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# INTERCOMPARISON OF TECHNIQUES FOR THE NON-INVASIVE MEASUREMENT OF BONE MASS *



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A variety of methods are presently available for the non-invasive measurement of bone mass of both normal individuals and patients with metabolic disorders. Chief among these methods are radiographic techniques such as radiogrammetry, photon absorptiometry, computed tomography, Compton scattering and neutron activation analysis.

In this review, the salient features of the bone measurement techniques are discussed along with their accuracy and precision. The advantages and disadvantages of the various techniques for measuring bone mass are summarized. Where possible, intercomparisons are made of the various techniques. For greater detail, the reader is referred to ref. 1.

## 1. RADIOGRAMMETRY

Radiogrammetry is the simplest and most widely used technique for the measurement of bone mass. Conventional radiogrammetry is basically employed for the measurement of cortical bone. As bone loss results primarily from endosteal resorption, cortical thickness reflects the loss quite well. Measurement of the cortical thickness of either the midshaft of the femur or metacarpal is utilized for estimation of the cortical bone mass. Correction for individual differences in bone size is effected by expressing cortical thickness as a percent of the total width at the midshaft.

The minimum level of cortical thinning that can be detected with this technique usually occurs in advanced stages of generalized osteoporosis. Thus, the metacarpal index provides useful data in large scale population surveys on the incidence of advanced osteoporosis. However, the technique is not appropriate for the identification of the population at risk with respect to osteoporosis, since it is relatively insensitive to small decreases in bone mass.

The metacarpal index correlates with both regional and total osteopenia, and with the number of fractures of the dorsal spine. Since this measurement primarily reflects endosteal bone resorption rather than intracortical resorption, it is, perhaps, somewhat less useful as an indicator of overall bone mass changes than are other techniques.

Bone loss resulting from intracortical porosity can best be evaluated by magnification radiogrammetry; standard radiogrammetry is of limited value for this assessment. Changes in bone mass in patients with renal dysfunction, endocrine dysfunction and other metabolic disorders have been widely measured by both standard and magnification radiogrammetry. Further work on the improvement of radiogrammetric measurements is required.

## 2. RADIOGRAPHIC PHOTODENSITOMETRY

Photodensitometric measurements with x-ray sources and radiographic films with standardized aluminum wedges have proved to be quite reproducible; it is perhaps a more sensitive measurement than the simple cortical measurement. Certain technical problems inherent in this technique reduce the accuracy of the measurement, and hence, tend to limit its clinical usefulness. A basic problem is the present inability to correct the effects on the measurement of variation in the amount of soft tissue and fat overlying the bone. A second problem stems from the hardening of low energy polychromatic x-ray beams; this hardening produces inaccuracies in the measurement.

Both radiogrammetry and radiographic photodensitometry involve errors in density measurement, and hence the inferred bone mass measurement, of the order of 10% or more. The errors are inherent in x-ray measurement; they derive from variability in energy and in the film response. Errors that result from the use of broad energy spectrum of x-rays, in addition to beam hardening, are non-uniformity of field intensity and energy, and radiation scattering. Most of these problems can be reduced or eliminated by the use of monoenergetic photon sources such as those used in photon absorptiometry.

Three basic problems remain to be solved for both radiographic densitometry and photon absorptiometry: 1) the need to convert a linear density measurement to an absolute measure of calcium; 2) the necessity for appropriately correcting for skeletal size; 3) validation of the extrapolation of density from a very small sample of one type of bone to the bone mineral content of the entire skeleton.

## 3. PHOTON ABSORPTIOMETRY

The present availability of monoenergetic radiation from radionuclide sources has led to the development of photon beam absorptiometric procedures. The principle of this technique is similar to that of roentgenography; the data obtained, however, are more precise. The bone mineral content is assumed to be directly proportional to the amount of photon energy absorbed by the bone being studied.

### A. Single Photon Absorptiometry

Photon absorptiometric measurements are made on the appendicular skeleton rather than the axial skeleton, as the problems inherent in the interference of soft tissue are minimized at the former sites. To a lesser degree, these errors also occur, of course, in measuring the radius. Significant correction of this error may be made by the application of the dual energy absorptiometric technique. There are also inherent errors resulting from the use of finite beam widths and from the non-uniformity of photon intensity across the beam width. Significant correction of these errors may be effected by numerical filtering methods.

The Norland-Cameron single energy ($^{125}I$) photon absorptiometer is the most widely used instrument for this measurement. Generally, cortical bone, (diaphysis of the radius), is measured. In field studies, the precision of the method is about 5%. In routine clinical scans (of the shaft of the radius) the precision is reported to be 2-4%. The imprecision is largely the result of repositioning error. This error is minimized by utilizing the ratio of BMC to radius width as the index. Precision of the measurement made on the distal portion of the radius is less than that made on the diaphyseal portion. The sensitivity to changes in bone mass in the former is one-half that of the latter. Thus, the metaphysis, while it contains proportionally more trabecular bone than the shaft, is nevertheless less frequently measured because of repositioning errors introduced by the irregularity of the bone architecture.

B. Dichromatic Photon Absorptiometry

Recently, dichromatic (dual-photon) absorptiometers with increased sophistication have been developed. These instruments employ several photon energies in order to correct for overlaying fat and tissue. Dichromatic (dual-photon absorptiometry permits measurement of bone density to be made in areas such as the spine; such measurements cannot be performed with single photon techniques. Numerous measurements have been made on long bones, but the site of most importance, clinically, is the spine. Considerable progress in dual-photon techniques has been made in recent years; much more progress is anticipated. The precision of dual-photon scans for a given source, while presently less than for single photon scans, could easily be increased. The correlation between the single photon absorptiometric measurements of the peripheral skeleton and the axial skeleton is, at best, moderate (i.e., 0.6-0.7). However, the correlation between total body calcium and radius shaft bone mineral with dual photon absorptiometry has been reported to be 0.97.

Photon beam absorptiometry has been a useful technique for tracing normal changes in bone mass with aging, and, in certain instances, changes resulting from therapeutic procedures. Considerable single photon normative data are available from its wide clinical application. While the precision of the method is high, the accuracy of this technique, at the present time, is markedly reduced when it is applied to the measurement of the spinal column or any irregularly shaped bone surrounded by a large volume of tissue. If an absolute measurement is required, the data must be normalized for the size of the skeleton in each individual.

4. COMPUTED TOMOGRAPHY (CT)

The recently developed technique of CT scanning has the potential advantage of being able to separate cortical and cancellous bone by transaxial display. Thus, theoretically, it is possible to measure linear absorption in a well defined volume of bone. The advantage of measuring cancellous bone lies in the high level of metabolic activity of this type of bone which rapidly and sensitively reflects on-going changes in bone mass.

CT measurements made with a single energy source may have errors as high as 20% for vertebral mineral content because of the effect of tissue and variable fat concentration in the vicinity of the spine. A higher resolution capability may be achieved with the use of a monochromatic source such as $^{125}I$ instead of x-rays for the measurement of trabecular bone. With dual energy capabilities, it is possible with CT (as with dual-photon absorptiometry), to correct for overlying tissue and fat, and thus to determine bone mass of the spine.

CT measurement of bone mass, however, is still limited by certain technical problems that require further experimental work for their resolution. Two areas requiring study for scanning independence are those of polychromatic errors and calibration problems (repositioning errors). With further development, this technique holds great promise as an investigative tool.

5. COMPTON SCATTERING TECHNIQUE (CS)

The Compton Scattering technique utilizes the scattering of a beam of gamma rays into a detector; the level of activity detected is a function of the density of the bone target. Two orthogonal photon beams are employed. The density measurement is the average density of both the organic and the inorganic components of the volume of bone studied; thus Compton Scattering reflects both components of bone.

One advantage of this technique is that the scattering volume can be located entirely within weight bearing trabecular bone. Another advantage of the Compton Scattering technique is that, unlike other interaction processes which depend on both effective atomic number and mean density, the CS technique depends only on density. Repositioning of the scattering volume is relatively simple; hence, the measurement is not a function of the thickness of the bone nor of its possible rotation. Thus, the precision of the method is very high. The combined features of high Compton interaction probability and the potential for optimizing the physical factors which determine the precision suggest that this technique has great potential for bone density measurement.

There are, however, several technical problems to be resolved. One of these problems is the evaluation of the contribution of photons which are multiply scattered. The principal disadvantage of the Compton Scattering technique results from the multiple scattering effects for a fixed point measurement.

Multiple scattering is a particular problem when the bone studied differs from the calibration standard. Constituents of bone other than the mineral content are also reflected in the measurement. As in all partial body studies, patient or sample area positioning is very important. In this technique, the precision depends largely on the size of the volume measured. Density measurements of the os calcis have been considerably more reproducible than density measurements of the distal radius. Unfortunately, the density of the os calcis is influenced by body weight (this bone reflects mechanical stress). It is possible that positioning problems may be encountered in the measurement of an area of cortical bone and that this will decrease the precision.

To date, it has not been possible to separate clearly osteoporotic individuals from normals on the basis of the density measurements of their trabecular bone. Clearly, more experimental work on CS must be performed with respect to density measurement before this technique can be usefully applied for measurement of bone mass.

6. NEUTRON ACTIVATION

In all of the techniques previously discussed, the precision or reproducibility is high for serial determinations in the same subject. Thus, even if absolute measurements are not accurate, relative measurements yield the data required for time related changes. For diagnostic determination, however, an accurate measure of bone mass is required for the evaluation of calcium deficit. Hence, in these studies, the bone mass must be measured absolutely. A technique which measures directly the calcium, and hence bone mass, is neutron activation analysis. With the neutron activation technique calcium may be measured in a portion of the body (e.g., the hand, the torso) or the entire body.

A. Partial Body — Hand

Determination of calcium and phosphorus in the hand is the simplest of the neutron activation measurements and produces the lowest radiation exposure to the individual. This low radiation dose and the relative simplicity of the technique are its most attractive features. The measurement permits normalization for size by determination of hand volume. The results must, of course, be extrapolated to the whole skeleton, and the validity of the extrapolation verified. However, while there is a degree of uncertainty in extrapolating from the hand to the entire skeleton, it is less than that involved in extrapolating from a few mm of bone in the radius to the whole body, as is the procedure with absorptiometric measurements.

B. Partial Body — Torso

Partial body neutron activation of the torso is a compromise between hand activation and total body activation. The partial body neutron activation technique essentially measures the calcium in the trunk and upper thigh. There are several advantages in irradiating the torso rather than a hand or the whole body. Since a large portion of the body is activated, the response reflects more accurately changes in the skeletal mass than the response of an extremity such as the hand. Moreover, changes in osteoporotic patients may be more sensitively detected than with total body irradiation, as the spine is a larger fraction of the irradiated skeleton in this technique. Finally, torso activation is somewhat simpler than the total body neutron activation technique. Partial body neutron activation of the torso has had very wide application in clinical studies.

There are some inherent disadvantages to the partial body neutron activation technique as compared to the total body neutron activation technique. As with all partial body measurement techniques, it is difficult to achieve an absolute measurement. In partial body activation techniques, the error introduced by repositioning alone can be substantial. In the torso activation technique, the size of the neutron irradiation field is fixed; hence, a variable portion of the skeleton is irradiated and counted, depending on the body habitus of the subject. The portion that lies within the irradiated volume varies from 33% of the skeleton of large men to 50% of that of small women. The precision (reproducibility) of the system is ± 4% (1 SD) for a phantom, and ± 5% for a human subject.

The $^{238}$Pu,Be sources used on this instrument are relatively weak and have to be placed close to the body; thus, the geometry corrections for thickness of the irradiated subject are especially critical for this technique. Further, the proximity of the sources produces a radiation dose of 500 mrem about twice the dose to this critical body area as that received in the $^{238}$Pu,Be total body neutron activation (277 mrem). An empirically derived factor is applied to the raw data to correct for the combined effects of non-uniformity of neutron fluence and gamma ray absorption.

As in all the measurement techniques, it is highly important both to normalize the data for skeletal size and to analyze the data in terms of a reference standard, so as to provide a rational uniform basis for the comparison of individuals of different sizes. For this purpose, the induced calcium counts are expressed as a calcium bone index (CaBI) normalized by the cube of the height of the individual. No correction is specifically provided for sex or age in the calculation of this index.

C. Total Body Neutron Activation

With the total body neutron activation technique, total body calcium is measured directly and absolutely. The measurement reflects the total skeletal mass. With this technique, the patient is uniformly exposed to a beam of partially moderated fast neutrons. This exposure to neutrons provides a small, but nevertheless significant dose to the whole body of the subject. (However, the average dose equivalent to the skin in the total body activation is approximately one-half of that delivered in the partial body activation of the torso.)

The induced $^{49}Ca$ is measured absolutely with an appropriate whole body counter. From the data, the absolute values of total body calcium, phosphorus, sodium and chlorine can be determined. The accuracy of this method, in an anthropomorphic phantom, is ±5%, and the precision ±1.0% (1 SD). Total body calcium values are normalized for body size, sex and age, so that the relative deficit in skeletal mass can be determined for each individual.

The non-invasive nature of the technique, and the low radiation dose to the subject allow the study of large normal populations as well as osteopenic populations. The precision of the technique also makes it useful as a sensitive indicator of overall therapeutic efficacy. An obvious disadvantage of the TBNAA technique is that it is incapable of revealing that a change is confined to a small volume of the body. Small changes in bone mass at a particular site are masked by the large amount of calcium in the total body. Also, TBNAA cannot distinguish between skeletal calcium and ectopic calcification, a condition which frequently occurs in renal osteodystrophic patients.

Because TBNAA facilities are relatively expensive, there are few presently available. The limitations of the application of TBNAA are hence both technical and economic. However, both of these limiting factors existed for the

CT scanning technique which now has wide acceptance and use in medical practice. The recent reduction in cost and increased availability of portable $\alpha$,n neutron sources, and the recognition of the general usefulness of highly sensitive whole body counters, should make this technique more readily available to medical research centers. It is most likely that there will be a considerable growth in the application of this technique in medicine.

## 7. SUMMARY AND CONCLUSIONS

The type of non-invasive measurement of bone mass selected for a study depends to a large extent on the nature and type of data required. Measurements of bone mass generally are employed in two basic types of studies, longitudinal and cross sectional.

Large scale cross sectional studies of osteopenia are easier and less expensive to conduct if bone mass can be ascertained by the relatively simple radiogrammetric and densitometric measurement of the metacarpals or the radius than by the more sophisticated neutron activation methods. Data accumulated by a number of laboratories indicate that measurements of the appendicular skeleton reflect total body calcium content reasonably well in most instances.

The most interesting observation to be drawn from the descriptions of the various bone measuring techniques is the considerable number of correlations that exist with respect to their clinical application. For example, the correlation coefficient of radial bone mineral content and total body calcium in crush-fracture osteoporotic patients has been reported to be as high as 0.826, $p<0.001$. The correlation in osteopenic patients is, generally, not as high as that observed in a normal control population. In a study by Manzke, high correlations (0.84 to 0.94) were found between the total body calcium and bone mineral content measured at six different sites in the radius, ulna and humerus. The rate of change of BMC at the six sites vary when compared with the rate of change of TBCa. This finding is not surprising in view of the differential rate of loss of bone in various parts of the skeletons of osteopenic patients. These differential rates are averaged in a total body calcium measurement.

Each of the presently available non-invasive methods used to determine the nature and degree of changes in skeletal metabolism has significant advantages and limitations. Radiographic techniques are applicable to all parts of the entire skeleton, but lack the sensitivity required for quantifying levels of change associated with the development of pathological conditions. Quantitative bone roentgenography or radiogrammetry, which measures cortical thickness of the appendicular skeleton, is relatively precise, but not necessarily indicative of the status of the axial skeleton. Photon absorptiometric techniques, although highly quantitative and precise, also provide information on a highly localized portion of the appendicular skeleton. Extrapolation of the findings to the axial skeleton cannot be assumed to be valid for all individuals. Computed tomography offers significant potential advantages over other techniques, but requires further work for the solution of inherent technical problems. Similarly, considerable additonal work is required for Compton Scattering techniques; the technical problems associated with these techniques are even more formidable. Neutron activation analysis permits the direct <u>in vivo</u> measurement of total calcium content of the body parts of the body, and hence skeletal mass, with a high degree of precision. However, while there is a large clinical and research experience with partial body and total body neutron activation, the techniques are not yet routinely available for application to population survey studies.

Although all of these non-invasive techniques have been used for many years to estimate bone mass, relative insensitivity to small early changes and the wide ranges for precision and accuracy inherent in each measurement have precluded general applicability of any single technique for the early detection of fracture-producing osteopenic disorders. A combination of techniques holds more promise for development of a useful diagnostic procedure. For example, combination of measurement of total skeletal mass with measurement of changes in selected sites such as the spinal column would provide much more useful data for the diagnosis of osteoporosis than does either measurement alone.

There is general agreement that an osteoporotic individual has a bone mineral content, 10-20% lower than a normal subject matched for age, size and sex. About 18-30% of a population with clinically apparent osteoporosis have calcium levels that are not characterized as osteopenic by any of the non-invasive bone measurement techniques. Discriminant analysis using both the total body calcium and BMC values as predictor variables and membership in the two populations as criterion variables, appear to provide an adequate separation of osteoporotic and normal subjects.

The application of all of these techniques should provide the basis for a more complete understanding of skeletal metabolism in a variety of pathological disorders characterized by osteopenia, and permit objective evaluations of efficacy of treatment of osteoporosis.

Ref. 1. Non-invasive measurements of bone mass and their clinical application, S.H. Cohn. Editor - CRC - Press Inc., Boca Raton, Florida, 1981.