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REVIEW

Photon absorptiometry, bone densitometry and the challenge of osteoporosis

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Abstract

During the lifetime of *Physics in Medicine and Biology*, osteoporosis has been recognized as the cause of a major health burden for societies, particularly within developed countries. The health detriment is associated with the consequences of bone fractures and the subsequent increases in morbidity and mortality. Much of the credit for the current availability of means for identifying groups of subjects at risk of fracture and the provision of means for the effective treatment of excessive bone loss can be attributed to the technique of dual photon absorptiometry. In this review, the history of the development of techniques based on the interactions of x- and γ-rays with bone is considered and the ultimate dominance of x-ray based absorptiometry is described. The advantages and disadvantages of current absorptiometric techniques are presented and the likely future path for bone measurement is outlined.

1. Introduction

Today, the term 'bone densitometry' encompasses the application of the technique of x-ray based dual photon absorptiometry (DXA) to the assessment of patients suspected to be suffering from osteoporosis. Bone densitometry measures tissue attenuation for x-rays of two distinct energies and, from such measurements, derives the mass of mineral per unit projected area (areal BMD). Arguably, during the time that has elapsed since the appearance of the first issue of *Physics in Medicine and Biology* (PMB), bone densitometry might be considered as the medical physics diagnostic technique developed during that period which has brought most benefit to the largest number of people. At the time of the first PMB issue, there was little focus on potential methods for the diagnosis of osteoporosis partly because osteoporosis had not long been recognized as a disease.

The development and application of DXA provided physicians with a means of categorizing patients into those who are unlikely to fracture a bone, those who may have an increased risk of fracture and those who have the greatest risk of fracture. In addition DXA has allowed the assessment of efficacy of various medications and treatment regimes thought to reduce the risk of fracture in susceptible patients. The ability to assign patients to specific, predetermined groups and the availability of effective medications have allowed physicians to reduce the risk that patients may, in the future, suffer a bone fracture.

In this paper, the development of bone densitometry will be reviewed from a personal perspective. The characteristics of this routine, clinically applied, diagnostic technique will be summarized particularly with reference to the interpretation and reporting of patient results. The advantages and limitations of DXA will be considered. Such considerations lead inevitably to the recognition of the desired properties of an 'ideal' technique both for the diagnosis of osteoporosis in a given patient and for the evaluation of the effectiveness of a treatment prescribed for that patient.

2. History

Before the advent of quantitative techniques such as bone densitometry, the term 'osteoporosis' was assigned to a patient who had suffered a bone fracture that was unexplained by any other disease. That is, osteoporosis was a diagnosis achieved by exclusion. Many physicians and most of the public viewed osteoporosis as an inevitable consequence of aging. In fact it was hardly thought of as a disease until Albright (1947) recognized osteoporosis as a disorder of tissue metabolism in which he considered there to be a relative decrease in bone anabolism. He also recognized the contributions of aging, menopause, corticosteroids, nutrition and lowered mechanical strain as contributing factors to the disease. The situation at the birth of PMB was that we had a disease, but no means of identifying sufferers or of following the natural history of bone loss or of assessing the impact of any intervention upon the apparently inexorable consequences of the disease.

The diagnostic difficulty existed because radiography was, at that time, an analogue technique. From a projectional image of a bone, mineral deficiencies could only be established with certainty after at least 30% of mineral had been removed (Lachman 1955). This is not surprising when the challenge of the diagnostic situation is considered. The most common osteoporotic fracture is the collapsed vertebral body. This relatively small, relatively low-density bone is separated from the x-ray detector by a considerable distance and by a sometimes extensive, thickness of soft tissue. The detector accepts x-rays of most energies and from multiple directions. The image will be dominated by scattered photons; the unscattered x-rays which convey the desired, true anatomical and quantitative information are vastly out-numbered. The consequence of this challenging imaging environment was that the available radiological techniques could not detect small, but significant, losses of bone mineral. Those same techniques were able to identify altered bone anatomy in patients who had suffered the consequences of osteoporosis by which time, of course, it was too late. The diagnostic challenge posed by osteoporosis required that scattered radiation be removed from the detector and that transmitted x-rays be counted rather than displayed as an image. The appreciation of these needs eventually led to bone densitometry.

The first demonstration of the principle of bone densitometry was, in fact, the famous radiograph made in 1895 of the hand of the wife of Röntgen (Mould 1993). The image shows clearly the greater extent of interaction of x-rays with bone than with soft tissues. Despite this early demonstration of photon transmission as a basis for bone evaluation, many decades

were to elapse before consensus existed concerning the most appropriate physical process upon which to base a clinical technique for the evaluation of bone. To indicate the variety of techniques under consideration and investigation during the early 1970s, PMB published papers dealing with the resonant frequency of the ulna (Jurist 1970); photon transmission (Watt 1973, Harrison 1974), neutron activation analysis (Bush 1972) and photon scattering (Clarke and Van Dyk 1973, Webber and Kennett 1976). The collection of abstracts for the First International Conference on Medical Physics at Harrowgate in 1965 included five papers on *in vivo* neutron activation analysis of bone, and only two abstracts on absorptiometry. One described an improved ^{125}I photon transmission device (Cameron and Sorenson 1966) while the other outlined a two-source transmission device using ^{241}Am and ^{137}Cs (Reed 1966). Eventually, photon transmission techniques emerged as the most useful and practical means for the routine evaluation of bone and for the diagnosis and treatment of patients with osteoporosis. Of course, techniques other than photon absorptiometry have been applied successfully to bone and any credible history of osteoporosis measurement would refer to other medical physics methods such as radiographic absorptiometry, quantitative ultrasound and quantitative magnetic resonance (Genant *et al* 1996).

3. Early applications of photon interactions to bone quantitation

Photons are absorbed by tissue through either the photoelectric effect or by pair production. Photons are scattered either coherently or by Compton interactions. It was not immediately obvious which of these four processes was the most appropriate as the foundation of a technique for the evaluation of bone. Part of this hesitancy arose from an uncertainty about the variable which needed to be measured. That is, how best to reflect the ability of a bone to withstand the mechanical loads imposed during normal daily activities? Part of the uncertainty was the question of which anatomical location was appropriate for the measurement of the chosen variable. Should it be trabecular bone or cortical bone? Was an appendicular site acceptable or was an axial site essential? Should measurements be confined to weight bearing or non-weight bearing bones? The clinical evidence suggested that osteoporotic fractures were expressed at weight bearing sites where there was a significant fraction of trabecular bone (vertebral bodies, proximal femur) and therefore osteoporosis was a consequence of trabecular bone loss. It could also be argued (but this argument was not heard) that osteoporotic fractures were expressed at weight bearing sites where there was only a small fraction of cortical bone and therefore osteoporosis was a consequence of cortical bone loss. It is also true that osteoporotic fractures occur at non-weight bearing sites such as the distal radius where Colles' fractures are expressed. Such fractures are now known to be an early warning of future, more serious, bone fractures particularly in men (Haentjens *et al* 2004). Despite the inconsistent nature of the fracture evidence, it was considered desirable to measure at weight bearing sites where trabecular bone was present.

One potential advantage of techniques based on scattering or pair production was perceived to be that a region of bone could be defined by the intersection of a photon beam and the field of view of a detector. Consequently, all procedures based on photon interactions other than photoelectric absorption should allow volume based measurements. Since this epoch preceded the broad availability of cross-sectional imaging, it was not obvious how photoelectric absorption could be used to provide volume based assessments of bone mass. Since the advent of image reconstruction techniques, both quantitated computed tomography (QCT) and peripheral QCT (pQCT) techniques have been developed to allow true volumetric measurements of bone mineral density (Rüegsegger *et al* 1976, Genant *et al* 1982).

Coherent scattering received some attention as the most appropriate interaction mechanism upon which to base a bone measurement technique because of the strong dependence of coherent scattering upon the atomic number of the irradiated material (White 1977). The difference in atomic number between soft tissue and bone would allow significant contrast between photons scattered coherently from bone and those scattered from soft tissue. Such a technique should offer a high sensitivity to time-dependent changes in bone mineral concentration and would have the advantage of a volume based measurement. Unfortunately, the coherent cross-section decreases rapidly as photon energy increases. This means that an instrument based on coherent scattering of low energy photons is unlikely to be applicable to central bone sites. Another difficulty was the discrimination of coherently scattered photons from the more intense Compton scattered photons. Lithium drifted germanium detectors were of limited availability at that time. The other, more significant reason that a scattering technique did not succeed was that it was not at all obvious how the region of interest could be positioned reliably and exclusively within either trabecular or cortical bone.

The cross-section for photoelectric absorption depends even more strongly upon atomic number than the coherent cross-section. A technique based upon measurement of the number of photons transmitted through bone and soft tissue would be highly dependent upon the amount of mineral present in the path of the beam. The envisaged difficulty with this procedure was that the measurement would depend upon both the size of the bone and the amount of mineral per unit volume of the bone. A small dense bone could produce the same result as a large low-density bone. It also meant that for sequential measurements, it would be essential that precisely the same bone site was measured since the result would be dependent upon the width of a bone. At the time, these objections were considered to be significant.

Compton scattering was explored as a technique which had the potential to yield a direct measurement of the mass of material within a defined volume of bone. While this was indeed true, the nature of the object under examination did not encourage clinical application of Compton scattering based techniques. If the region of interest in a Compton scattering device is positioned within trabecular bone, then the major contributor to the measured density would be bone marrow rather than mineralized collagen. It would be extremely difficult to imagine how the scattering volume could be confined reliably to cortical bone in order to take advantage of the greater volume fraction of mineralized collagen. Some clinical applications were initiated using the calcaneus or the distal radius but no general applications emerged.

Some thought was also given to the application of pair production interactions to clinical measurements of bone. In principle, discrete regions of interest could be defined as the common volume of a beam of high-energy photons and a detection system designed to observe annihilation photons. Such considerations did not proceed to any great extent because of the relatively weak dependence of the pair production cross-section upon atomic number and the problems of collimation of high-energy photons.

Around the time of the birth of PMB, the most common measurement technique applied to bone was neutron activation analysis. The prime advantage of neutron activation was that it yielded a direct measure of calcium. Unfortunately the radiation dose associated with the technique and the perceived difficulties of housing neutron sources in clinical areas meant that there was little extension of neutron activation into health care provision. The void created by the urgent need for a diagnostic technique and the absence of any suitable radiographic or biochemical procedure stimulated a flurry of developmental work on radiation based techniques which ultimately led to the domination of photon absorptiometry.

4. SPA, DPA, TPA and, finally, DXA

4.1. SPA

The start of clinical bone densitometry is probably best assigned to the year 1963 when Cameron and Sorenson published their paper on single photon absorptiometry (SPA). There were other groups working with photon absorptiometry in England (West and Reed 1970), Scandinavia (Christiansen *et al* 1975) and elsewhere but the Cameron and Sorenson paper can be considered the beginning of the development, the initial clinical application and the commercialization of single and dual photon absorptiometry.

There were three essential advances made with the development of SPA: the polyenergetic radiographic x-ray spectrum was replaced by monoenergetic γ-rays; the film was replaced by a scintillation crystal and severe collimation was introduced for the source and the detector. The introduction of an isotope source meant that incident γ-rays were monoenergetic and therefore the energy of any scattered photon would be less than that of incident photons. The introduction of a scintillator allowed discrimination in favour of transmitted photons and against scattered photons on the basis of photon energy. The severe collimation allowed further discrimination against scattered photons on the basis of allowed paths between the source and detector.

There was one major assumption behind the SPA technique which applies to, and bedevils, all absorptiometry techniques. The measurement object can only consist of two radiologically distinct materials. The two materials are bone mineral and soft tissue. The two components can be intimately mixed, as in the collagen and hydroxyapatite constituents of bone, but each can have only a single density and effective atomic number. In SPA it was necessary to measure transmissions through adjacent tissue locations of equal thickness, one location consisting of both mineral and soft tissue and the other consisting of soft tissue alone. This requirement meant that SPA could be applied only to peripheral locations where it was feasible to arrange for the thickness of the two transmission locations to be the same by the use of tissue equivalent material. The consequence of this limitation was that SPA could not be used at the sites of relevance from the perspective of a physician. Nevertheless considerable progress was made using SPA.

There were a number of secondary choices which had to be made to optimize SPA for clinical applications. The energy of the radioisotope source had to be chosen as a compromise between the need to maximize the difference between the photoelectric cross-sections for bone mineral and soft tissue and the need to transmit photons through the object of interest. The requirement for uniform thickness of soft tissue and the low photon energy restricted SPA to peripheral sites such as the radius and the calcaneus. This constraint clashed with the clinical perspective which considered the sites of interest to be those where bone fractures were most frequent (spine) and were associated with significant morbidity and mortality (proximal femur). It seemed that the essential features of a skeletal measurement site were: (1) a significant fraction of trabecular bone; (2) weight bearing and (3) a central location. SPA could not satisfy these needs.

4.2. DPA

The restriction to peripheral sites was overcome when the monoenergetic photon beam of SPA was replaced by a beam containing photons at two distinct energies. The requirement for measurement of transmission at adjacent tissue locations of equal thickness was eliminated and the method was now able to measure thicknesses of mineral and soft tissue at a single location. The technique was referred to as dual photon absorptiometry (DPA) and used radioisotope

sources such as ^{153}Gd (Mazess *et al* 1970, Roos *et al* 1970). This seemingly minor advance opened up the possibility of measuring bone mass at central locations such as the lumbar spine and the proximal femur and galvanized the medical community into clinical application of the technique. There was an explosive application of DPA into the clinical realm which was, to some extent, stimulated by commercial interests but did have the beneficial outcome of focusing attention on patients suffering the consequences of a fractured bone.

There was still the limitation imposed by the assumption that the object consisted of only two radiologically distinct materials each of which was characterized by a single-valued mass attenuation coefficient of μ_b for bone mineral and μ_s for soft tissue. The expression of this limitation can be appreciated from the equation for areal density measurement. For bone mineral, the areal density, m_b, is given by the expression

$$m_b = \frac{\ln I_{0,l}/I_l - R_{ST} \ln I_{0,h}/I_h}{(\mu_{b,l} - R_{ST}\mu_{b,h})} \tag{1}$$

where I_0 and I are the incident and transmitted photon intensities and the subscripts l and h denote low- and high-energy photons respectively. R_{ST} is termed the soft tissue ratio and is equal to $\mu_{s,l}/\mu_{s,h}$. At first glance, it would seem that equation (1) requires values for the attenuation coefficients which are fixed and applicable to all subjects. If the assumption is made that there is a universal composition of soft tissue, then R_{ST} is a constant and equation (1) can be solved for area bone mass simply from measurements of the intensities of low- and high-energy photons at a single tissue location occupied by bone mineral and soft tissue. Unfortunately, soft tissue composition varies considerably from person to person and differences between patients are encapsulated in the value of R_{ST} which must be determined for each patient. This is accomplished by application of equation (1) to an anatomical location where bone mineral is not present (i.e., $m_b = 0$). Once R_{ST} is determined for a specific patient, the assumption has to be made that the soft tissue ratio measured at the non-mineral site applies to the soft tissue at the mineral/soft tissue site. The contribution of this factor to the accuracy of DXA measurements is considered further in section 5.

The deficiencies of an areal density assessment were recognized and there were various efforts made to recover a mass density from the attenuation measurements (Carter *et al* 1992, Lu *et al* 1996). These techniques assumed that all people have the same relation between bone volume and projected bone area and therefore DPA results could be converted to volumetric density. Since this assumption is unlikely to be valid, such manipulations are most likely to introduce additional uncertainty and adversely affect precision. It appears that such volumetric measurements do not improve fracture predictions over the ability of areal BMD alone (Cummings *et al* 1994).

4.3. TPA

It might have been anticipated that the restrictions imposed by variable physical properties of soft tissue could be eliminated by increasing the number of photon energies in the incident beam. The feasibility of triple photon absorptiometry (TPA) was examined and demonstrated on phantoms but it could not be applied *in vivo* because the small difference in attenuation coefficients between lean and fat components of soft tissue resulted in considerable uncertainties in the mass of either component. To reduce the uncertainty to a clinically useful level would require an increase in the number of incident photons producing an unacceptable radiation dose (Farrell and Webber 1990, 1992).

4.4. DXA

Essentially, the final development in bone densitometry was the replacement of the radioisotope source with a suitable x-ray tube. A different acronym was employed (DXA) even though the technique still required measurements of attenuation at two photon energies. Different x-ray energies were generated either by rare earth filtration (Mazess *et al* 1989, 1992) or by rapid switching of the x-ray tube voltage (Kelly *et al* 1988). The development of DXA was a major advance because the increased photon intensity meant that the time of measurement could be reduced dramatically. The precision of measurements improved because of the greater photon intensity and the decreased likelihood of patient movement. Subsequent developments in bone densitometry have involved technical refinements such as fan and cone beam geometries with the application of line and area detectors, each of which has produced additional incremental improvements in precision.

Manufacturers of bone densitometers use different means of x-ray production and have developed machine specific analysis software. Consequently, areal BMD measured for a single subject will be different when measured on machines from different manufacturers. The important consequence of such differences is that patient follow-up measurements should be made on the same equipment or, at worse, equipment from the same manufacturer. There are published methods for the interconversion of results which depend upon equations derived from BMD results obtained from 100 adult women measured on Hologic, Lunar and Norland densitometers (Genenat *et al* 1994). Such conversions will inevitably introduce greater uncertainties into reported results.

The limitations of an area density measurement using either DPA or DXA were not appreciated clinically for some time. Areal BMD was, by common usage, synonymous with the term 'bone mass'. Intuitively, it would be expected that as 'bone mass' increases, bone strength increases. However, areal density is not a measure of the mass of mineral within a bone. A larger, stronger bone will have a greater mass of mineral, referred to as the bone mineral content (BMC). A greater BMC will be reflected in an *increased* areal BMD. A larger, stronger bone will have a greater projected area which will be reflected in a *decreased* areal BMD (Seeman 1997, Heaney 2005). This is not important when the areal BMD for a patient is compared with expected values. But it is significant when bone size may change. The most common situations where bone size changes are during growth and during treatment for osteoporosis. In such situations, the changes observed in areal BMD do not reflect true changes in bone strength. A bone which increases in size whilst maintaining the same total mass of mineral is likely to be a stronger bone but the measured outcome will be a reduced areal BMD. The converse situation is also worth emphasizing; when bone size falls such as in vertebral collapse due to decreased bone strength, the measured outcome will be an increased areal BMD.

The above discussion implies that DXA was a logical outgrowth of DPA. In fact, an *in vivo* DXA system was evaluated in 1964 in Sweden (Jacobson 1964). The system was based on an analogue computer. Triple photon absorptiometry was discussed and the challenges of material uniformity and of scattered radiation were examined. However, this premature development of DXA did not achieve general acceptance.

5. The entrenchment of DXA

Whenever a new clinical technique is developed there are a number of obligatory steps that must be taken and DXA was no exception to this requirement. For example, reproducibility had to be well understood so that the difference observed between successive measurements

could be attributed either to chance or to a real change produced by disease or by treatment of disease. In addition, factors which might impact accuracy needed to be elucidated so that the validity of a single measurement could be assessed. A means had to be established for predicting an expected value for a patient so that results could be classified into valid diagnostic categories. For DXA, the categories are normal, osteopenic and osteoporotic. It was also necessary to examine the applicability of these categories to children where changes in areal BMD would be produced by growth as well as by disease. A link needed to be established between an assigned diagnostic category and the subsequent consequences of the disease for the patient. In the case of bone densitometry, this meant that the association between a DXA result and the risk of future bone fracture needed to be established. The influence of such factors as ethnicity, physical activity, diet and concomitant disease had to be understood. As the clinical experience broadened and results accumulated, it was possible to evaluate the impact of DXA on clinical practice, on patient outcomes and health care costs. Finally, as seems inevitable with useful, newly developed, clinical techniques, institutional recommendations were developed for the practice of DXA technology and the interpretation of DXA results. Some of these topics are considered further in the following paragraphs.

5.1. Precision

The reproducibility (precision) of a measurement determines the confidence that can be placed in an observed difference between two DXA measurements. In any discussion of precision it is important to appreciate the time scale over which bone changes are expected to occur. The nature of bone formation and resorption dictate that areal density changes only very slowly with time. Even the consequences of disease are unlikely to be detectable with any degree of certainty in less than 2 years and to be certain of change due to normal aging in adults requires much longer. Because it is difficult and time consuming to measure long-term reproducibility, the precision of DXA measurements is frequently characterized as 'same day' or 'short term'. Neither of these measurements is particularly helpful to the physician who has to interpret a result obtained today in the light of a result obtained 2 years ago. The most valid evaluation of reproducibility has to be that established over a time period measured in years.

To measure precision, pairs of areal BMD results are obtained in representative subjects. The best estimate of the precision for each subject is the difference between the measurements. The precision of the technique is given by the root mean square average of the differences between pairs of results obtained from each subject (Glüer *et al* 1995). Frequently reproducibility is expressed as the coefficient of variation which is calculated as the technique precision expressed as a percentage of the mean areal BMD. Alternative expressions such as the intraclass correlation coefficient have also been used. If precision is expressed as the coefficient of variation, then inevitably, reproducibility appears to be worse in older subjects and patients with bone disease because of the lower areal BMD. There would seem to be an advantage in expressing precision in absolute units. When measured *in vitro* using a phantom, reproducibility is typically 0.005 g cm^{-2}. When measured *in vivo* from studies repeated in young healthy adults on the same day or over a period of a few weeks, reproducibility is worse and is typically about 0.01 g cm^{-2} (Fuleihan *et al* 1995) suggesting that densitometers are only half as precise when measuring humans as they are when measuring inanimate objects. Of course, it is not the machine that should be blamed, it is the fact that a human introduces uncontrollable variables into the measurement which are not present in phantoms. Long-term precision increases yet again to typically 0.014–0.025 g cm^{-2}

(Patel *et al* 2000, Phillipov *et al* 2001) or about a factor of 4–5 greater than the reproducibility measured for a phantom.

5.2. Accuracy

Considerably less is known about the accuracy or bias of DXA measurements. There are many factors which will affect the inaccuracy of a patient result. Likely the most important is the non-uniformity of the fat content of soft tissue. As stated previously, soft tissue composition has to be estimated for each patient measured with DXA and that estimate is derived from a transmission measurement at a location which contains only soft tissue and no bone. The assumption has to be made that the measured value applies to the soft tissues included at the sites where areal BMD is measured. Other contributions to inaccuracy depend on the correctness of a number of adjustments made to the transmitted data. Some higher energy photons will scatter in tissue, lose energy and could appear as lower energy transmitted photons. If higher energy photons are incompletely absorbed within the detector, they could appear as lower energy photons. Corrections must be made for photon losses due to dead time, not a trivial proposition when it is considered that the correction must be valid over count rates ranging from direct air transmission to attenuation through 20 cm of tissue. Since it is probable that corrections for these and other effects are dependent on patient characteristics, accuracy will vary from patient to patient. It is likely that in some patients measurement inaccuracies will amount to 10% or more (Farrell and Webber 1989, Tothill and Pye 1992, Formica *et al* 1995, Bolotin 2001, Tothill 2005).

5.3. Normal values in adults

There have been many studies of apparently normal populations with the intent of producing reference values against which measurements obtained from patients can be interpreted and reported. In general, manufacturers of densitometers have adopted and synthesized the results of such studies to produce sets of normal, reference data which are included as a database with the densitometer. Reference data are normally supplied for Caucasian, Black and Asian adult male and female populations. A reference value for a specific patient is defined as the mean bone mass expected for a normal subject of the same age and gender. Population standard deviations, which, for adults, are generally not dependent on age, are also supplied so that the extent of any deviation of the patient result from expected can be expressed with respect to the distribution of bone mass in the normal population.

5.4. Normal values in children

There are less manufacturer supplied reference data available for paediatric, infant and neonate populations. There are publications which present normal values for children using Hologic equipment (Faulkner *et al* 1996), Norland densitometers (Zanchetta *et al* 1995) or Lunar machines (Boot *et al* 1997). The principle contrasts with adult normal ranges are that age-dependent values change dramatically over a relatively short period of time and population standard deviations steadily increase with age. Changes in areal BMD can be attributed to a steady increase related to growth and a rapid peri-pubertal increase and the age dependence of each of these contributions can be described by logistic functions of age (Gordon *et al* 1991). In contrast to adults, the interpretation of areal BMD measurements in patients less than 20 years of age requires the prediction of both an age and gender specific expected areal BMD and an expected population standard deviation.

5.5. T scores, Z scores and fracture risk

The goal of a densitometric measurement of bone mass is either to identify the patient who is going to fracture a bone within a given time period or to evaluate the effectiveness of an intervention prescribed to lower the risk of future fracture. No technique in use around the time of the birth of PMB came close to achieving such goals. It is still not possible today to identify an individual, at-risk, patient. One component that is in place, thanks in large part to bone densitometry, is the ability to define a relative fracture risk for a group of people such as 70 year old post-menopausal women. The second positive development that can be attributed in part to bone densitometry is the availability of a number of medications that reduce fracture risk. Areal BMD results when expressed in relation to fracture risk or when assessing the effectiveness of a treatment are given as *T* scores or *Z* scores.

T scores and *Z* scores express the difference between the areal BMD measured for a patient and the expected value for a gender matched, young adult (*T* score) or the expected value for an age and gender matched subject (*Z* score) expressed in terms of population standard deviations. The relationship between the extent of reduction in a DXA measurement of bone mass and the likelihood of subsequent bone fracture was established from many studies in which subjects, generally post-menopausal women, had a baseline DXA measurement and were followed for a period of years in order to record the occurrence of atraumatic bone fractures. Such prospective cohort studies allowed the establishment of the relation between baseline *T* score and future fracture risk. A meta-analysis was performed (Marshall *et al* 1996) in which 11 such studies were identified involving 90 000 person years of observation with more than 2000 fractures. The outcome of this analysis was that a reduced baseline bone density at the spine or hip equal to one population standard deviation ($T = -1$) was associated with an approximate doubling of the relative risk for future fracture. This study also showed that the ability of decreased areal BMD at the spine and hip to predict fracture was better than the ability of an increase in blood pressure to predict stroke and the ability of an increased circulating cholesterol concentration to predict cardiovascular disease.

5.6. Impact on patient outcomes

The impact of DXA measurements upon patients has been extensive and most of this impact has been beneficial. For example, there are now several pharmaceutical means available for the effective reduction of fracture risk (Cranney *et al* 2002, Strewler 2004, Boonan *et al* 2005). In many of the clinical trials which established the benefits of these treatments, spine or hip areal BMD was one of the trial outcome measures. It should again be stated that only a small BMD gain of typically 5% was achieved in many of the trials while there were dramatic reductions in fracture incidence amounting to around a factor of 50%.

5.7. Standards of practice

A newly developed clinical discipline can be considered to have achieved maturity when Clinical Practice Guidelines, Position Statements and Standards of Practice have been introduced. Many such standards now exist for bone densitometry such as those published by the International Society for Clinical Densitometry (ISCD 2002, 2004) and by various national agencies and societies. Such documents serve a valuable purpose in establishing validated measurement techniques with standardized means of interpretation and reporting of clinical results. There are occasional recommendations which cannot be justified but somehow become embedded in practice lore. For example, it is difficult to accept a recommendation that results from a technique with a typical precision of 2% should be reported to three

significant figures. Another quibble is the recommended use of the term 'least significant change (LSC)'. The LSC is the smallest difference between two areal BMD measurements which is statistically significant and is not due to chance and is defined as the upper limit of the 95% confidence interval for the uncertainty of the difference between measures. The recommended means of derivation of the LSC is to establish the precision from repeated measurements in a representative group of volunteers. The problem arises when the LSC is derived from short-term precision and is used by reporting physicians as a universal constant which applies to each and every patient. The precision in question has to be the long-term reproducibility. Use of short-term reproducibility will give a falsely low LSC, perhaps resulting in the administration of therapy to those who do not require treatment. However, these criticisms should not detract from the potential contribution that clinical practice guidelines can make upon the diagnosis and care of patients suffering from osteoporosis (Compston 2005).

6. Alternatives and the future

DXA will be here for a long time. However, DXA is not the ideal method for identifying and managing a patient suffering from bone disease. In many instances, the limitations of areal BMD are not recognized and measures are used inappropriately. The fundamental DXA variables are the amount of mineral present (BMC) and the projected area of bone occupied by that mineral (Area). The result is expressed as a quotient, the areal BMD, in an attempt to compensate for the influence of bone size. From a clinical perspective this makes sense for a patient suspected to be suffering from bone disease. Unfortunately, areal BMD became known inappropriately as 'bone mass' or 'bone density' and was assumed to be directly related to the ability of a bone to resist fracture when subjected to the mechanical demands of everyday living. However, areal BMD is not a surrogate measure of bone strength. Since both BMC and Area are related to bone strength, it may be that their product rather than the quotient is the more appropriate variable to reflect bone strength.

A second limitation of areal BMD is that it does not indicate the improvement in bone health produced by treatment of osteoporosis. Anti-resorption therapies produce reductions in fracture risk of approximately 50% while areal BMD rises only by about 5%. If treatment increases bone size with no change in mineral concentration, areal BMD will barely change while bone strength will increase according to the increase in bone size. Muller *et al* (2003) showed that hormone replacement therapy produced endocortical deposition of mineral at the distal radius which thickened cortical bone. In this situation, there will be a small increase in areal BMD which will not reflect the rearrangement of bone mineral and which will underestimate a substantial gain in bone strength. It seems that BMD changes due to anti-resorptive treatments are barely detectable using DXA because the consequence of the treatment is a redistribution of mineral rather than a gain of mineral per unit projected area.

DXA can never provide a robust estimate of the likelihood of fracture in a given bone, simply because it cannot capture all of the variables which determine fracture risk. For two bones with the same areal BMD, the bigger bone is stronger. For two bones with the same areal BMD and the same size, the bone with the thicker cortical width (and therefore smaller quantity of trabecular bone) will be the stronger bone. To anticipate the strength of a bone we need to measure the spatial distribution and the concentration of mineral throughout the whole bone. This requirement dictates one of the necessary characteristics of future generations of bone assessment techniques: mineral distribution must be determined with millimetre spatial resolution. The strong dependence of photoelectric interactions upon

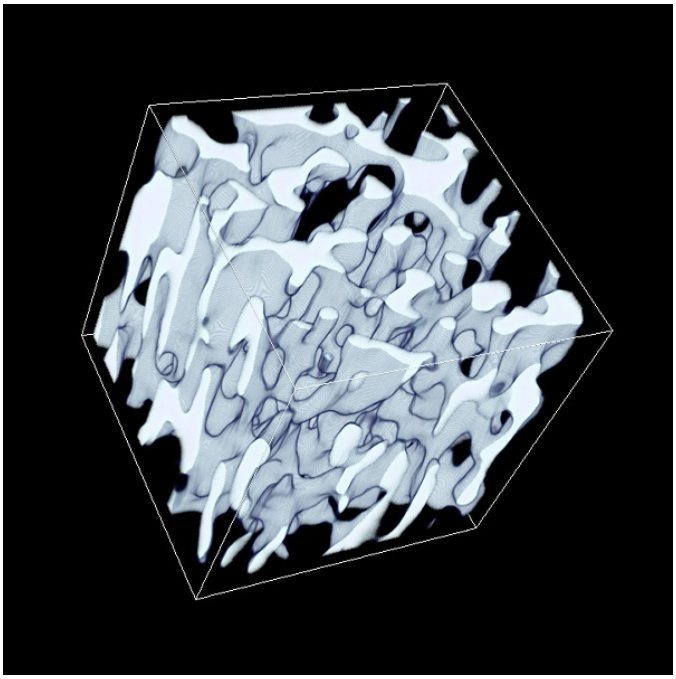

Figure 1. Volume rendering of trabecular bone extracted from MRI images of the distal radius of a normal subject.

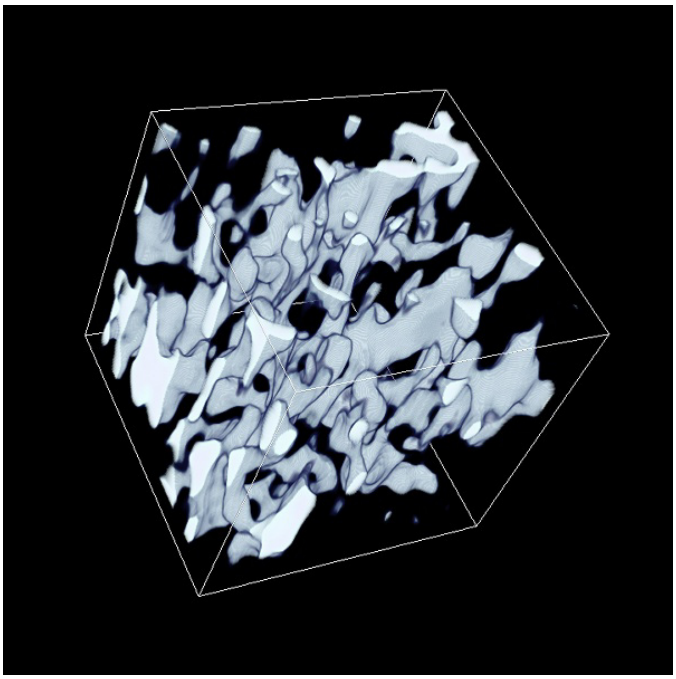

Figure 2. Volume rendering of trabecular bone extracted from MRI images of the distal radius of an osteoporotic subject.

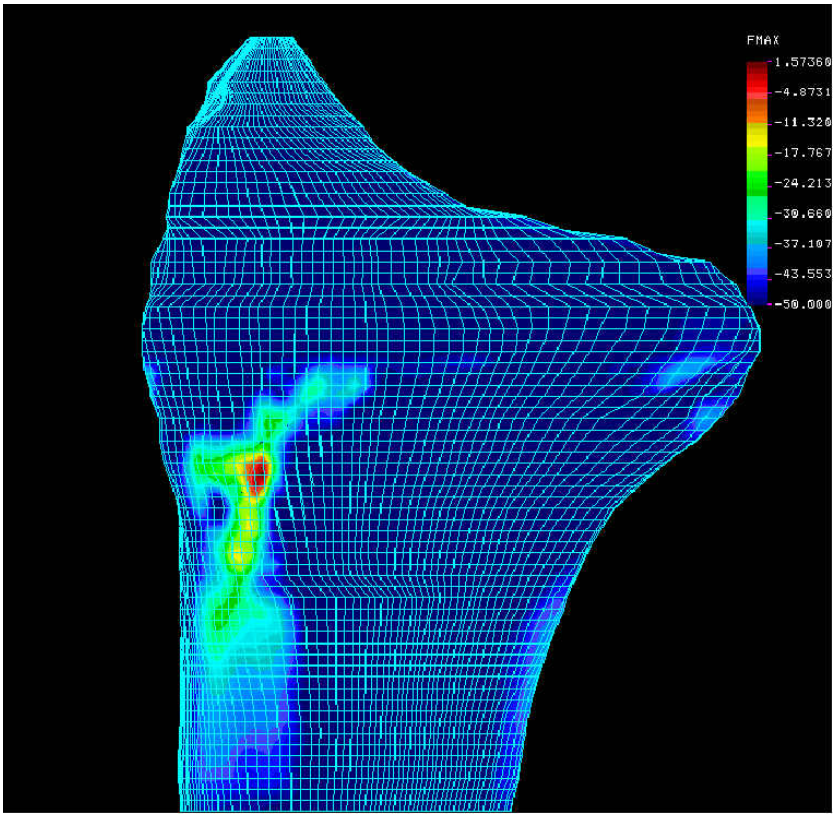

Figure 3. Finite element model derived from CT images of a dried human radius. The colour indicates the level of tensile stress when the bone is subjected to a load imposed by a fall onto an outstretched hand. The red area indicates the onset of bone failure.

effective atomic number and density means that this objective could be achieved using computed tomography (CT). Unfortunately, the radiation dose associated with CT and the restricted access to CT scanners will be barriers to the universal acceptance of a CT based technique for evaluation of fracture likelihood in the at-risk population. This view is supported by the fact that QCT for the determination of volumetric density of trabecular bone in vertebral bodies is a technique that has been shown to be of value and has been available for almost as long as DXA (Genant *et al* 1982) but has never achieved the same clinical penetration. Even if clinicians accepted an appendicular measurement at the radius for example using pQCT, the small radiation dose would likely still prevent universal acceptance of the technique.

The more likely candidate upon which to base a means of measuring whole bone mineral distribution is magnetic resonance imaging (MRI). Excellent images of bone are obtained by MRI through the contrast provided with marrow signals (Gomberg *et al* 2004, Pothuaud *et al* 2004). An example of such an image is given in figure 1 which shows a volume rendered display of the spatial distribution of trabecular bone derived from *in vivo* images of the distal radius of a normal subject. Figure 2 shows the corresponding display for a patient with osteoporosis. There is an obvious deficit in the structural integrity of the trabecular bone in the patient with osteoporosis. These displays of bone structure were derived from images obtained from a 1 T, small bore MRI device (OrthOne, ONI Medical Systems, Wilmington,

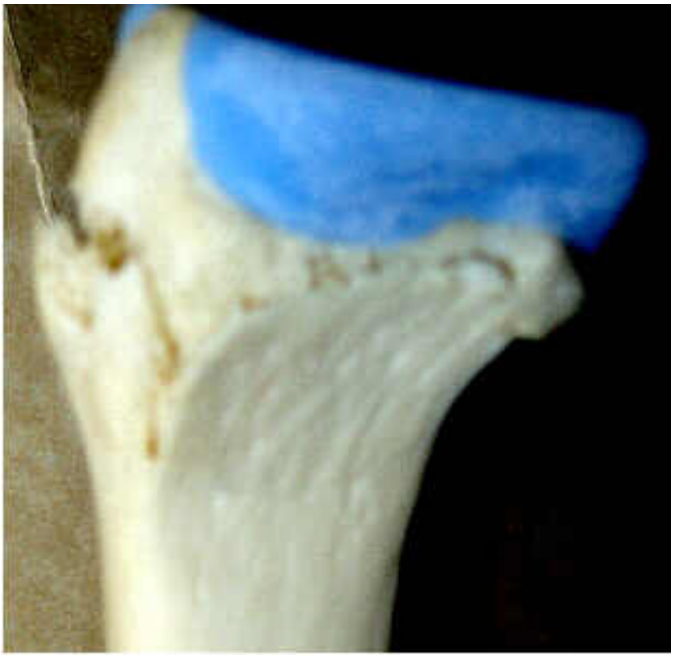

Figure 4. The outcome of the mechanical test for the radius modelled in figure 3. The blue substance is embedding material to facilitate the application of the load to the radius.

MA) designed specifically for appendicular imaging. It is plausible that such instruments could provide a cost-effective, readily accessible means of high spatial resolution imaging of appendicular bones. Images such as these, obtained either by CT or MRI scanning, have formed the basis of *in vivo* measures of bone structure (Gordon *et al* 1996, 1998, Laib and Rüegsegger 1999, Link *et al* 1998, Wehrli *et al* 2001).

Once a geometrical description of a bone such as the radius is available, it is possible to construct a finite element model of the bone. If the material properties of the modelled bone are known, the bone could be subjected, computationally, to the mechanical load expected if that patient should fall onto an outstretched hand. The material properties for the patient of concern could be derived from a single slice image obtained from an appropriately calibrated pQCT scanner. With suitable establishment of bone failure criteria, the likelihood of fracture and the expected location of the fracture could be anticipated (Pietruszsczak *et al* 2006). An example of such a possibility is shown in figure 3 where an isolated, dried human radius was imaged using CT scanning prior to being subjected to a mechanical test. Figure 3 shows the finite element mesh constructed from the CT images. Also shown in figure 3 is the computationally predicted tensile stress distribution. The red colour corresponds to the predicted onset of fracture. Figure 4 shows the result of mechanical testing of the same radius. There is a satisfying agreement between predicted bone failure and the observed outcome of the mechanical test.

If a finite element analysis such as that shown in figure 3 was applied to a patient suspected to be at risk of bone fracture, an individual measure of bone fracture susceptibility (BFS) could be derived. If the measured BFS is combined with a reliable estimate of the likelihood of falling, it will be possible to make a robust prediction of absolute fracture risk. When this methodology for BFS measurement becomes available clinically, it will provide the

opportunity to estimate fracture risk in individual patients so that the need for therapy can be evaluated with confidence and the effectiveness of a selected therapy can be assessed in terms of absolute fracture risk reduction.

7. Summary

It is to the credit of bone densitometry that major advances have been made in reducing the impact of osteoporosis upon society. Despite the inherent limitations of the technique, densitometry has been responsible for a raised awareness of osteoporosis and has contributed significantly to (a) improvements in diagnosis and (b) the development of effective therapies. Future diagnostic advances in the arena of bone fracture risk assessment will require the involvement of engineering assessments of bone fracture resistance.

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References

Albright F 1947 *Osteoporosis Ann. Int. Med.* **27** 861–82

Bolotin H H 2001 Inaccuracies inherent in dual-energy x-ray absorptiometry *in vivo* bone mineral densitometry may flaw osteopenic/osteoporotic interpretations and mislead assessment of antiresorptive therapy effectiveness *Bone* **28** 548–55

Boonan S, Laan R F, Barton I P and Watts N B 2005 Effect of osteoporosis treatments on risk of non-vertebral fractures: review and meta-analysis of intention-to-treat studies *Osteoporos. Int.* **16** 1291–8

Boot A M, de Ridder M A J, Pols H A P, Krenning E P and de Muink Keizer-Schrama S M P F 1997 Bone mineral density in children and adolescents: relation to puberty, calcium intake, and physical activity *J. Clin. Endocrinol. Metab.* **82** 57–62

Bush D 1972 Measurement and control of dose equivalent to patients undergoing whole-body neutron irradiation for *in vivo* activation analysis *Phys. Med. Biol.* **17** 32–41

Cameron J R and Sorenson J A 1963 Measurement of bone mineral *in vivo* an improved method *Science* **143** 230–2

Cameron J R and Sorenson J A 1966 Improved instrumentation for bone mineral measurement *in vivo Phys. Med. Biol.* **11** 174

Carter D R, Bouxsein M L and Marcus R 1992 New approaches for interpreting projected bone densitometry data *J. Bone Miner. Res.* **7** 137–45

Christiansen C, Rödbro P and Jensen H 1975 Bone mineral content in the forearm measured by photon absorptiometry *Scand. J. Clin. Lab. Invest.* **35** 323–30

Clarke R L and Van Dyk G 1973 A new method for measurement of bone mineral content using both transmitted and scattered beams of gamma rays *Phys. Med. Biol.* **18** 532–9

Compston J 2005 Guidelines for the management of osteoporosis: the present and the future *Osteoporos. Int.* **16** 1173–6

Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P and Rosen C 2002 IX: summary of meta-analyses of therapies for postmenopausal osteoporosis *Endocr. Rev.* **23** 570–8

Cummings S R, Marcus R, Palermo L, Ensrud K E and Genant H K 1994 Does estimating volumetric bone density of the femoral neck improve the prediction of hip fracture? A prospective study *J. Bone Miner. Res.* **9** 1429–32

Farrell T J and Webber C E 1989 The error due to fat inhomogeneity in lumbar spine bone mineral measurements *Clin. Phys. Physiol. Meas.* **10** 57–64

Farrell T J and Webber C E 1990 Triple photon absorptiometry cannot correct for fat inhomogeneities in lumbar spine bone mineral measurements *Clin. Phys. Physiol. Meas.* **11** 77–84

Farrell T J and Webber C E 1992 Phantom studies of triple photon absorptiometry and bone mineral measurement at a hip prosthesis *Acta Radiol.* **33** 103–9

Faulkner R A, Bailey D A, Drinkwater D T, McKay H A, Arnold C and Wilkinson A A 1996 Bone densitometry in Canadian children 8–17 years of age *Calcif. Tissue Int.* **59** 344–51

Formica C, Loro M-L, Gilsanz V and Seeman E 1995 Inhomogeneity in body fat distribution may result in inaccuracy in the measurement of vertebral bone mass *J. Bone Miner. Res.* **10** 1504–11

Fuleihan G E-H, Testa M A, Angell J E, Porrino N and Leboff M S 1995 Reproducibility of DXA absorptiometry: a model for bone loss estimates *J. Bone Miner. Res.* **10** 1004–14

Genant H K *et al* 1996 Noninvasive assessment of bone mineral and structure: state of the art *J. Bone Miner. Res.* **11** 707–30

Genant H K, Cann C E, Ettinger B and Gordon G S 1982 Quantitative computed tomography of vertebral spongiosa: a sensitive method for detecting early bone loss after oophorectomy *Ann. Int. Med.* **97** 699–705

Genenat H K, Grampp S, Glüer C C, Faulkner K G, Jergas M, Engelke K, Hagiwara S and Van Kuijk C 1994 Universal standardization for dual x-ray absorptiometry: patient and phantom cross-calibration results *J. Bone Miner. Res.* **9** 1503–14

Glüer C C, Blake G, Lu Y, Blunt B A, Jergas M and Genant H K 1995 Accurate assessment of precision errors: how to measure the reproducibility of bone densitometry techniques *Osteoporos. Int.* **5** 262–70

Gomberg B R, Wehrli F W, Vasilić, Weening R H, Saha P K, Song H K and Wright A C 2004 Reproducibility and error sources of μ-MRI based trabecular bone structural parameters of the distal radius and tibia *Bone* **35** 266–76

Gordon C L, Halton J M, Atkinson S A and Webber C E 1991 The contributions of growth and puberty to peak bone mass *Growth Dev. Aging* **55** 257–62

Gordon C L, Lang T F, Augat P and Genant H K 1998 Image-based assessment of spinal trabecular bone structure from high-resolution CT images *Osteoporos. Int.* **8** 317–25

Gordon C L, Webber C E, Adachi J D and Christoforou N 1996 *In vivo* assessment of trabecular bone structure at the distal radius from high-resolution computed tomography images *Phys. Med. Biol.* **41** 495–508

Haentjens P, Johnell O, Kanis J A, Bouillon R, Cooper C, Lamraski G, Vanderschueren D, Kaufman J-M and Boonen S 2004 Evidence from data searches and life-table analyses for gender-related differences in absolute risk of hip fracture after Colles' of spine fracture: Colles' fracture as an early and sensitive marker of skeletal fragility in white men *J. Bone Miner. Res.* **19** 1933–44

Harrison R M 1974 A computer simulation of the measurement of bone mineral content by photon beam scanning *Phys. Med. Biol.* **19** 79–85

Heaney R P 2005 BMD: the problem *Osteoporos. Int.* **16** 1013–5

ISCD (International Society of Clinical Densitometry) 2002 *J. Clin. Densitom.* **5** S1–S45

ISCD (International Society of Clinical Densitometry) 2004 *J. Clin. Densitom.* **7** 1–63

Jacobson B 1964 X-ray spectrophotometry *in vivo* *Am. J. Roentgenol.* **91** 202–10

Jurist J M 1970 *In vivo* determination of the elastic response of bone: II. Ulnar resonant frequency in osteoporotic, diabetic and normal subjects *Phys. Med. Biol.* **15** 427–34

Kelly T L, Slovik D M, Schoenfeld D A and Neer R M 1988 Quantitative digital radiography *versus* dual photon absorptiometry of the lumbar spine *J. Clin. Endocrinol. Metab.* **67** 839–44

Lachman E 1955 Osteoporosis: the potentialities and limitations of its roentgenological diagnosis *Am. J. Roentgenol.* **74** 712–5

Laib A and Rüegsegger P 1999 Calibration of trabecular bone structure measurements of *in vivo* three-dimensional peripheral quantitative computed tomography with 28-μm-resolution microcomputed tomography *Bone* **24** 35–9

Link T M, Majumdar S, Augat P, Lin J C, Newitt D, Lu Y, Lane N E and Genant H K 1998 *In vivo* high resolution MRI of the calcaneus: differences in trabecular structure in osteoporosis patients *J. Bone Miner. Res.* **13** 1175–82

Lu P W, Cowell C T, Lloyd-Jones S A, Briody J N and Howman-Giles R 1996 Volumetric bone mineral density in normal subjects, aged 5–27 years *J. Clin. Endocrinol. Metab.* **81** 1586–90

Marshall D, Johnell O and Wedel H 1996 Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures *Br. Med. J.* **312** 1254–9

Mazess R, Chestnut C H, McClung M and Genant H 1992 Enhanced precision with dual-energy x-ray absorptiometry *Calcif. Tissue. Int.* **51** 14–7

Mazess R, Collick B, Trempe J, Barden H and Hanson J 1989 Performance evaluation of a dual-energy x-ray bone densitometer *Calcif. Tissue. Int.* **44** 228–32

Mazess R B, Ort M and Judy P 1970 Absorptiometric bone mineral determinations using ^{153}Gd *Proc. Bone Mass Conf. (Washington, DC)* ed J R Cameron pp 308–12

Mould R F 1993 *A Century of X-rays and Radioactivity in Medicine with Emphasis on Photographic Records of the Early Years* (Bristol: Institute of Physics Publishing) p 7

Muller M E, Webber C E and Adachi J D 2003 Hormone replacement therapy improves distal radius bone structure by endocortical mineral deposition *Can. J. Physiol. Pharmacol.* **81** 952–8
Patel R, Blake G M, Rymer J and Fogelman I 2000 Long-term precision of DXA scanning assessed over seven years in forty postmenopausal women *Osteoporos. Int.* **11** 68–75
Phillipov G, Seaborn C J and Phillips P J 2001 Reproducibility of DXA: potential impact on serial measurements and misclassification of osteoporosis *Osteoporos. Int.* **12** 49–54
Pietruszsczak S, Gdela K, Webber C E and Inglis D 2006 On the assessment of distal radius fracture risk *Eng. Fract. Mech.* at press
Pothuaud L, Newitt D C, Lu Y, MacDonald B and Majumdar S 2004 *In vivo* application of 3D-line skeleton graph analysis (LSGA) technique with high-resolution magnetic resonance imaging of trabecular bone structure *Osteoporos. Int.* **15** 411–9
Reed G W 1966 The assessment of bone mineralization from the relative transmission of ^{241}Am and ^{137}Cs radiations *Phys. Med. Biol.* **11** 174
Roos B, Rosengran B and Skoldborn H 1970 Determination of bone mineral content in lumbar vertebrae by a double gamma-ray technique *Proc. Bone Mass Conf. (Washington, DC)* ed J R Cameron pp 243–53
Rüegsegger P, Elsasser U, Anliker M, Gnehm H, Kind H and Prader A 1976 Quantification of bone mineralization using computed tomography *Radiology* **121** 93–7
Seeman E 1997 From density to structure: growing up and growing old on the surfaces of bone *J. Bone Miner. Res.* **12** 509–21
Strewler G J 2004 Decimal point-osteoporosis therapy at the 10-year mark *N. Engl. J. Med.* **350** 1172–4
Tothill P 2005 Dual-energy x-ray absorptiometry measurements of total body bone mineral during weight change *J. Clin. Densitom.* **8** 31–8
Tothill P and Pye D W 1992 Errors due to non-uniform distribution of fat in dual x-ray absorptiometry of the lumbar spine *Br. J. Radiol.* **65** 807–13
Watt D E 1973 Beam diameter and scan velocity effects on linear bone mass measurement by photon attenuation *Phys. Med. Biol.* **18** 673–85
Webber C E 1995 Dual photon transmission measurements of bone mass and body composition during growth *New Horizons in Pediatric Exercise Science* ed C J R Blimkie and O Bar-or (Champaign, IL: Human Kinetics) pp 57–76
Webber C E and Kennett T J 1976 Bone density measured by photon scattering: I. A system for clinical use *Phys. Med. Biol.* **21** 760–9
Wehrli F W, Gomberg B R, Saha P K, Song H K, Hwang S N and Snyder P J 2001 Digital topological analysis of *in vivo* magnetic resonance microimages of trabecular bone reveals structural implications of osteoporosis *J. Bone Miner. Res.* **16** 1520–31
West R R and Reed G W 1970 The measurement of bone mineral *in vivo* by photon beam scanning *Br. J. Radiol.* **43** 886–93
White D R 1977 An analysis of the z-dependence of photon and electron interactions *Phys. Med. Biol.* **22** 219–28
Zanchetta J R, Plotkin H and Avarez Filgueira M L 1995 Bone mass in children: normative values for the 2–20 Year-old population *Bone* **16** 393S–399S

Biography

Colin Webber worked for 6 years as a hospital physicist in the National Health Service, first in London and then Southampton. During this time he completed a collaborative Master's degree in biochemistry with the University of Surrey. Following a move to Canada in 1970, the link with Surrey was maintained and eventually resulted in a transatlantic PhD in medical physics. While at the Department of Nuclear Medicine at McMaster University Medical Centre, he has tried to assure that radioactive materials are used safely, that graduate students perform well and that the development, evaluation and application of bone assessment techniques proceeds apace.