IMPORTANCE OF MEASUREMENT OF BONE DENSITY IN THE MANAGEMENT OF OSTEOPOROSIS

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ABSTRACT

Bone mass is the primary, although not the only, determinant of fracture. Over the past few years a number of noninvasive techniques have been developed to more sensitively quantitate bone mass. These include radiogrammetry (RG) and radiographic photodensitometry (RD), single and dual photon absorptiometry (SPA and DPA), quantitative computed tomography (QCT), and single and dual-energy X-ray absorptiometry (SEXA and DEXA). These techniques provide bone mass quantitation at the spine, wrist, hip and total body skeletal sites that are the principal areas usually involved in osteoporosis. The evaluation of the aetiology, progression, and treatment of osteoporosis has been clearly improved with the use of these methods. It is the intent of this review to discuss the pros and cons of these techniques, in particular their applications to the detection and management of osetoporosis.

INTRODUCTION

Osteoporosis, an absolute decrease in bone mass, has been described as the commonest of all diseases [1] and is a major underlying cause of bone fractures in the elderly. Women, in particular, are affected as a result of acceleration in the rate of bone loss after menopause [2,3]. Osteoporosis may also be drug induced, idiopathic, or as a result of ageing [4]. In patients with osteoporosis, vertebral fracture, fracture of the proximal femur as well as fracture of distal forearm commonly occur with minimal trauma [5].

IMPORTANCE OF BONE DENSITY MEASUREMENT

The definition, rational treatment and prevention of osteoporosis depend on reliable methods for the assessment of skeletal mass [6]. However, the need for bone mass measurement in osteoporosis has never been so acute. In the past, diagnosis of severe osteoporosis could not be made until a fracture had occurred. Now it is clear that reduced bone mass, even in the extremities, indicates bone fragility. The spinal bone mineral content provides an even better indication of the fracture risk in that particular area [7]. Moreover, it is now apparent that a number of agents such as diphosphonates, 1,25-dihydroxyvitamin D3, parathyroid hormone, all of which stimulate osteoblastic activity and promote bone formation, can correct osteoporosis and thereby prevent fractures. Other agents (calcium, oestrogen) which reduce bone turnover may prevent osteoporosis though they seem not to correct it [8]. None of these therapeutic agents are however effective in all subjects. Precise measurement methods are therefore required to monitor treatment efficacy so that a pattern of treatment most appropriate to the patient can be carried out.

Measurement of bone mass is of value in predicting the risk of fracture, assessing the severity of bone wasting, and following the response to treatment [3,9,10]. Although decreased bone mineral content is not the only determinant of fracture incidence [11], it may help to differentiate patients prone to osteoporosis from those without this tendency [4]: A number of sensitive, non-invasive techniques are currently available for quantitation of bone mass at sites comprising both cortical and trabecular bones. It is the intent of this review to discuss briefly their principles and applications to the clinical problem of osteoporosis.

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METHODS OF BONE MASS MEASUREMENT

Radiogrammetry (RG)

This utilizes the thickness of cortical bones seen on radiographs to provide an indicator of bone mass or density. Due to the tubular shape of these bones in cross-section, geometric formulae can then be applied to calculate total cross-sectional area, area of compact bone (for mass), or compact bone area relative to total area (for apparent density) [8]. Initially major long bones (ulna, humerus, femur) were examined but over the past 10 to 20 years the metacarpals have been the major focus [12-14]. The results have been useful in defining normal changes at specific sites with growth and ageing [15-17]. The method is simple and involves low exposure of the patient to radiation. However, the results generally have been too imprecise (5 to 10% error) and inaccurate (10 to 25% error) for use in clinical studies [18-20].

Radiographic Photodensitometry (RP)

The optical density of bone on X-ray films obtained under standardized conditions has been used as a quantitative indicator of bone mineral content and probably is the oldest nontraumatic method of assessing bone mineral [21]. As routinely obtained radiographs vary widely in density, a strict standardization of kilovoltage, exposure time, and film processing is essential for these measurements. The measurements on the film are made with a densitometer as spot measurements, or with a more sophisticated instrument as line or area measurement. The method is very sensitive to changes in overlying tissue, and is therefore restricted to appendicular bones, particularly the phalanges, although radius, tibia, and less frequently other appendicular bones have been studied [22].

Single Photon Absorptiometry (SPA)

SPA was first introduced in 1963 by Cameron and Sorensen [23], and has been widely used for clinical application [24,25]. It is based on a transmission scan from an external radioisotope point source through an object (in this case bone and soft tissue) to a photon scintillation detector. The detector is a collimated sodium iodide scintillation crystal-PM tube combination. The source most commonly used is 200 mCi of iodine-125 (I-125, 27.5 keV, 60-day half-life). The source is also collimated to obtain a beam of monoenergetic photons. As the beam is scanned across the bone and soft tissue, a continuous readout of transmitted beam intensities is detected and the bone mass per unit length is then calculated from the following equation [26]:

$$m_{Bm} = \frac{d_{BM}\ln(I_1/I_2)}{u_{BM}d_{BM} - u_{ST}D_{ST}} \quad \ldots\ldots\ldots\ldots\ldots\ldots 1$$

$$M_{BM} = X(cm) \times m_{BM} (g/cm^2)$$

$$= \frac{Xd_{BM}}{(u_{BM}d_{BM} - u_{ST}d_{ST})} \times \ln(I_1/I_2) \ldots\ldots\ldots 2$$

Where m_{BM} = mass of mineral per unit area (g/cm^2) along beam path, u_{ST} and u_{BM} = mass absorption coefficients (cm^2/g) of soft tissue and bone mineral respectively, d_{BM} and d_{ST} = density of bone and soft tissue (g/cm^3), I_1/I_2 = beam intensity through soft tissue and bone, M_{BM} = mass of bone in cross-section 1 cm in axial length, x = length in cm. The actual absolute quantitation of bone mineral content is obtained by scanning a series of dried, defatted human radii in a tissue-equivalent material or using a set of aluminium tubes as standard.

This technique requires a uniform soft tissue layer surrounding the bone, thus limiting its use to extremities. Moreover, it does not distinguish cortical from trabecular bone. Thus, a major criticism of this technique is the poor correlation between measures of appendicular skeletal densities (composed mostly of compact bone) and lumbar spine density (composed mostly of trabecular bone) [10]. This technique has also failed to predict vertebral fractures [27].

Dual Photon Absorptiometry (DPA)

The technique of DPA, developed by Reed et al [28], Roos et al [29,30], and Mazess et al [31], was adapted for peripheral bone measurements by Smith et al [32], for total body calcium and lumber spine measurements by Wilson and Madsen [33,34], Bohr et al [35], Riggs et al [10], and for the hip by Dunn et al [36]. It is based on transmission measurement of two separate photon energies through a median consisting primarily of two materials (bone and soft tissue), and hence eliminate the need to have constant thickness of soft tissue around the bone. A collimated 1-Ci Gadolinium 153 source, which has photoelectric peaks at approximately 44 and 100keV, is held in rigid parallel geometry with a collimated Na(T1)scintillation detector. To study the spine, a patient is placed supine with both hips flexed on the table. The beam is scanned in a rectilinear manner by a stepping motor. The detector senses the amount of radiation emitted at both energy levels that are not absorbed by the spine and soft tissue. Computerized analysis separates soft tissue from vertebral bone absorption to yield bone mineral content.

In vitro precision of 1 to 2% and in vivo precision of 2 to 3 % for the spine and 3 to 5 % for the hips have been reported [36-38]. Studies on accuracy of DPA for total body calcium compared with total body neutron activation analysis show a precision of 0.99 % [36]. The technique, however, does not distinguish between vertebral trabecular bone and compact bone and is inaccurate when osteophytes and crush fractures are present [39]. Extensive aortic calcification may also falsely elevate the calculated bone mineral content of the spine. Nevertheless, it can define to a good extent patients with nontraumatic spinal fractures who routinely have a bone mineral content less than 1.0 g/cm^2 [27].

Quantitative Computerised Tomography (QCT)

QCT measures the distribution of attenuation coefficient (CT number) within the cross-section of an object [6]. The effective total CT number in a cross-section of known thickness is computed for each point from a set of X-ray transmission measurements. Thus the technique permits both the display of anatomy and determination of bone

mineral at any location in the transverse section. The method has been applied to trabecular bone mineral in the spinal vertibral bodies [40]. Sections of 1 cm thick are scanned at each vertebral level, along with calibration standards consisting of known concentrations of dipotassium hydrogen phosphate solution (K_2HPO_1). Mineral content analysis is then performed on the region of interest of the vertebral body.

The technique is capable of separately measuring trabecular or cortical bone. Recent modifications in standard CT scanners, with the use of special software and calibration techniques, have specifically allowed determination of vertebral cancellous bone mineral content with a precision of 2 to 3 % [41]. Excellent correlation has also been found between vertebral trabecular mineral determined by computerized tomography and iliac crest trabecular bone volume determined by histomorphometry [40]. Variable fat content may produce inaccurate result in the single-energy technique. This is solved by using the dual-energy configuration [41,43] which is more expensive, less precise, and results in higher radiation exposure [39].

X-Ray Absorptiometry (XA)

XA was developed to compensate for the low output of radionuclide source and their inability to adjust optimal energies for certain tissue thickness. Initially, single-energy X-ray absorptiometry (SEXA) was used [44]. The X-ray beam is usually filtered heavily to gain effective monochromaticity. The system typically consists of a narrow radiation beam, coupled with a scintillation detector. Precision of measurements on the proximal femur, distal radius and lumbar spine have been reported at about 2% [45].

The dual-energy configuration has also been developed for measurement of both the spine and the femur [46]. This is known as dual-energy X-ray absorptiometry (DEXA). Typical examples are the Hologic QDR 1000 System (QDR stands for Quantitative Digital Radiography) and the Norland XR-26 X-ray Bone Densitometer. QDR uses an X-ray tube in place of a radioisotopic source and consequently can measure spine with higher resolution and greater speed, than existing DPA instruments [48]. The X-ray source provides alternating pulses at 70 kVp and 140 kVp, and an average tube current of 1 mA which produce 500 to 1000 times more photon flux than 1 Curie Gadolinium source. In the Norland XR-26 system, a stable X-ray source housed in the bottom of the scanner arm serves as the instrument's photon source. The collimated X-ray beam is filtered to produce two energy peaks at approximately 45 keV and 80 keV. The beam is scanned across the region of interest in a rectilinear fashion while independent low and high energy scintillation detectors, mounted in the top of the scanner arm, monitor the amount of radiation which passes through the subject (Fig. 1). Bone mineral content (BMC) calculations are then performed by a computer interfaced to the scanner [47].

QDR consistently demonstrated precision values of phantom measurements in the range of 0.3 to 0.4 %, which were 3 to 8 times better than corresponding values obtained from the DPA machine [48]. The accuracy, as assessed by repetitive scanning of a phantom containing known K_2HPO_4 concentration, was high (r = 0.99, slope = 1.005) [49]. Compared to known values for the Hologic

Fig 1

A schematic diagram showing the construction and principle of the Norland XR-26 X-ray Bone Densitometer (Norland XR-26 Operation Manual 1989)
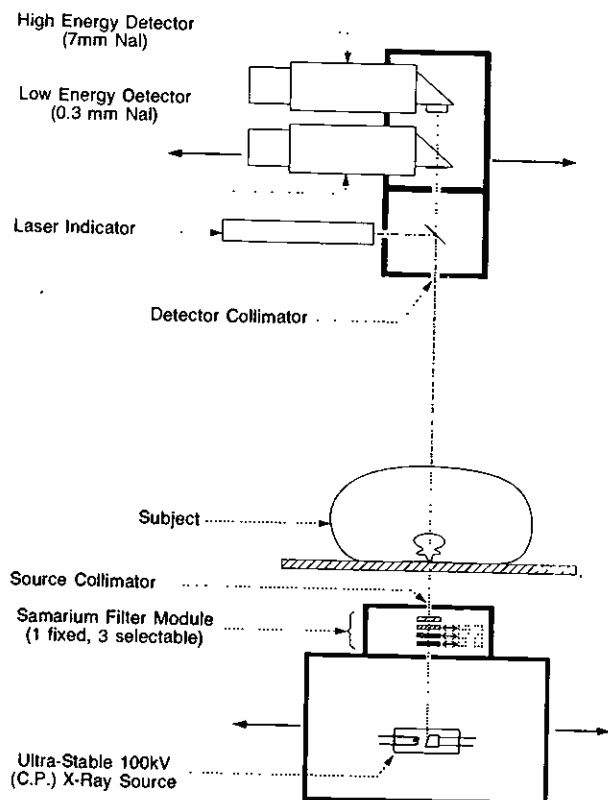
anthropomorphic spine phantom, the XR-26 system demonstrated measurements of BMC (in gram hydroxyapatite) within 0.3%, and of BMD (Bone Mineral Density in gram hydroxyapatite per cm^2) within 0.13%. Precision of BMD measurements were comparable to that of the QDR system.

The dual-energy system is also free from beam hardening effect due to tissue thickness [48].

DISCUSSION

Bone loss and associated fractures are increasingly recognised as a significant health problem in our ageing population. The promising advances in finding effective treatment for accelerated bone loss have stimulated the seach for a laboratory test to aid in the diagnosis of osteoporosis prior to the development of disabling fractures. Because bone mass at a given skeletal site is correlated with the compressive strength of bone under laboratory condition [50,51], its measurement in vivo is attractive as a diagnostic test for the early detection of osteoporosis. Radiographs are of limited value if vertebral deformity or compression fracture is not considered as end point in making the diagnosis of osteoporosis (about 50% of the bone mass of the spine has to be lost before this demineralization becomes apparent on standard radiograph)[52].

Practical methods for measuring bone mineral non-invasively have been reviewed in this paper. Of particular clinincal interest are methods based on photon absorptiometry and on quantitated computed tomography, because these make possible measurement in axial

skeleton, where fractures occur. Bone mineral measurements by absorptiometry assess the quantity of bone mineral on the irradiated volume of tissue, independently of the actual shape of the bone in that volume. In DPA or DEXA, the results are expressed in units of bone mineral content (in gram) or bone mineral density (BMC divided by bone area, in gram per square centimetre), and it is assumed that the anatomic volume of the vertebrae is the same in all individuals. Because area is less sensitive to small changes in the size of the region of interest, normalization based on area allows a better precision of measurement than when mass alone is used [53, 54]. When using QCT, volume information is readily available and the data can be expressed with reference to the anatomic bone volume measured.

In bone mineral measurement, in vivo precision of the densitometer is the degree to which the instrument gives the same bone mineral value when a measurement

Fig 2

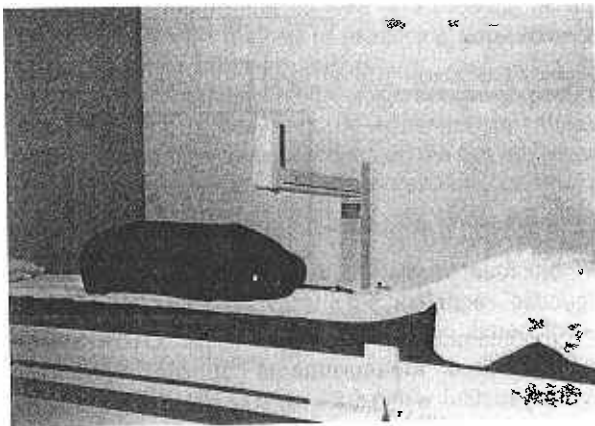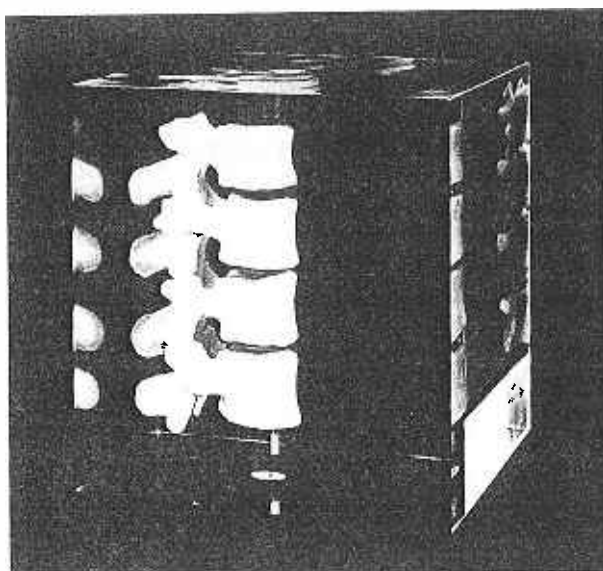A Vertebrae Phantom: a standard used in the calibration of the bone densitometer

Fig 3

The Hologic X-Caliber Anthropomorphic Spine Phantom (Hologic Inc., 200 Prospect St., Waltham, Massachusett 1987).

is repeated at the same site on the same subject. Imprecision may be usually reduced by averaging a number of repeated measurements. Accuracy is the degree to which a measurement value estimates the actual value of the quantity being measured. This depends primarily on the accuracy of the calibration of the instrument, as well as on the "standard" adopted for the calibration. The Hologic X-Caliber Anthropomorphic Spine Phantom (Fig 3), which is constructed of calcium hydroxyapatite and epoxy, has recently been adopted as the industrial standard for X-ray-based instruments.This removes sources of error in ash studies which have led to wide differences in calibration in instruments from different manufacturers.

As mentioned earlier, SPA measurements are made on areas of the skeleton that are primarily cortical, and therefore they do not predict spinal bone mineral content as measured either by DPA (DEXA) or QCT. When DPA and QCT measurements are made to encompass the integral bone mineral (both trabecular and cortical) over the same region, there is relatively good correlation [55]. However, comparison of regions involving only trabecular bone mineral as studied by QCT and the integral bone mineral value by DPA have shown widely differing correlation [56-58]. Part of this poor correlation may be due to the different units of measurement of the two techniques. As suggested by Wahner, the comparison of different regions of interest and the difference in measurement units may in and of itself decrease the strength of any correlation, and this may in turn limit the value of a given study [58].

Bone mineral measurement has been found to be of use in three groups of patients. In patients who have symptoms associated with bone loss and osteoporosis such as fractures, initial radiographic assessment of the axial skeleton may suggest bone loss from metabolic bone disease and help rule out bone disease not related to osteoporosis. In asymptomatic patients with increased risk for bone loss, bone mineral measurement is the only reliable means for detecting loss of bone mineral prior to the occurrence of irreversible changes on the radiograph. Important risk factors for bone loss include positive family history, premature or postmenopause, low calcium intake, short stature and small bones, leanness, thyrotoxicosis, hyperparathyroidism, smoking and heavy alcohol use. In these patients, measurement of bone density in the lumbar spine helps to determine if significant bone loss has already taken place and allows assessment of the fracture risk. At present, screening of normal women for bone density prior to menopause or at an earlier age is controversial and on a large scale debated [59].

As noted previously, bone density alone as an indicator of future fracture risk is questionable. Low sensitivity (about 35%) [60], of the tests have been reported with all the previously mentioned techniques. The explanation for such findings is that bone mass is not the only determinant of fracture. Factors such as the increased tendency of the elderly to fall, the decrease in neuromuscular coordination with ageing and environmental factors such as throw rugs may also contribute to the occurrence of fracture in older individuals [61]. Despite this, the fact that fracture risk increases with decreasing bone mass allows bone density at present to be used to represent bone fragility. The non-invasive techniques (particularly CT, DPA, & presumably QDR)

may be of great benefit in the clinical evaluation of those at risk for osteoporosis, as well as in those who already have the disease [62].

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