Bone Densitometry: Applications and Limitations

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Abstract: Osteoporosis is clinically diagnosed in its advanced stages, usually following a fracture. Accurate, precise, and noninvasive skeletal assessment is now possible for early detection of osteoporosis at a preclinical stage. Currently, the gold standard in bone mass measurement and fracture prediction is dual energy X-ray absorptiometry (DEXA) of the hip and spine. Exponential increases in fracture risk have been observed with small decreases in bone mineral density. Bone mineral density (BMD) should be considered in conjunction with independent clinical risk factors for fracture, including: low body weight, history of postmenopausal fracture, family history of fracture, and poor neuromuscular function. The World Health Organization (WHO) diagnostic criteria for osteoporosis and osteopenia are appropriate for postmenopausal Caucasian women and are applicable to DEXA assessments at the hip, spine, or forearm. This review explores the relationship between BMD and fracture risk, the principles of bone densitometry interpretation, and the applications as well as the limitations of DEXA technology, and presents cases illustrating common errors seen in the interpretation of DEXA studies.

INTRODUCTION

Osteoporosis is associated with an increased risk of fracture (II-1). Vertebral fractures result in the development of dorsal kyphosis and height loss and can also result in chronic back pain. A significant proportion of vertebral fractures are not identified and only one-third of vertebral fractures come to medical attention (II-1). Hip fractures are associated with a significantly increased morbidity and a mortality of approximately 20% within the first year following a hip fracture (II-A). Clinically, the diagnosis of osteoporosis is made in its advanced stages and usually following a bone fracture. As the presenting fracture is associated with an increased risk of subsequent fractures, it is important to diagnose and treat osteoporosis prior to the development of the first fracture (II-1). Osteoporotic fractures are preventable (I). Spinal X-rays are of value in identifying the presence of vertebral compression fractures and also in excluding the presence of other skeletal conditions, which can result in vertebral compression such as metastatic bone disease or osteomyelitis. X-rays, however, are not as helpful in evaluating bone mineral density (BMD), as significant bone loss is necessary before bone loss becomes evident on plain films (II-1). Currently, the gold standard in bone mass measurement and fracture prediction is dual energy X-ray absorptiometry (DEXA) of the hip and spine.

This paper reviews the relationship between BMD and fracture risk, the principles of bone densitometry interpretation, and the applications as well as the limitations of DEXA technology, and presents cases illustrating common errors seen in the interpretation of DEXA studies. The quality of evidence has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.
Noninvasive bone densitometry utilizing X-ray absorptiometry enables accurate evaluation of bone mass and the diagnosis of osteoporosis in asymptomatic individuals prior to fracture. DEXA uses two X-ray beams of different energy levels to scan the lumbar spine or the hip site. The degree of attenuation is measured as the beam passes through the bone. Using the dual energy beams, corrections for soft tissue are made, enabling an assessment of BMD. DEXA technology can also be used to measure bone density at peripheral skeletal sites such as the radius or finger.

There is a strong inverse relationship between bone mineral density and fracture risk. A two- to three-fold increase in the incidence of fractures has been seen for each standard deviation reduction in bone mineral density (II-1). This relationship between BMD and fracture risk has been confirmed prospectively in a number of large well-designed studies (II-1). The Rotterdam study prospectively observed 7046 men and women over the age of 55 for an average of 3.8 years, following baseline DEXA of the femoral neck. For each standard deviation decline in femoral neck bone density, the relative risk of hip fracture increased 2.5-fold (II-1).

The Study of Osteoporotic Fracture prospectively followed approximately 10,000 Caucasian women 65 years of age or over. During the observation period, 192 women experienced their first hip fracture. In this study, each standard deviation decrease in baseline femoral neck bone density was associated with a 2.6-fold increase in the age-adjusted risk of hip fracture. Similar relationships between declines in bone density and relative risk for fracture have been prospectively observed in other large studies.

Schott and colleagues followed approximately 8000 postmenopausal women over the age of 75 for a 3-year period. The incidence of fracture was found to be greatest in those women who had a low bone mineral density as well as low stiffness on heel ultrasound. Schott et al.’s study prospectively confirmed the relationship between bone density and fracture, utilizing either central or peripheral technology. The predictive power of BMD for hip fracture is similar to the predictive power of blood pressure for stroke and better than the predictive power of serum cholesterol for cardiovascular disease (II-1).

A meta-analysis of 11 prospective cohort studies confirmed that measurement of BMD predicts fracture risk (II-1). Bone mineral density measurements at the hip, spine, calcaneous, or radius have been shown to be similar in their predictive ability for future fragility fractures. However, assessment of BMD at the hip has been shown to be the best predictor for future hip fractures. Similarly, assessment of BMD at the spine has been shown to be the best predictor for future spine fracture. Diagnostic thresholds utilizing DEXA have been best validated at the hip, and the hip remains the best single site for assessment.

Bone mineral density assessments should include DEXA evaluation of the hip and spine. Both sites are of value in global fracture prediction. Spine scans are of particular benefit in the younger postmenopausal female as the spine is a site rich in cancellous bone and is often the first site to reflect early postmenopausal bone loss (II-1). The lumbar spine bone density may be falsely elevated due to the presence of degenerative change, vertebral compression fractures, or aortic calcification, all of which increase with age. Thus, in the elderly population, the diagnosis of osteoporosis may be missed if the spine BMD is falsely elevated, and in this population, it is important to supplement a central spine assessment with a hip or lateral spine DEXA or peripheral evaluation. In the elderly population, as the spine assessments are more likely to be falsely elevated, it is particularly important to review the hip scan and consider intervention based on the bone density at the hip site.

The World Health Organization (WHO) definition of osteoporosis is based on the relationship between BMD and fracture risk. It is based on data for postmenopausal Caucasian women. The WHO criteria are only applicable to DEXA assessments at the spine, hip, and forearm in this population. WHO defined osteoporosis as a BMD more than 2.5 standard deviations below the mean for young adult women. Osteopenia is defined as a bone density between 1.0 and 2.5 standard deviations below the mean for young adult women. The T-score is defined as the number of standard deviations the patient’s BMD is above or below the sex-matched mean reference value for young adults. The T-score thus provides a comparison of the patient’s BMD to the mean peak bone mass. The Z-score is defined as the number of standard deviations the patient’s BMD is above or below the sex-matched mean reference value for individuals of the same gender and age.

The Z-score, therefore, enables a comparison of the patient’s BMD to individuals of the same age. The precise relationship between bone mineral density and fracture risk in younger, premenopausal women is currently not clear as fracture data have been obtained predominantly in the elderly over the age of 65. There is insufficient data regarding the relationship between BMD and fracture risk in non-Caucasian women and men. In the absence of suitable diagnostic criteria, the WHO definition of osteoporosis may be used for men and non-Caucasians as it represents the only diagnostic classification currently available.

There are no established diagnostic criteria for osteoporosis for technologies other than central DEXA or for sites other than the spine, hip, and forearm.

FRACTURE RISK ASSESSMENT

Assessment of an individual’s risk of fracture requires consideration of the BMD in conjunction with clinical risk factors for fracture. Independent risk factors for fracture include age, positive family history for hip fracture, personal history of a fracture, low body weight (< 127 lb or 57 kg) as well as a history of...
smoking.\textsuperscript{22} The risk of falls will also determine how likely an individual is to sustain a fracture. Individuals with an increased rate of bone turnover are also at an increased risk of fracture.\textsuperscript{22} It is necessary to take the BMD in conjunction with other clinical risk factors for fracture in order to help define an individual’s absolute risk of fracture. Currently, we do not have a useful tool to calculate an individual’s absolute fracture risk.

The National Osteoporosis Foundation recommends initiating pharmacologic intervention if an individual’s hip BMD reveals a T-score of less than –2.5 in the presence of risk factors for fracture.\textsuperscript{2} In those women with a hip T-score of less than –2, pharmacologic intervention is recommended as there is strong evidence (I) that intervention effectively prevents fractures and is a reasonable use of resources.\textsuperscript{19}

\textbf{NEW DENSITOMETRY TECHNOLOGY}

Although over the past five years new technologies utilizing ultrasound as well as other radiographic techniques have become available, DEXA technology remains the gold standard for measuring BMD at the hip and the spine.\textsuperscript{20} Other technologies available for measuring BMD include quantitative computed tomography (QCT),\textsuperscript{20} single energy X-ray absorptiometry (SXA),\textsuperscript{20} ultrasound,\textsuperscript{20} and radiographic absorptiometry.\textsuperscript{20}

QCT is capable of distinguishing between cortical and cancellous bone and can exclude artifact, which may be a problem with DXA assessments of the spine in the anteroposterior view.\textsuperscript{20} QCT, however, does result in a relatively high radiation exposure and this limits its usefulness in clinical practice.\textsuperscript{20} Single X-ray absorptiometry (SXA) can only be used to measure bone density at peripheral sites such as the wrist or the heel where there is minimal soft tissue present.\textsuperscript{20} Peripheral DEXA technology has essentially replaced SXA in clinical practice today.

Radiographic absorptiometry (RA) allows assessment of the BMD at the metacarpal and the phalangeal sites using plain radiographs of the hand.\textsuperscript{20} An aluminum wedge allows correction for radiation exposure and voltage settings. Ultrasound densitometry is available for assessment of the heel and the tibia.\textsuperscript{20} As the ultrasound wave passes through bone, attenuation occurs due to scattering and absorption of the wave. Higher attenuation is seen in normal bone in comparison to osteoporotic bone.\textsuperscript{20}

\textbf{HEEL ULTRASOUND DENSITOMETRY}

Two large studies have prospectively evaluated the use of heel ultrasound in elderly women and assessed the risk of hip fracture.\textsuperscript{12,16} These studies showed that a decrease in broadband ultrasound attenuation of one standard deviation was associated with an increase in the relative risk for hip fracture by two-fold.\textsuperscript{12,16} Further trials are needed, however, to evaluate the risk of fracture prospectively based on heel ultrasound assessments.

The correlation noted to date between broadband ultrasound and bone density measurements obtained by DEXA is modest ($r = 0.7$).\textsuperscript{20} Currently, there are no agreed-upon diagnostic criteria for osteoporosis based on heel ultrasound assessments or with utilizing other peripheral technologies. The WHO diagnostic criteria cannot be applied to bone mineral density measured at peripheral skeletal sites. As there are differences in the rates of bone loss in the peripheral skeleton in comparison to the central skeleton, as well as differences in technology, a T-score of –1 at the heel may not necessarily imply that the patient has normal bone density with a T-score of –1 at the hip or spine. An individual with low bone density, as assessed by heel ultrasound or other peripheral technologies, should be considered for a central DEXA assessment in order to determine if the WHO diagnostic criteria are met. Currently, due to the lack of established diagnostic criteria for peripheral skeletal sites, the information obtained from a peripheral BMD assessment can be considered as useful data in estimating the risk of fracture and used in conjunction with other risk factors for fracture.\textsuperscript{20}

\textbf{BMD INDICATIONS AND CONTRAINDICATIONS}

National\textsuperscript{23} and international\textsuperscript{19} guidelines recognize the need to identify individuals at risk for osteoporosis. Targeted bone densitometry screening is recommended for postmenopausal Caucasian women who have one or more risk factors for osteoporosis and for all postmenopausal women over the age of 65.\textsuperscript{19} The guidelines published by the Osteoporosis Society of Canada\textsuperscript{23} as well as the National Osteoporosis Foundation\textsuperscript{19} advise targeted screening for postmenopausal women at risk for osteoporosis.

Bone densitometry is indicated in premenopausal women with significant risk factors for osteoporosis. These risk factors include prolonged periods of amenorrhea.\textsuperscript{23} In the presence of conditions associated with bone loss, bone densitometry is also recommended. This would include conditions such as hyperparathyroidism, hyperthyroidism, hyperprolactinemia, hypercortisolism, renal and liver diseases, as well as the use of medications such as anticonvulsants, glucocorticoids, and heparin.\textsuperscript{22-24}

Contraindications for bone densitometry include pregnancy,\textsuperscript{20} although radiation exposure with central DEXA assessments is minimal (1–5 microsieverts per scan).\textsuperscript{20} In individuals who have recently had gastrointestinal contrast or a nuclear medicine test, BMD should be delayed by at least 72 hours as these tests can affect the results of the scan.\textsuperscript{20} As obese individuals weighing more than 250 pounds or 114 kg cannot be accommodated in the central DEXA units, peripheral assessments are appropriate.

\textbf{WHICH SITES TO ASSESS}

It is preferred that at least two sites be evaluated,\textsuperscript{25} particularly in circumstances where one of the central sites (either the lumbar spine or the hip) may not be a clinically useful assessment.
The spine assessment may be falsely elevated in the presence of extensive degenerative change, aortic calcification, or vertebral compression fractures (Figure 1). External artifacts such as navel rings can also result in a falsely elevated spine assessment. The hip bone density can be falsely elevated in the presence of osteoarthritis due to the presence of increased bone mineral deposition along the medial aspect of the femoral neck. The presence of hardware such as Harrington spinal rods or hip replacements preclude a useful BMD assessment at the affected site. In situations where differing T-scores are obtained at the two skeletal sites, the diagnosis of osteoporosis is based on the lower T-score.

It is recommended that bone density at the lumbar spine be evaluated from the first to the fourth lumbar vertebrae. At the hip, the diagnosis of osteoporosis can be based on the T-score obtained at the femoral neck, total hip, or trochanteric regions. It is not recommended to base the diagnosis solely on Ward’s region as this area is too small to be adequately accurate or precise. The total hip bone density provides greater precision than the femoral neck as a larger area of the skeleton is evaluated. The use of additional peripheral sites is of value in conditions such as primary hyperparathyroidism, in which preferential bone loss occurs at sites rich in cortical bone. The one-third radial site reflects the effect of primary hyperparathyroidism to a greater degree than BMD measurement at the lumbar spine or the total hip as this site is essentially purely cortical bone.

**INTERPRETATION OF RESULTS**

When evaluating a lumbar spine scan, it is important to ensure that the patient has been positioned properly and that the spine is centred and straight with both iliac crests being visible. The tops of the iliac crests correspond to the level of the L4/L5 intervertebral disc in the vast majority of women (III). This landmark can be used to assist in labelling the lumbar vertebrae. The bone mineral density of the lumbar vertebrae increases from T12 to L3 as bone mineral content and area increase. Therefore, has a lower bone mineral density than L1. It is important not to mislabel the smaller and less dense T12 as L1 as this can result in falsely lower T- and Z-scores. By convention, therefore, it is recommended that labelling of the lumbar vertebrae be from the bottom up, utilizing the iliac crests as the L4/L5 landmark. This will avoid mislabelling the lumbar vertebrae (Figures 2 and 3) and will result in a more appropriate comparison of the patient’s bone mineral density to the normative reference data.

Proper positioning of the hip is necessary for appropriate interpretation of the scan (Figure 4). The hip should be positioned such that the femoral shaft is straight and the lesser trochanter is barely visible. The femoral neck region of interest box should not overlap portions of the ischium or the greater trochanter as this can result in a falsely elevated assessment of bone mineral density.

**ETHNIC DIFFERENCES IN BONE DENSITY**

Racial differences in bone mineral density values have been well recognized. African-Americans have a higher bone density than Caucasians. It is thus important to compare women to the appropriate ethnic normative reference data. The relationship between bone mineral density and fracture risk is not well defined in the non-Caucasian population. Although Asians have a lower bone density than Caucasians, data from the National Health and Nutrition Examination Survey (NHANES) study in fact have demonstrated that Asian women actually have a lower risk of hip fractures. This may be explained on the basis of differences in skeletal size between Asians and Caucasians. Areal BMD measured by DEXA does not adjust for vertebral depth. Wider and larger vertebrae are deeper, thus not adjusting for depth will result in overestimation of BMD in individuals with larger skeletons. Similarly, BMD is underestimated in individuals with smaller skeletons. Correcting for the differences in skeletal size significantly reduces the differences in BMD seen among Asians and Caucasians. Asians have a shorter hip axis length, which may also affect the bone mineral density fracture risk relationship as the risk of hip fracture increases by approximately two-fold for each standard deviation increase in the hip axis length. This effect is independent of bone density and also contributes to the differing rates of hip fracture observed in different ethnic groups.
Figure 2 illustrates the common pitfall of incorrect labelling of the lumbar vertebrae. This patient has 6 vertebrae without ribs. The vertebrae should have been labelled by following convention from the bottom up, as it is more common to have 5 lumbar vertebrae with the lowest set of ribs on T11, rather than having 6 lumbar vertebrae. In this scan, the lumbar vertebrae have been labelled from the top down, and T12 has been mislabelled as L1, resulting in an unfavourable comparison to the normative database. This patient has been inappropriately diagnosed as having osteopenia.

Figure 3 illustrates the same patient with appropriate labelling from the bottom up. The tops of the iliac crests have been used as a landmark to identify the L4/L5 disc level. By following convention and labelling from the bottom up, we correctly identify this patient as actually having a normal bone density.
It is important for the technologist to ensure that the appropriate race is identified when scanning a non-Caucasian patient as misidentification will affect the results of the study (Figures 5 and 6). Standards and guidelines for the practice of densitometry have been developed by the International Society for Clinical Densitometry (ISCD), a nonprofit global organization addressing continuing medical education and certification for physicians and technologists.36

SERIAL ASSESSMENTS

Serial assessments are of value in following an individual’s response to therapy.25 When performing serial assessments, it is important to ensure that progressive bone loss has not occurred after introduction of antiresorptive therapy, and that BMD has improved or remained stable. A number of pharmacologic interventions are now available that have been shown to be effective in reducing the risk of vertebral and nonvertebral fracture.19 The different classes of antiresorptive agents have differing mechanisms of action, and significant reductions in fracture risk have been seen with agents providing only a modest gain in BMD.19 If patients demonstrate progressive bone loss, then a reassessment of the diagnosis is recommended to ensure that a secondary cause of osteoporosis has not been overlooked. It is also possible that the patient is a nonresponder to that particular form of intervention, and management may need to be revised in the presence of progressive bone loss.

In order to determine if a significant change has occurred in the patient’s BMD, it is necessary to know the precision error of the measurement with the technology being utilized at that particular site. The precision error, expressed as a coefficient of variation at the spine in the PA projection in most centres, is usually 1–1.5%.20 To ensure that a statistically significant change at the 95% confidence level has occurred, the minimum change in BMD from baseline to follow-up must be 2.8 times the site-specific precision error.37-39 To calculate the change from baseline, the difference between the initial and subsequent BMD values in g/cm² is divided by the initial BMD:25

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\frac{BMD_1 - BMD_2 \times 100}{BMD_1}
\]

BMD 1 = Baseline BMD
BMD 2 = Follow-up BMD

For example: Baseline BMD at lumbar spine = 0.725 g/cm²
Follow-up BMD at lumbar spine = 0.754 g/cm²
Difference = 0.029 g/cm²
Percent change = 0.029/0.725 = 0.04 or 4% increase

If the coefficient of variation at the spine is 1%, then the least significant change necessary to be statistically significant at the 95% confidence level is 2.8 times 1% (2.8%). Thus, the change from baseline to follow-up in the above example is a statistically significant change as it is greater than 2.8%.

The total hip precision error is comparable to the precision error at the spine. The femoral neck precision error, however, is larger than the total hip precision error, as the femoral neck is a smaller region and greater error can be introduced by differences in positioning. The femoral neck precision error can vary from up to 2% to 2.5%.20 Thus, when comparing serial assessments completed at the femoral neck, a greater change is necessary for the difference to be statistically significant. A precision error of 2% would require a change of 5.6% to be statistically significant at the femoral neck. The precision at the proximal radius is usually in the 1–1.5% range, requiring a change of approximately 3% to be significant.20

Serial assessments are appropriate when initiating pharmacologic intervention to assess response to therapy and to ensure that progressive bone loss is halted. An assessment may be completed in 1 to 2 years following initiation of therapy. In certain circumstances, such as glucocorticoid-induced osteoporosis or primary hyperparathyroidism, a more frequent evaluation may be appropriate.

BIOCHEMICAL MARKERS OF BONE TURNOVER

The skeleton continually undergoes a process of remodelling, which maintains skeletal strength, repairs microfractures, and is also essential for calcium homeostasis.40 During the remodelling
process, osteoblasts synthesize a number of cytokines, peptides, and growth factors. These peptides are released into the circulation and can be measured, thus reflecting bone formation rates. The osteoclasts also produce bone degradation products which are released into the circulation and eventually cleared renally. These collagen cross-links can also be measured in the urine and provide an estimation of bone resorption. Bone formation markers include serum osteocalcin, alkaline phosphatase, and procollagen I carboxy terminal propeptide (PICP). Bone resorption markers include urinary hydroxyproline, urinary pyridinoline, urinary deoxypyridinoline as well as urinary collagen type I cross-linked N-telopeptide (NTX) and urinary collagen type I cross-linked C-telopeptide (CTX). These markers of bone turnover are useful in complementing the BMD assessment and evaluating response to therapy. Biomarkers also serve as an independent risk factor for fracture. The clinical usefulness of biomarkers is currently debatable as there is considerable variability in the biomarkers and lack of adequate standardization of the assays.

Figure 5 illustrates an African-Canadian female who was mistakenly identified as Caucasian at the time of the scan. Upon comparison to the Caucasian young adult normative data, she was identified as having osteopenia with a T-score of \(-1.6\).
Over the past decade, major advances in bone densitometry have occurred and now allow accurate and precise assessment of central, peripheral, and total skeletal bone mineral density, as well as estimation of bone strength and prediction of the likelihood of fracture. It is also possible to monitor drug therapy. Large prospective studies utilizing both central and peripheral technologies have confirmed that the likelihood of fracture can now be predicted. In evaluating fracture risk, bone density should be considered in conjunction with other clinical risk factors for fracture. Important independent risk factors for fracture include low body weight, history of postmenopausal fracture, family history of fracture, and poor neuromuscular function. Intervention should be based on the assessment of bone mineral density and other clinical risk factors for fracture (I). Although bone density is currently the best method for assessing and quantifying fracture risk, it is important to interpret bone density assessments with caution, being aware of the limitations of current densitometry technology.

SUMMARY

Figure 6 illustrates the same African-Canadian female of Figure 5, now correctly identified as African, enabling the use of race appropriate normative data. She is actually osteoporotic in comparison to the African young adult normative data.