen levels return to normal (13). In both treated hyperprolactinemia and GnRH analog treatment, some women do not regain bone. Unless other tests are found to correlate with bone density changes, this subset may drive the requirement for routine bone mass measurements in these populations. Serial measurements in the renal dialysis population may be useful in defining those patients in whom therapy such as 1,25(OH)2D should be instituted. The postmenopausal woman who sustains a vertebral fracture before age 60 may be a "rapid loser" or a patient who will continue to lose bone in the late postmenopausal period; serial measurements and some form of treatment may be indicated. On the other hand, an initial mild fracture at age 70 may be more related to the slow bone loss with aging. Both these situations should be evaluated on a case by case basis. Any postmenopausal osteoporotic patient managed with aggressive therapy (such as high dose fluoride) should probably be followed with serial bone measurements.

For the practicing internist, or gynecologist, or orthopedist, the indications for use of either single or serial bone measurements can be classified on the basis of several factors. The response of bone to a metabolic stimulus (such as estrogen withdrawal) is generally biphasic. There is a period of increased bone turnover and rapid bone loss in response to the stimulus (1–5 years duration) followed by a return of

bone turnover to normal levels at which time bone loss slows down again. During the high turnover period, bone is relatively responsive to therapy, that is, at least some of the bone lost can be regained if therapy is instituted in time. Examples of this are following oophorectomy (6) or disuse (14). Frequent serial bone mass studies can provide valuable information for patient management during this time. On the other hand, if bone turnover is low, the rate of bone loss or a response to therapy is difficult to measure, and longer intervals between measurements are indicated, if indeed serial studies are used at all. Examples are steroid osteoporosis of long standing and postmenopausal osteoporosis in the 65–70 year old patient. A single bone mass measurement is useful in those patients with any risk for developing osteoporosis, especially in the younger (perimenopausal or immediately postmenopausal) female population. It is not so useful in the patient with established osteoporosis unless aggressive therapy is to be started.

Bone mass measurements are not absolute predictors of fracture risk. Only very limited data are available from prospective studies to relate the amount of bone to the subsequent incidence of fractures, and for a given measurement value, it is difficult to determine what the risk for a fracture is per year in an individual patient. However, a substantial body of associative evidence exists between quantitative measurements of bone mass in a population and the prevalence of fracture in that population, including the presence of threshold values above which fractures generally do not occur and below which they may occur. This evidence, while not allowing prediction of fracture risk, allows risk assessments to be made which can be valuable in the clinical management of the individual patient. This is an important consideration in the discussion of the available techniques and their clinical utility.

## The Physiology of Bone

Bone is a complex, heterogeneous organ. This heterogeneity can be classified in many ways. Anatomists classify bone as skull, spine, long bones or plate–type. Bone morphometrists classify it relative to the four envelopes, haversian (intracortical), endosteal, periosteal and trabecular. Radiologists classify it as compact or spongy. All bone formed by the osteoblasts is lamellar, that is, it is laid down in layers, whether it be on a trabecular surface, the periosteum of a growing long bone, or within a newly-resorbed haversian canal within the cortex of a bone. The geometry and rate at which bone is resorbed or reformed is defined by the envelope in which the process is occurring and the stimulus.

Bone is constantly being remodeled in the adult skeleton, at a rate as high as 20–25% per year in spinal trabecular bone or as low as 1–2% per year in femoral cortical bone. Bone resorption normally occurs first at any site, where the osteoclasts eat out both bone mineral and bone matrix; osteoblasts then lay down new collagen matrix which slowly mineralizes. Thus, at any point in time, the bone has some complement of holes (resorption cavities) and partially-mineralized areas of new formation. If skeletal turnover is stimulated, for example by estrogen deficiency, bone mass or density as measured by external means will necessarily decrease because the first event is increased resorption. If the stimulus is maintained, a slow decrease in bone mass over and above the initial drop will occur because osteoblasts never completely refill the cavities produced by osteoclasts. However, if the stimulus is removed and the number of bone resorption sites goes back to normal, the excess sites will eventually mineralize and bone mass will increase again. As the instrumentation for measurement of bone mass improves, these "remodeling space transients" will become more and more important in interpreting measured bone changes. The four envelopes of bone respond differently to metabolic stimuli, when evaluated quantitatively and temporally. As noted previously, all the bone formed is qualitatively the same. The primary factor leading to differences in individual bone response to stimulus is the capacity to recruit osteoclasts from the blood and bone marrow to initiate the remodeling process. Intracortical haversian systems must bring their own blood supply with them, the periosteal surface has a blood supply both from the muscle and from within the bone, the endosteum, including such regions as the compact lamellar bone in the vertebrae, has marrow on one complete surface, and the trabeculae are surrounded by bone marrow. The bone marrow in contact with endosteal and trabecular bone also can have variable content of hemopoetic tissue (red marrow), so the response of trabecular or endosteal bone is both site specific and changes with age as marrow composition changes. The ability of each bone to recruit osteoclasts and the time taken to do so can be used to advantage if this knowledge forms the basis for choice of bone measurement technique in any given clinical situation.

The skeleton as an organ serves two functions, as a reservoir for calcium homeostasis to maintain the serum calcium level constant, and as the support structure to which muscles attach to enable locomotion and maintain posture. Three primary organs are involved in maintenance of calcium homeostasis, the bone, the kidney and the intestine. While a dysfunction such as intestinal calcium malabsorption can lead to slow wasting of the skeleton at a rate of 50–100 mg calcium per day, or 2–3% of the whole skeleton per year, a decrease in renal tubular reabsorption of calcium from 99% to 97% would lead to urine calcium loss of 400–500 mg/day and rapid skeletal loss. The skeleton also has its own homeostatic mechanisms independent of blood calcium. For example, removal of estrogen in women through surgical, chemical or natural menopause apparently signals the skeleton that the "skeletal reserve" built up at puberty for the calcium drain due to pregnancy and lactation is no longer needed, bone turnover increases dramatically, and about 20% of total bone is lost in the ensuing 10 years. The bone loss is exponential, occurs first from the trabecular bone and more gradually from the compact bone, but the whole skeleton is involved. Another example is disuse; as loads are removed from the skeleton through bed rest, paralysis or general lack of activity, bone is lost preferentially from the unloaded areas. In paralyzed patients, as much as 40% of the skeleton is lost as the functional reserve necessary for weight bearing is thrown away. The difference between systemic and local stimulus as well as site specificity based on type of bone and marrow composition mentioned earlier all must be considered in choosing and interpreting a bone measurement.

## The Measurement of Bone Mass

In the past, the techniques routinely available for qualitative or quantitative assessment of bone included standard radiographs of the hips, spine and hands from which were determined a Singh index, fracture number and severity, and metacarpal thickness, respectively. In the mid-60's, single photon absorptiometry of the radius was introduced (15) for measurement of the mass and density of cortical bone in the arm. For 15 years, these were the only widely available measurement techniques. Starting in about 1980 two new methods became available to the clinician for measurement of bone mineral content in the spine, dual-photon absorptiometry (DPA) and computed tomography (CT). SPA of the radius and DPA and CT of the spine and/or hip are the mainstays of bone mass measurements. SPA of the calcaneus and other more specialized, techniques are also used at some centers. Table 1 shows the sites and techniques used for bone mass measurements for both research and clinical purposes.

***Table 1***

Measurement sites and techniques used for quantitative bone determinations. Routinely available techniques are marked with *.

| Site | Technique |
|---|---|
| Peripheral skeleton | |
| Metacarpals | Radiogrammetry*, SPA, Photodensitometry |
| Radius, ulna | SPA*, CT, Compton Radiogrammetry |
| Humerus | CT |
| Tibia | SPA, CT |
| Distal femur | SPA, CT |
| Proximal femur | DPA*, CT |
| Calcaneus | SPA*, CT, Compton |
| Axial skeleton - spine | DPA*, CT*, NAA, Compton |
| Whole body | DPA, NAA |

Abbreviations: SPA–single photon absorptiometry, DPA–dual photon absorptiometry, CT–computed tomography, NAA–neutron activation analysis

## Radiography and Radiogrammetry

By far the most widely available method of assessing the skeleton is routine radiography; an internist or orthopedist can easily order a set of x-rays of hand, spine, and pelvis and obtain a radiologist's interpretation. This may be as simple as a qualitative assessment of the radiographs for presence or absence of fracture or an estimate of the amount of bone compared quantitatively to age-matched norms. It can include semiquantitative indices such as the Singh index (16), a measure of intracortical resorption in the metacarpals (17), or a vertebral fracture index based on number and severity of compression fractures, or it can include quantitative data such as metacarpal thickness (18) or femoral calcar thickness. Of these quantitative or semiquantitative measurements, the Singh index and the metacarpal thickness measurements are perhaps most useful in a clinical setting. A grade 3 or below Singh is generally classified as indicative of osteoporosis and suggests an increased risk for clinically-important hip fracture (16). Its relationship to the presence or absence of vertebral compression fracture is less clear. Most patients classified as osteoporotic by Singh index also will have vertebral fractures, although a subset of hip-fracture patients have normal vertebral density and no spinal fractures (19).

A vertebral fracture index may give a semi-quantitative assessment of the severity of osteoporosis, but its clinical use is not defined. A patient with one or two atraumatic vertebral compression fractures is more likely to suffer more fractures than a patient without any existing fractures (20, 21); once a patient has sustained more than 3–4 fractures the severity of the osteoporosis is no longer in doubt even in the older patient. More important clinically is the presence or absence of atraumatic vertebral compression fracture. At the present time osteoporosis is still defined as low bone mass coupled with at least one atraumatic fracture, and the primary decision whether to treat or how aggressively to treat the osteoporotic patient will depend upon a number of factors such as age past menopause and age at first fracture coupled with a qualitative assessment of the severity of the disease.

A quantitative measurement of the thickness of a bone is termed radiogrammetry, or measuring from a radiograph. The most widespread method in use is the simple measurement of the combined cortical thickness (CCT) of the second metacarpal, midway between the base and head of the bone, quantified by subtracting the inner diameter from the outer diameter (measurements are made with a hand lens with

micrometer or under magnification with precision calipers). This technique has a substantive normative data base as defined by Garn (18), and is of use in assessment of cortical bone. It is best used as a static measurement, to give some information of the status of the cortical bone. CCT can be measured with a reproducibility approaching 1.5% in a research setting; however, the rate of change in this parameter is slow enough to preclude its use for quantitative changes in the individual patient if the study period is less than 2–3 years. For screening patients, CCT is a fast and inexpensive measurement to make and may relate more to the risk of hip fracture than will a trabecular bone measurement in a region such as the spine.

If a high quality hand radiograph can be obtained, other information can be extracted. In particular, intracortical resorption ("tunneling") can be seen when x-rays are taken with fine grain industrial film (17) or with a high contrast screen-film system such as a mammography combination (for example, Kodak Min-R screen with OM-1 film at 48–50 kVp). The presence of intracortical resorption is indicative of high skeletal turnover (17, 22), especially in the immediate postmenopausal period, and may be useful in predicting who is losing bone at that point in time.

## Single Photon Absorptiometry (SPA) of the Radius

The introduction of photon absorptiometry for measurement of bone mineral content (15) provided the clinician a rapid method for assessment of peripheral cortical bone outside the radiologist's office. The Cameron-Sorenson technique uses the attenuation of a highly-collimated beam of photons from iodine-125 to determine bone mineral content; as the beam of gamma-rays traversing the arm passes from soft tissue into bone more photons are absorbed, and a detector on the other side of the object quantifies this change in transmitted photons. This change is then compared to data generated by scanning a reference standard, and the bone mineral content is calculated and read out in terms of grams of mineral per centimeter length of the bone. This technique differs slightly in its information content from the metacarpal thickness in that it measures the combination of bone loss from endosteal resorption (cortical thinning) and intracortical resorption. Thus, it is well suited to the study of diseases such as renal osteodystrophy where intracortical resorption is a significant factor. For most clinical situations, however, CCT and SPA provide similar information.

Several instruments have been marketed in the US and Europe for SPA, including the original Norland-Cameron Bone Mineral Analyzer and similar devices based on scanning at a single place in the radius and the Molsgaard-type instrument which uses a rectilinear scanning pattern to cover a much larger region of the bone. With proper attention to technique, reproducibility for measurement of radial cortical bone is approximately 2%, although it can be significantly worse in the clinical setting, up to 3–4%. The rectilinear scanning methods can improve reproducibility to the order of 1% in research settings.

Some investigators have attempted to use SPA to measure "trabecular" bone in the wrist. The routine scanning site in the radius (one-third the distance proximally from the ulnar styloid) is virtually all (>95%) cortical bone; the "trabecular" site is approximately 75% cortical bone and the "ultra-distal" site is about 50% cortical bone (23). It is therefore very difficult to make any statements about trabecular bone changes using SPA of the radius.

## SPA of the Calcaneus

Recently the technique developed for measurement of bone loss in the astronauts has become commercially available. The calcaneus contains a substantial proportion of trabecular bone and so has been thought to be a good site to monitor changes in this more metabolically active type of bone. Unfortunately, this bone is also very responsive to weight bearing (14, 24), so the factors of body weight and physical activity must be properly considered when interpreting these measurements. Prospective data have been published relating calcaneal mineral density to fracture incidence in a large ethnic population (25), but the utility of this technique in following bone changes with time is not established other than for bed rest subjects.

## Dual Photon Absorptiometry (DPA) of the Spine and Femoral Neck

A logical extension of the SPA technique was development of methods to measure areas of the body besides the radius. Specifically, the spine and the femoral neck are two regions which are very important clinically because these are the areas in which fractures occur often in the osteoporotic patient. Unfortunately, the extension of SPA was not straightforward; two characteristics of the regions to be measured required significant technical development. First, scanning through a thick object such as the abdomen or pelvis precluded use of low-energy iodine-125 as the photon source. Secondly, these body parts were uneven in their geometry and not easily covered with a tissue-equivalent material, as was the radius, to provide a constant thickness or path length for the photon beam passing through the tissue. In addition, a much larger area needed to be scanned to provide a representative sample of bone for measurement.

Several different approaches have been used to attack these technical problems. Photon absorptiometry using two different photon energies can solve the problem of variable object thickness (26). The original techniques used radioisotopes of moderately high energy (principally gadolinium-153) to provide these two photon energies (26, 27), although some investigators used filtered x-ray sources (28). As x-ray sources became refined, newer instruments have come to market using these sources because of their inherent advantages of high photon output and lower replacement cost. In addition to compensating for variable object thickness, DPA systems must incorporate some form of imaging subsystem to allow identification of the region of interest to be analyzed, excluding ribs and ilium from spine scans and the acetabulum from hip studies. This can be done in two ways: 1) a single well collimated beam scanning across the third lumbar vertebra, localized by a low-dose AP x-ray (29), and 2) a rectilinear raster scanning pattern with post-acquisition processing of data to define the region of interest (30, 31). The second approach is the one used by commercially available systems.

X-ray source DPA systems have been commercially available for a couple of years, and eventually will replace radioisotope source systems. These instruments have been labeled with as many names as there are manufacturers: dual energy digital radiography, dual energy x-ray absorptiometry (DEXA), quantitative digital radiography (QDR), new advanced method enhancements: digital imaging with spatial enhancements and spectral engineering (NAME DISEASE). In fact, the basic physics underlying the x-ray based techniques falls into two categories: 1) an extension of classical DPA algorithms where filtered x-ray spectra are treated as though they are broadened isotope sources, with appropriate corrections, or 2) a projection-image implementation of the material-selective imaging techniques developed for computed tomography and in use since 1975 (32). The main advantage of the x-ray based DPA techniques is speed; the high output of the x-ray source overcomes the limitations of the low photon output of Gd-153 sources. A "high-resolution" scan which used to take 30–45 minutes can be done in 8–10 minutes, minimizing errors due to patient motion. With the x-ray source has come other improvements. The focal spot of an x-ray tube (50–500 microns) is significantly smaller than the size of a 1-Curie Gd-153 source (3–4mm diameter), and with a smaller detector aperture has improved the image quality of DPA instruments by a factor of 2–3 over the radioisotope-based systems. The combination of speed and image quality improvements has led to an improvement of about a factor of 2 in reproducibility for DPA. Recent publications have shown that the x-ray DPA systems can measure spinal bone mineral density with a short-term reproducibility of 1–1.5% (33, 34), compared to 2–3% for Gd-153 based systems.

The technical development of DPA has reached a stage where the technique is clinically useful. Further refinements will continue, but the capability to measure bone in the lumbar spine and femoral neck with reasonable accuracy and reproducibility has been demonstrated. Reproducibility has been reported to be about 2% for radioisotope DPA (35) and 1–1.5% for x-ray DPA (33, 34) and accuracy for mineral content in normals about 3–5% (36) in the research setting. Present research is directed at defining the clinical situations where DPA is most useful, and at solving the biologic problems which affect the accuracy and reproducibility of measurement. DPA measures all mineral in the path of the beam. In the spine, this consists of approximately one-fourth trabecular bone and three-fourths compact bone in the vertebrae in normal subjects and perhaps as much as 80% compact bone in osteoporotics (37), in addition to any extravertebral calcification in the aorta and osteophytes or reactive sclerosis in the endplates. This "non-vertebral" mineral content can be as much as 10–15% of the total mineral in the beam in older

subjects (38), so this must be taken into account when a "vertebral mineral" value is reported or compared to normal. One point to be remembered is that spinal compact bone is not the same as cortical bone in the radius or femur; it is much more labile, similar to endosteal cortical bone, because one-half of its surface is in contact with bone marrow. Thus, DPA of the spine, even with a high proportion of compact bone, can be much more sensitive than SPA depending on the clinical situation.

As with peripheral cortical bone measurements, quantitative spinal bone mass values are not diagnostic of osteoporosis. Osteoporotics have lower spinal mineral content than age-matched controls when measured with DPA (39), but significant overlap between the groups exists. A measurement of bone mass below a "threshold" value of 0.95 g $cm^{-2}$ (39) is permissive but not predictive of fracture, that is, patients with mineral content above this level generally do not have fractures while those below it may have fractures. However, a bone mass measurement in an individual patient cannot be used to predict at what risk the individual is for sustaining a fracture within a given time period.

The primary clinical utility of DPA rests in its ability to provide a reasonably reproducible measurement of total spinal mineral content. Because the spine contains substantial quantities of trabecular and labile compact bone, the sensitivity of DPA is greater than SPA measurements of radial cortical bone, and DPA will be expected to show a change in responses to treatment or progression of disease earlier than will SPA. In addition, trabecular bone responds differently than cortical bone in some diseases or therapies (40, 41), so both measurements of trabecular and cortical bone can be useful. DPA is (like SPA) often accessible to the clinician in his office, without necessity of a radiologist's involvement. DPA is not a screening procedure; at present the technique requires 15–20 minutes of setup and scanning time. Cost is approximately $150 in the San Francisco area.

DPA is well suited for measurement of total bone mass in the femoral neck; the improved image quality of x-ray DPA has also allowed regional measurements to be investigated, although with lower precision. However, because of the large overlap between these measurements in normal and osteoporotic patients, the measurements cannot be used to predict an individual's risk of hip fracture, irrespective of manufacturers' claims. It is quite possible that the rate of falls or simple mechanical stresses from torsional forces in the hip may have more to do with determining who will sustain a hip fracture and who will not than will bone mass. There is significant cortical bone in the hip and trabecular patterns are visible on plain x-ray. A combination of a peripheral cortical measurement and evaluation of the Singh index may prove as useful or more useful than a measurement of total bone mass at this site.

## Quantitative Computed Tomography (QCT) of the Spine

At about the same time DPA was under development for measurement of spinal bone, the new technique of computed tomography (CT) was being introduced into radiology as a powerful new diagnostic tool. CT is another extension of photon absorptiometry, but for a much more general purpose. Rather than a simple measurement of the photon attenuation along a fixed line through an object, as in SPA, a series of measurements are made at any point along that line by (in effect) rotating the source and detector about that point. Thus, a point on the line is "viewed" from up to a thousand different directions. Through the mathematical process known as projection reconstruction these points along the line are separated from one another, as are points along other lines which make up the two-dimensional axial image plane. This process of reconstruction of the CT image produces a map of the x-ray attenuation coefficients in a cross-sectional "slice" of the body, and these coefficients can be used to determine tissue density at any point in the image (Figure 3). The size and number of points along a line in current CT scanners is variable depending on the object being scanned, but ranges from points 0.25 mm up to 1.5 mm in size, and typically 256–512 elements lie along the line. Each "slice" of a patient scanned can also have variable thickness (the portion exposed to the x-ray beam), ranging from 1 mm up to 10 mm thick. Each point, or element, in a given reconstructed image is the same size, but this size can vary from 0.25 x 0.25 x 1 mm (0.0625 $mm^3$) to 1.5 x 1.5 x 10 mm (22.5 $mm^3$). When viewed on a display monitor, these points are called picture elements, or "pixels"; when stored in the computer and used for quantitative purposes, they represent volume elements because of the finite slice thickness, and are termed "voxels."

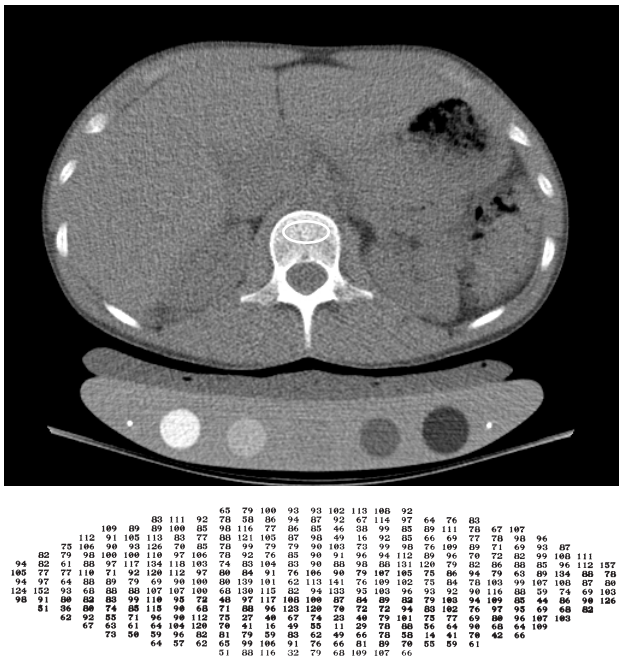


***Figure 3*** *Top: CT scan through a lumbar vertebra in a patient. Bottom: Map of CT attenuation values defined by region of interest outlined in vertebral body.*

A single CT scan is a two-dimensional representation of a three dimensional object. A projection image, such as obtained by DPA, is also a two-dimensional form of three-dimensional data. The difference between CT and DPA is basic, however. By taking multiple CT scans adjacent to each other, a true three-dimensional representation of the data in the volume can be obtained, and each voxel is uniquely identified in space (Figure 4). This is not possible with DPA, because the superposition of structures cannot be eliminated in a pure projection method. Thus, more data is always obtained from CT than from DPA.

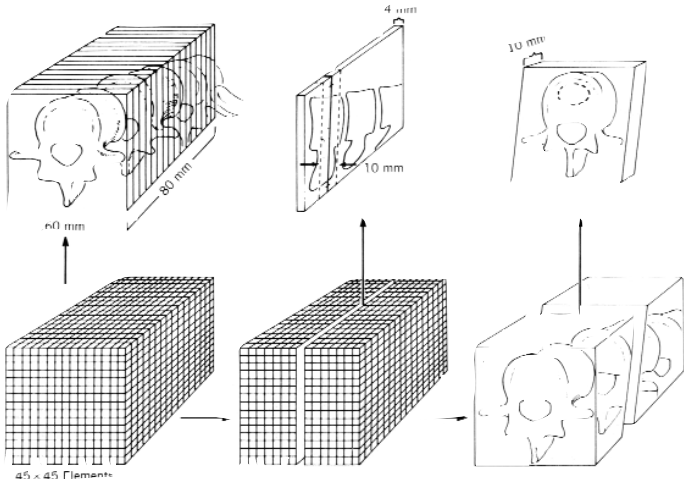



***Figure 4*** *A schematic representation of three-dimensional nature of CT scans. Multiple contiguous images define a volume of individual voxels, each defined as a volume in space with a measurable x-ray attenuation coefficient.*

As with the other techniques, CT has its technical problems. In early studies, the accuracy and reproducibility of measurement of vertebral mineral content was severely limited by machine inaccuracies and lack of a means of precisely positioning a volume of bone for analysis. These problems were largely solved in the late 70's by use of a reference calibration phantom to reduce machine inaccuracies and sophisticated repositioning algorithms (42). However, because of the computer time required to implement these methods, they were restricted to a few research centers. With the introduction of high-accuracy computed radiographic localization systems built into CT scanners in 1980–82 (ScoutView, Pilotscan, Scanogram, Topogram, etc.) an adequate capability for positioning the scan plane to the center of a vertebra was made available to virtually everyone with an advanced CT scanner (Figure 5).

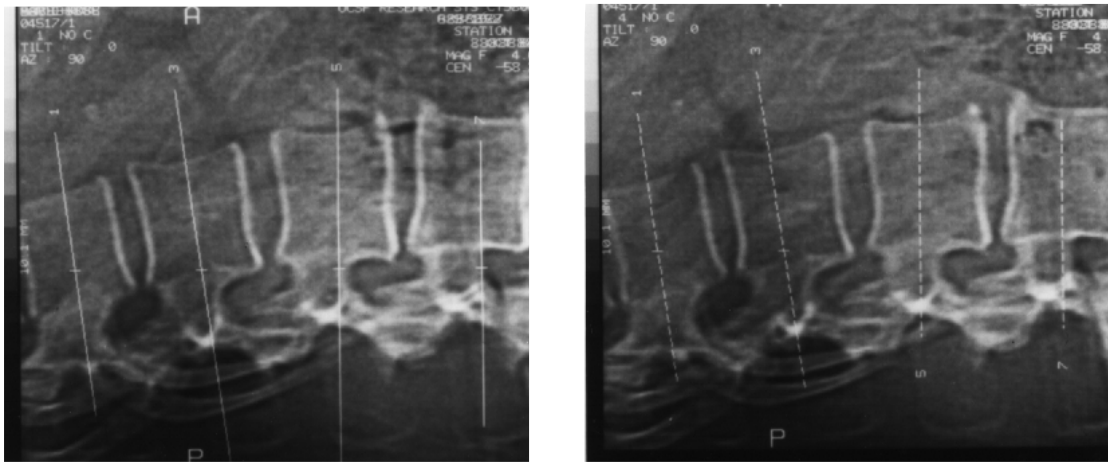



***Figure 5*** *Left: Computed radiograph of the lumbar spine showing localization of mid-vertebral planes for CT scans. A single 10 mm thick scan is obtained at the location and angle of each cursor. Right: Repeat scan after study is finished, showing that patient has moved. This is one source of error for the technique.*

In addition, a standardized version of the UCSF CT Mineral Calibration Reference Phantom was made commercially available and distributed to over 600 centers worldwide (Figure 6) and other versions of the same concept have also been marketed. While cross calibration between different models of CT scanners must still be done, these data are available (43) and allow one researcher or clinician to compare results with others. Reproducibility in the clinical setting ranges between 1.6% to 4% in osteoporotic patients, with the better values seen at institutions where good quality control procedures have been used (44). At UCSF, development of advanced repositioning algorithms continues, and at present in vivo reproducibility for techniques similar to those used over the last 8 years (45, 46) is about 0.7% in normal and early postmenopausal women (13, 47). While still computationally intensive, hardware improvements in newer CT scanners promise that these techniques may become generally available.


***Figure 6*** *Photograph of standardized version of CT mineral calibration phantom in use at over 500 centers worldwide. The phantom contains bone equivalent materials and is scanned with the patient to provide an internal reference standard (see figure 3).*

Other improvements in CT scanners have significantly lowered the x-ray dose necessary to make quantitative measurements. Early scanners operated at a dose of approximately 2–3 rads for imaging purposes and this was lowered by a factor of two in more recent scanner models (48). However, these doses of 0.8–1 R are too high to do multiple scans in an individual over a 1–2 year period. Fortunately, the use of a calibration standard allows the x-ray dose to be reduced significantly (49). Typical doses at the present time are 0.1–0.3 R (100–300 mrem) per study, with the dose localized to about 10 cm in the abdomen, and with no gonadal radiation exposure. At UCSF, this dose is used in studies in which three scans are obtained in 6 months in premenopausal, fertile women, and dose is no longer considered a significant factor in the decision whether or not to order a vertebral mineral measurement by CT.

All bone mass measurement techniques have some inaccuracies due to physiologic variables such as body composition. For peripheral cortical bone measurements these errors tend to be small; for spinal measurements they can be somewhat larger. Some of the errors for DPA were mentioned earlier. CT, because of its ability to measure an isolated region of purely trabecular bone, is sensitive to one physiologic variable, marrow fat, that produces a smaller error when using such methods as DPA which cannot measure isolated trabecular bone. CT using a single effective x-ray energy (single energy CT) measures the x-ray attenuation of a region of interest with an accuracy of approximately 1%. In a two-component system, such as bone and red marrow or fat mixed with muscle, each component within a region of interest can be determined independently because of the known properties of each of the two materials and the fact that the sum of the volumes of the two materials must equal the volume measured. However, if a third component of known properties (density, x-ray attenuation) is introduced into the mixture, but at unknown concentration, the concentration of any one of the components cannot be calculated uniquely. This is the situation with the vertebral trabecular space–it is filled with a mixture of bone, red marrow and yellow (fatty) marrow (Figure 7).

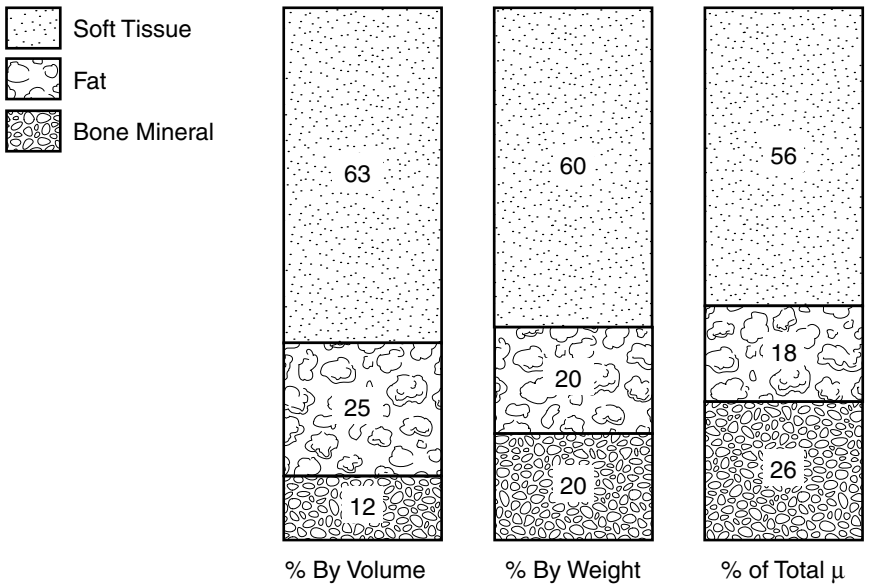



***Figure 7*** *Composition of the vertebral cancellous bone mixture of a typical adult in terms of weight, volume, and x-ray attenuation coefficient for an 80 kVp incident beam. Bone mineral represents a small fraction by volume but a more significant fraction by attenuation. Variable composition of the marrow space (fat plus soft tissue) can cause underestimation of true bone mineral content unless correction factors are applied or dual energy CT is used.*

Fat in the marrow space lowers the attenuation coefficient of the region of interest, and the vertebra looks like it has less bone than is actually there. Fortunately, this error can be corrected in one of two ways. First, rather than scanning at a single energy, we can scan at two energies (dual energy CT) and determine the bone mineral content independently of the soft tissue components. Theoretically, this is the preferred method; in practice it is often difficult to implement because of machine limitations. In population studies, it is not necessary to use dual energy CT for comparison of groups because it does not appear that specific metabolic bone disease processes alter the marrow composition significantly (50). Age-related changes in marrow fat do occur (51) but the interindividual variations in marrow fat as a function of age are known so an empirical correction can be applied to single energy CT data to provide a "fat-corrected" result (Figure 8). This empirical correction, determined for each model of scanner using a known bone-fat mixture (43), has been shown to reflect the results from dual energy CT (52), and the accuracy of bone mineral density is 5–8% using these corrections or dual energy scanning. For routine clinical studies, dual energy CT is not necessary; however, if available it is a procedure useful in obtaining a more accurate baseline measurement in each individual before treatment is initiated.

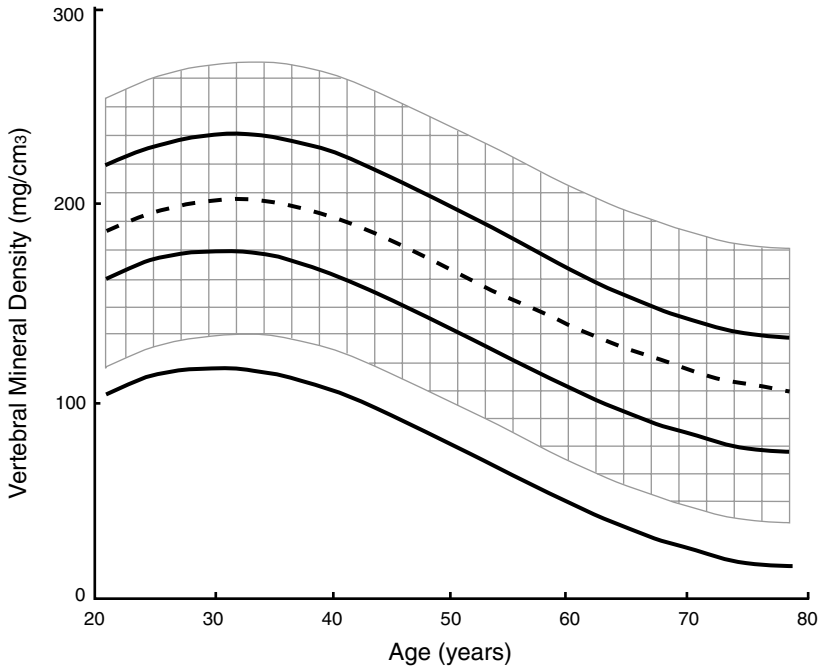



**Figure 8** *Effect of fat on normal curve for vertebral mineral content in females. Solid lines show mean and 90% confidence intervals for single energy CT data. Dashed lines are mean and 90% confidence intervals for "fat-corrected" single energy data, based on known CT scanner characteristics and measured vertebral fat data from reference 51. For population studies, this empirical correction is supported by dual energy CT data (52).*

What is the clinical utility of CT for vertebral bone mass measurements? As for the other techniques, it is not used to diagnose osteoporosis, because significant overlap in bone mineral density exists between subjects with and those without vertebral fractures (46). Threshold levels are again defined, above which patients do not normally fracture and below which they may fracture; for single energy CT this level is approximately 110 mg/cm$^3$ (46, 53). Figure 9 shows the distribution of measurements in 50–80 year old females, with and without fracture. It is apparent that a bone mass measurement is not sufficient to classify a patient as osteoporotic. However, we can reasonably assume that a patient with a bone density less than the fracture threshold is in a group with a higher risk of fracture, although we cannot determine what that risk is for the individual patient.

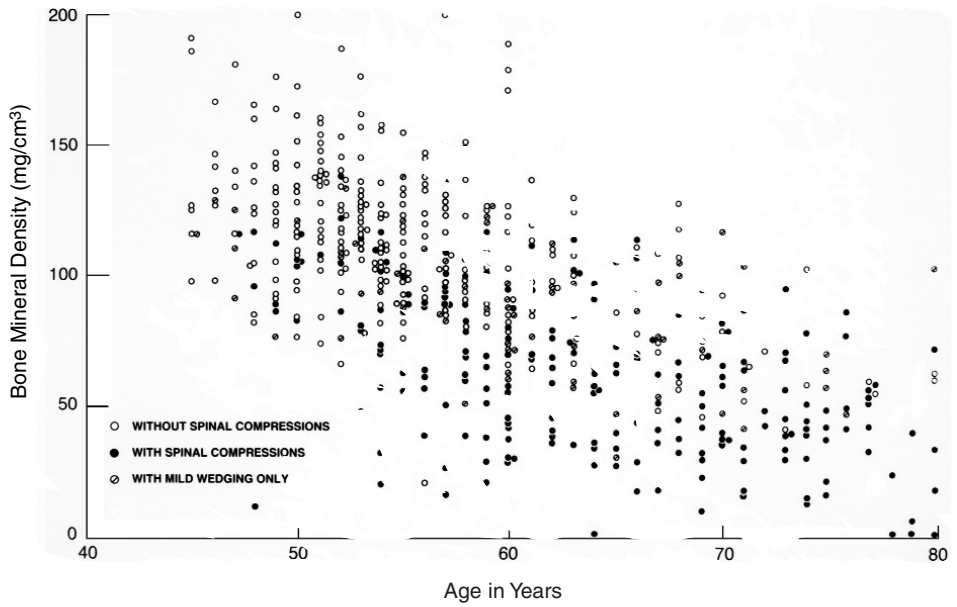



***Figure 9*** *Vertebral trabecular mineral content in normal postmenopausal (o) and osteoporotic (•) women age 40-80. Threshold level at approximately 100 mg cm$^3$ must be reached before fractures occur; however, they do not necessarily occur once this level has been reached.*

In the younger population (premenopausal or immediately postmenopausal women) a single measurement of bone mass may provide information useful in the clinical management of that patient. CT can measure purely trabecular bone in the spine, and this is the area of bone which will respond most rapidly to a metabolic stimulus because of its very high turnover rate. This is important in serial studies because the sensitivity to change will be greatest with CT. When we obtain an initial measurement, however, we do not know what the value was in an individual subject before the metabolic change, so we cannot calculate how much bone was lost. This is true for all bone measurements. The range for bone mass measurements can be defined from one standard deviation above the normal mean to one standard deviation below the osteoporotic mean, however, and this range is quite narrow for the radius, moderate for DPA and very wide for CT (Table 2).

***Table 2***

Range of mineral values in normal and osteoporotic females: one standard deviation above normal mean to one standard deviation below osteoporotic mean. Mean age 65 years. Data from reference 39 and reference 46.

| | Mean | | Range | |
|---|---|---|---|---|
| | Normal | Osteoporotic | % Decrement | (% of normal mean) |
| Radius (g cm$^{-2}$) | .610 | .575 | 5.7 | 80–115% |
| DPA (g cm$^{-2}$) | .963 | .777 | 19.3 | 67–116% |
| CT (mg cm$^{-3}$) | 113 | 65 | 42.5 | 29–129% |

The expansion of this range with CT is predominantly due to more bone loss in the osteoporotics rather than extension of the normal range upward from the normal mean, and the fact that individuals never lose all their radial or vertebral cortical bone while it is not inconceivable to lose virtually all vertebral trabecular bone (Figure 10).

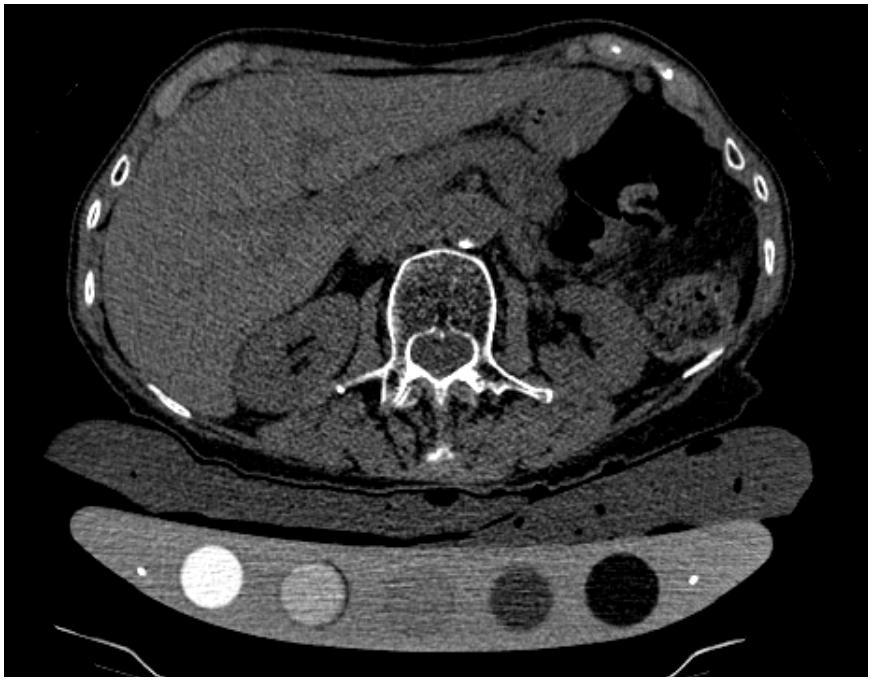


***Figure 10*** *CT scan of the lumbar vertebra of an elderly osteoporotic woman. Note almost complete absence of vertebral trabecular mineral. CT number of –21 at 80 kVp gives a measured mineral content of -10 mg $cm^{-3}$; dual energy results confirm low mineral at 6 mg $cm^{-3}$ (trabecular bone volume of approximately 3%).*

An individual losing bone may be more likely to drop below a "fracture threshold" earlier as measured by CT, and a low measurement by CT in such an individual within the first few years following a stimulus (such as estrogen withdrawal at the menopause) may be an indication for treatment. In contrast, because of lower turnover a measurement of cortical bone or integral spinal bone may take longer to define the person with "low" bone mass in the early menopausal years, even though at age 65 the measurements may provide essentially the same information as CT.

The greatest potential clinical value of CT lies in its use in serial patient studies. In our studies at UCSF we have seen maximal losses of 19% per year in the spine in oophorectomized women while maximal radial losses were 3.5% per year (6). The reproducibility of the CT and SPA techniques in our hands is comparable, so that the sensitivity to change is 5–6 times greater for CT. It is now possible to follow the progression of bone loss or the response to therapy in a two-year time frame rather than the 4–5 year period normally necessary when using peripheral cortical bone measurements.

More recently, studies in women treated with GnRH analogs shows the extreme lability of trabecular bone; average loss of 7–8% in 6 months is almost completely recovered by 9–12 months post-treatment (Figure 11), with individual variability in patterns of loss evident (Figure 12). This is in contrast to DPA measurements in a similar population, where only group data can be used to show an effect of treatment (Figure 13). With the recent improvements in DPA reproducibility, the intermediate sensitivity of DPA (between CT and SPA) should allow an improvement in individual patient management using this technique. Similar improvements are possible in CT, but have not yet been implemented for the majority of users.

***Figure 11***
*Change in spinal trabecular density by CT in women treated for 6 months with a GnRH analog. Rapid loss of 7–8% in 6 months is almost completely recovered within 6 months post-treatment. Also noted is the fact that the changes are well within the normal range seen for this age group.*

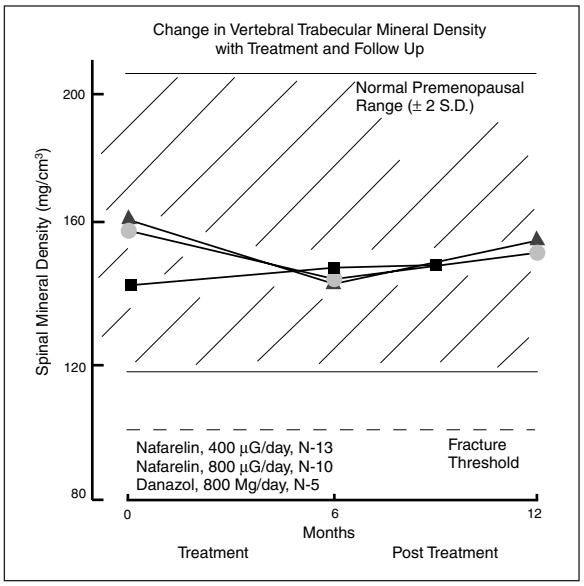



***Figure 12***
*Individual changes in the same women; data shown for 3 months, 6 months of treatment and 6 months follow up. Error bars for each data point are + 1.1 mg/cm³. Different individual patterns of bone change can be observed.*

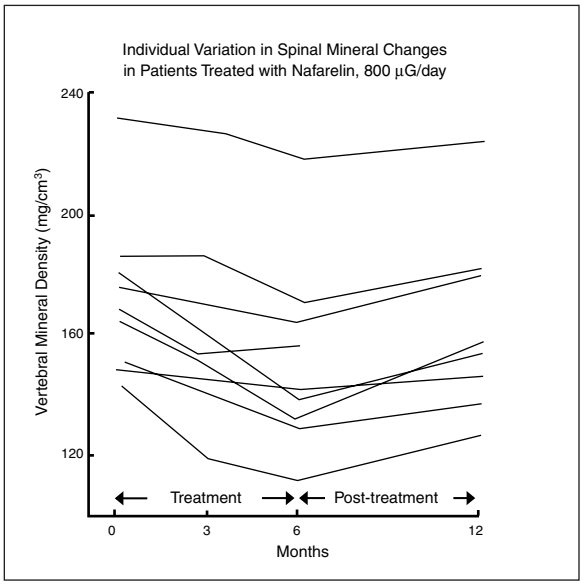
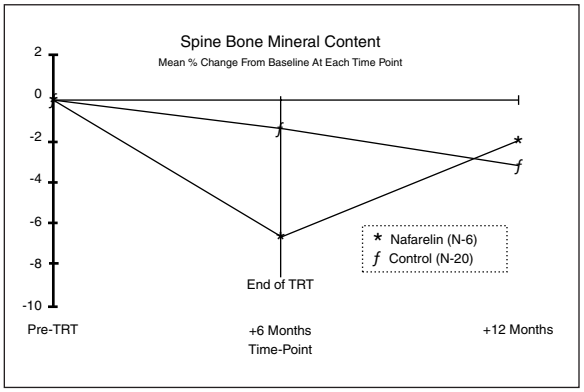



***Figure 13***
*DPA results in a similar population show wide variation in the data, although group means show the same pattern of bone change as is seen by CT.*



The fundamental advantage of CT over all other bone measurement techniques is its three-dimensional nature. The quantity of bone is important in evaluating patients; however, the quality of bone is recognized as a major factor as well. Mechanical stability of bone, that is, resistance to fracture under applied loads, depends on the amount, microscopic quality and distribution of the complete bone, including mineral and matrix components. Three-dimensional mathematical models can be used with real data obtained from CT to determine fracture resistance of individual bones (54). While these 3-D methods are not yet available to the average user of CT bone mineral methods, there is no fundamental reason they cannot be used in routine clinical practice, similar to the way both routine CT and DPA have evolved from the research setting.

## Radiation Exposure

All methods to measure the "density" or "mass" of bone use the attenuation of photons as an index of the amount of bone mineral. Therefore, they involve the exposure of a subject to small amounts of radiation. Unfortunately, the perception of radiation exposure to clinicians as well as their patients is anathema; any amount for medical diagnosis is to be avoided but a week-long ski vacation in Vail bears no risk. The primary risk organ from bone densitometry procedures is the bone marrow, because most measurements are made in the spine or wrist. Hip measurements expose the gonads as well. Many people try to relate the exposure to "a chest x-ray" or "a lumbar spine series". However, bone density measurements are localized; they do not expose the whole body to radiation. A 10 mrem spine exposure plus a 10 mrem hip exposure does not equal 20 mrem, it equals 10 mrem to a larger volume. This basic concept is misunderstood by most patients and clinicians, and this misunderstanding is reinforced by manufacturers of equipment touting the "lowest dose exam". In fact, the radiation exposure risks from all bone densitometry exams are very small compared to natural background radiation.

Bone marrow composition changes with age, with a gradual decline in the radiation-sensitive hemapoetic tissue. An estimate of the risk of any bone densitometry procedure can be made by using the marrow composition of the area exposed, the volume of that area, and the radiation dose delivered by the procedure to that area to calculate a "whole body equivalent" exposure risk, that is, the risk resulting from an exposure to the whole bone marrow space (for example from a whole body DPA exam or from a cross-country plane flight). Table 3 gives these "whole body equivalent" exposures from most commonly used procedures (55). The most recent National Commission on Radiation Protection report has estimated a natural background whole body exposure of approximately 350 mrem per year, or 1 mrem per day, and estimates that the lifetime cancer risk increases at the rate of 1 cancer per 10,000 man-rem exposure. Thus, the relative increase in risk due to these procedures are in the range of $10^{-6}$ to $10^{-7}$, compared to a lifetime cancer risk from all sources of 10–15% ($10^{-1}$).

***Table 3***

Whole Body Equivalent Doses (mrem)

| Exam Age | 5 | 10 | 20 | 30 | 50 | 70 |
|---|---|---|---|---|---|---|
| Chest X-ray | 4.2 | 3.9 | 3.2 | 2.9 | 2.5 | 2.2 |
| AP Lumbar Spine | 2.1 | 2.0 | 1.8 | 1.7 | 1.6 | 1.4 |
| Lateral Lumbar spine | 13.1 | 12.2 | 11.2 | 10.7 | 9.9 | 8.8 |
| Bilateral Industrial Hand | 35.1 | 18.9 | <4 | <4 | <4 | <4 |
| Bilateral Mammo Hand | 1.0 | 0.5 | <0.1 | <0.1 | <0.1 | <0.1 |
| SPA Radius | 0.2 | 0.1 | <0.02 | <0.02 | <0.02 | <0.02 |
| QCT Spine | | | | | | |
| ScoutView | 4.8 | 4.5 | 4.1 | 3.9 | 3.6 | 3.2 |
| Single Energy | 0.9 | 0.9 | 0.8 | 0.7 | 0.7 | 0.6 |
| Dual Energy | 2.6 | 2.5 | 2.2 | 2.1 | 2.0 | 1.8 |
| DPA Spine | 0.4 | 0.3 | 0.3 | 0.3 | 0.2 | 0.2 |
| DPA Hip | 0.7 | 0.7 | 0.6 | 0.6 | 0.5 | 0.5 |
| Natural Background (per month) | 22.4 | 18.1 | 10.7 | 9.3 | 8.4 | 7.5 |
| Transcontinental Flight | 3.7 | 3.0 | 1.8 | 1.5 | 1.4 | 1.2 |

## Combination of Measurements and Choice of Measurement

For the practicing clinician, several choices must be made. First, the decision is made that a bone measurement is indicated, based on clinical impression. The question then arises which measurement or combination of measurements will provide optimal clinical return. Not only do cortical and trabecular bone have different turnover rates, but they behave differently in different metabolic diseases. We also know that multiple metabolic disorders can coexist in a patient. The choice of measurement(s) on an initial visit may depend somewhat on the diagnosis—for example, a patient being started on steroids or with existing Cushing's Syndrome may not need a cortical bone measurement but a spinal measurement would be necessary. However, if this patient was going through menopause concurrently a cortical measurement would also be indicated. Most patients are sent for a bone mass measurement with the anticipation of an eventual follow up study, whether it be at 6, 12, 24 months or greater intervals. Thus, even if the initial measurement is done for a "diagnostic" purpose, a technique should be used which will afford the capability of follow up at a later date with a sensitivity adequate to determine if bone mass has changed. For the vast majority of patients, a spinal mineral measurement is best for this purpose; to determine changes in 1–2 years CT is optimal, for 2–3 years either CT or DPA can be used. Peripheral cortical measurements are less sensitive, needing 3–5 years with routine methods to show a significant change in most cases. However, a peripheral cortical measurement at the time of the first study is useful in staging the patient.

A significant change in bone mass can be defined in several ways, either on the basis of two measurements or a series of measurements. When only two data points are available, the measurements must typically be separated in magnitude by three times the coefficient of variation of the technique, normally on an absolute bone mass basis. For example, a radial measurement of 0.750 g/cm, with a 2% reproducibility, would have to change by 0.045 g/cm between two measurements to be considered significant; a CT measurement of 100 mg/cm$^3$ with 2.5% reproducibility would have to change by 7.5 mg/cm$^3$. Care must also be taken to specify how the reproducibility is measured. Most investigators quote reproducibility as a percent of some normal young healthy population mean, and it should actually be quoted in terms of absolute bone mass units because a significant fraction of errors tend to be absolute rather than relative. Thus, for CT, 2.5% of a mean of 175 mg/cm$^3$ for premenopausal women, or 4.4 mg/cm$^3$ could be a 5%

reproducibility in an osteoporotic population. In practice, errors are part relative and part absolute. For the use of the CT measurement, a nominal absolute change of greater than 8–10 mg/cm$^3$ would be considered significant if proper quality control procedures are observed.

For women in the immediate postmenopausal period, annual vertebral mineral changes of 5–10% can easily be seen in 1–2 years. The discrimination of those women losing at a relatively fast rate from those losing more slowly or not at all can normally be made in this time. For the older postmenopausal woman managed conservatively, the 1–2% per year bone loss normally seen with aging may require 3–4 years before it can be quantified. If, however, aggressive treatment is started that may be expected to result in rapid changes in bone mass (such as sodium fluoride) a more frequent measurement is indicated.

A major drawback to the use of frequent measurements to determine the rate of change of bone mineral is the clinician's response to the second measurement. A clinician must both recommend to the patient when a follow up measurement is indicated and then provide the result to the patient. Oftentimes patients will not wish to have frequent tests, especially if they cost $100–150; when a repeat test is done they want to know if they are better or worse. A change in mineral density from 100 mg/cm$^3$ to 97 mg/cm$^3$ would not be significant, but a patient may want to know why the physician is unresponsive to demands that treatment be changed to halt this terrible bone loss. The recommendation to the patient to wait another 6–12 months to really find out what is happening may cause the patient to change physicians. It is up to the clinician to be as knowledgeable as possible about the techniques being used. The expert opinion of the radiologist or other responsible party must not be isolated—it must be incorporated by the clinician into an overall assessment of the change in the patient's status since the last visit.

Lastly, the choice of measurement may have nothing to do with the patients being studied, and may depend solely on availability of a method. The combination of a metacarpal index measurement and a Singh index may be all that is available, and all that is necessary, in an older osteoporotic population. Initial studies for most patients should include one peripheral cortical (hand film, SPA) and one spinal (CT, DPA) measurement. In order to follow patients with time, the more sensitive spinal measurements are preferred; cortical bone measurements can be used but the frequency of measurement need not be as great and one must recognize that it may take 3–5 years before a definite change can be seen (the newer devices for radial measurement may improve on this). The decision whether or not to treat a patient may not need a quantitative measurement for support. However, the decision to modify treatment when it does not appear to be working is generally made based on quantitative results. A clinician must be familiar with the techniques available to him or her and to interpret the results accordingly.

## Illustrative Clinical Scenarios

For the general internist or orthopedist the primary clinical decision for the individual patient is whether or not to treat that patient. Part of that decision-making process may be the use of a bone mass measurement. The following cases are representative of the situations which arise and in which these decisions are necessary. They are not intended to be inclusive or representative of every patient–each case must be considered in the context of other clinical information.

### Case 1

A 32–year old woman reads an article on osteoporosis in the newspaper which discusses premature menopause. She tells her gynecologist her normal menstrual cycles stopped 3 years ago, but she did not seek treatment at the time. At the present time, FSH and LH levels are elevated indicating premature ovarian failure. There is no family history of osteoporosis but she is of slight stature and dietary calcium is estimated to be 500–600 mg/day.

*Indication:* Women with premature ovarian failure have lower bone mass than normal, with spinal trabecular values 25% below age-matched controls (7). These women are generally not yet at or below the vertebral fracture threshold and of 60–70 seen at UCSF none have had vertebral compression fractures. However, in premature menopause as in natural menopause and surgical menopause (oophorectomy) it

appears that bone turnover is high for several years during which time most bone is lost. During this time treatment can be effective in actually restoring some of the bone which has been lost. A patient three years past her last menstrual cycle would be considered in this "treatable" category. A spinal bone measurement with relatively high reproducibility should be done, along with a high quality hand radiograph to judge intracortical resorption or biochemical measurements to determine if turnover is grossly elevated (osteocalcin, alkaline phosphatase, urinary Ca/creatinine or hydroxyproline/creatinine). If the bone measurement is low, treatment should be recommended; if it is normal or high and turnover is low, the patient is probably not losing bone and could be followed with a repeat bone measurement in 2–3 years.

**Case 2**

A 64–year old woman, 13 years past menopause, consults an orthopedic surgeon because of back pain; two vertebral compressions are noted, one of which appears to be recent on a Tc-99m bone scan. Interview reveals another, less painful episode 2 years earlier. The woman has had no treatment since menopause except estrogens prescribed by her gynecologist for 6 months following menopause. Calcium intake is normal for a postmenopausal woman (400–500 mg/day).

*Indications:* A woman in whom vertebral compressions first appeared 10 years following menopause probably lost a significant amount of bone in the first few years after menopause, after which the rate of bone loss decreased. Of particular concern at this point is the later possibility of hip fracture; a hand film for metacarpal thickness measurement coupled with evaluation of a Singh index would be useful. Quantitative measurement of spinal bone would be of little use if the patient is managed conservatively, with calcium supplements and counseling to become somewhat more active by mild exercise. Because the patient was still relatively young at first fracture she should be followed carefully, especially noting if the Singh index changes. If the cortical bone measurement is low, more aggressive treatment may be considered.

**Case 3**

A 52–year old male with chronic low back pain finally goes to the orthopedic surgeon, with injury traced to an episode 12 years earlier. A CT scan reveals a broad-based disc at L4–5 and on x-ray the spine appears to be undermineralized. The patient admits to significant bed rest, as well as moderately high alcohol intake. Surgical treatment of the disc is indicated, but the options are chymopapain or fusion. The surgeon has had problems with fusions in osteoporotic males.

*Indications:* The question arises, is the "poorly mineralized" spine on x-ray a true representation of osteoporosis or is the patient really normal. Spine x-rays generally do not show "demineralization" until 30–40% of the bone has been lost, but for technical reasons a normal spine can often be read as osteoporotic. Alcohol-induced osteoporosis is generally considered low-turnover osteoporosis (4). This would be a contraindication to fusion because bone remodeling is depressed and the fusion may not take easily. In this case, a tetracycline-based analysis of a bone biopsy may be the only way to determine if bone turnover is normal or depressed. A quick analysis of the CT scan done for diagnostic purposes of the disc could provide a ballpark estimate of bone mineral content, even without calibration, and determine if the patient was moderately undermineralized or normal. Highly accurate or reproducible bone mineral determinations would probably not add to the interpretation of this case. However, a poorly mineralized spine may in general be a consideration in choice of treatment; in this case a rapid and inexpensive assessment of spinal mineral content may be useful.

**Case 4**

A 70–year old woman has a consistently elevated serum calcium (10.8–11 mg/dl) and mild elevation of serum PTH. Menopause was at age 49 and she has no vertebral fractures. She does not want to undergo parathyroid surgery.

*Indication:* Some investigators have recommended surgery in virtually all cases of primary hyperparathy-

roidism (56), others have preferred conservative management, often with estrogens (57). A woman age 70 with no vertebral fractures would not be considered to have postmenopausal osteoporosis, and whether the mild hyperparathyroidism would aggravate the bone loss with age is debatable. A measurement of spinal bone mass may be useful in determining if the patient is demineralized compared to age-matched controls, at which point careful management is indicated to see if the elevated PTH may be causing continued bone loss.

#### Case 5

A 40–year old male has been on renal dialysis for 10 years and a spine film shows normal or even increased vertebral density especially near the center of the vertebrae. A bone biopsy is read as moderate osteomalacia. Treatment with 1,25(OH)2D is considered.

*Indication:* This illustrates the problem of using a spinal measurement in renal bone disease. Often the bone is not osteoporotic but has a significantly increased amount of osteoid, or it can be sclerotic with woven bone. A patient can improve with an increase, a decrease, or no change in mineral content. Cortical bone is generally decreased due to endosteal resorption. It is useful to monitor the changes in spinal bone with CT or DPA, and in this case one would expect to see an eventual decrease in mineral as woven bone was resorbed and replaced by normal trabecular bone. However, this is a situation where the data may be quite good but the result depends solely on the interpretation of the data.

## Summary

Bone mass measurement techniques, both routine procedures and some of the newer methods, are becoming generally available to the clinician. In many cases, the clinician may be approached by the purveyor of the method rather than the other way around as some of the newer procedures are "marketed" to the clinical community. In this review I have tried to discuss the techniques themselves, their strengths and weaknesses, as well as some of the clinical indications for using them. Some methods are better than others in specific clinical situations. Most practicing physicians will not have the full complement of tests available but will use only two or three which are judged to be most useful in his or her practice and are available. In established osteoporosis, the old standbys of routine radiography and the Singh index still may play a major role. The strengths of the new techniques lie in their capability for reproducible serial measurements of the axial skeleton, and they provide very sensitive assays for the efficacy of therapeutic regimens to prevent rapid bone loss at the menopause. The new aggressive therapies for established osteoporosis such as the use of high-dose sodium fluoride and the ADFR scheme (58) may also necessitate serial studies to see if they are working to increase bone mass.

The simple diagnostic use of a bone mass measurement is limited; we cannot yet quantify the risk of fracture in an individual patient with a given amount of bone. At best frequency of fracture can be associated with bone mass in population studies. A measurement of bone mass is useful, however, in staging the patient and contributes significantly to clinical decisions whether or not to treat an individual. This is especially true if the treatment is prophylactic, initiated at the time that bone loss is expected to be rapid.

The choice of which measurement to use and when to use it is still the choice of the clinician. As research continues and the relationship between bone mass and the biomechanical stresses which cause mechanical failure of bone are explored further, the new techniques will be improved and become more useful in prediction of fracture. At the present time, bone mass is one test in the armamentarium of diagnostic procedures which the clinician must use in the evaluation and management of patients.

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