

Bone Mineral Density – Clinical Relevance and Quantitative Assessment

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ABSTRACT

Bone mineral density (BMD) measurement by dual-energy x-ray absorptiometry (DXA) is an internationally accepted standard-of-care screening tool used to assess fragility fracture risk. Society guidelines have recommended which populations may benefit from DXA screening and the use of the Fracture Risk Assessment Tool (FRAX[®]) to guide decisions regarding pharmacologic treatment for osteoporosis. According to the United States National Osteoporosis Foundation guidelines, postmenopausal women and men ≥ 50 years with osteopenic BMD warrant pharmacologic treatment if their FRAX-calculated 10-year probability of either a hip fracture is $\geq 3\%$ or a major osteoporotic fracture is $\geq 20\%$. Patients with osteoporosis defined by a clinical event, namely a fragility fracture, or with an osteoporotic BMD should also be treated. Patients who are treated for osteoporosis should be monitored regularly to track expected gains in BMD by serial DXA scans. With some drug therapies, BMD targets can be reached whereby further improvements in BMD are not associated with further reductions in fracture risk. While reaching this target might suggest a stopping point for therapy, the reversibility of most treatments for osteoporosis, except for the bisphosphonates, has dampened enthusiasm for this approach. In the case of denosumab, it is now apparent that stopping therapy at any point can lead to an increase in multiple fracture risk. For patients who do not respond to antiosteoporosis pharmacologic therapy, with an improvement in BMD or an incident fragility fracture, other intervening issues, such as vitamin D deficiency, and/or compliance should be considered.

Key Words: bone mineral density, DXA, fracture risk, osteoporosis, FRAX

Learning Objectives:

1. To understand the benefits and limitations of evaluating BMD by DXA and FRAX to assess fracture risk.
2. To learn the uses of various pharmacologic therapies available for the treatment of osteoporosis.
3. To understand the process of monitoring and ensuring patient response to osteoporosis therapy.

INTRODUCTION

Osteoporosis is highly prevalent but underdiagnosed and undertreated, partly because it is often clinically undetected until a fragility fracture occurs. Among adults aged >50 years, 1 of 3 women and 1 of 5 men will experience a fragility fracture (1). Hip fractures are associated with >20% mortality rate at 1 year (2), and about 50% of patients lose their ability to live independently (3). Spine fractures are similarly painful, impair quality of life, and often, with the development of height loss and kyphosis, contribute to a loss of self-esteem (4). Figure 1 shows common fractures in the United States (US) in 2005 (5).

The components of bone are both inorganic (hydroxyapatite crystals composed of calcium and phosphate) and organic (90% type I collagen plus other non-collagenous proteins). Lamellar type I collagen is strengthened by pyridinoline crosslinks between the collagen fibrils. The concerted and coordinated activities of osteoclasts, bone resorbing cells, and osteoblasts, bone-forming cells, constantly remodels bone, a dynamic tissue. The accessibility of remodeling the mineralized bone matrix and its vulnerability to deterioration when remodeling becomes unbalanced is determined by the ratio of the internal surface area/mineralized bone matrix volume (6). The surface area/mineralized bone ratio is low in cortical bone and high in trabecular bone (6). Sites that have high trabecular bone content (posterior-anterior spine) are more metabolically active; therefore, a significant change in bone mineral density (BMD) is likely to occur earlier at the spine than at the hip or forearm (7).

Osteoporosis is associated with an imbalance in bone remodeling, in which there is relatively greater bone resorption than bone formation. However, the actual rate of bone resorption or bone formation could be above normal (accelerated bone remodeling), normal, or below normal (reduced bone remodeling). In each case, the result of the bone remodeling process

leads to a net loss of bone material because of an imbalance in the process, independent of the rate of bone remodeling. Deterioration of skeletal microstructure and bone strength, both associated with loss of bone material, leads to increased susceptibility to fracture (Figure 2) (8).

BMD measurement by dual-energy x-ray absorptiometry (DXA), since its approval by the US Food and Drug Administration (FDA) in 1988, has become the main method by which fracture risk is assessed in the US. This safe and cost-effective method of bone mass measurement predicts fracture risk as shown repeatedly in epidemiologic studies and randomized clinical trials (9,10). Low BMD is associated with increased fracture risk. Increases in BMD, using approved drugs for osteoporosis, are associated with a reduction in fracture risk (9-11). This article describes the clinical usefulness of evaluating osteoporosis and risk for fragility fractures by DXA measurement of BMD, as well as current treatment guidelines and pharmacotherapy used to lower the osteoporotic fracture risk in patients.

DXA: THE ‘GOLD STANDARD’ FOR ASSESSING FRACTURE RISK

Current DXA systems have similar operating principles, comprising a radiation source emitting two x-ray energies, a radiation detector, and a table to support the patient. Images and quantitative measurement of bone and soft tissue density are produced by software that assesses the difference in attenuation between the two different energies (12). Prior to the advent of current DXA systems, the earliest attempts to measure BMD comprised of utilizing plain radiographs for quantitative and qualitative morphometry (13). Nuclear Medicine would play a role in early BMD measurement with Single-Photon Absorptiometry (SPA) and Dual-Photon Absorptiometry (DPA). While current systems utilize an x-ray tube as the radiation source, the

earliest forms of photon absorptiometry operated using radionuclides as the photon emitting source. Iodine-125 (27.3 keV) was most commonly used to generate the single photon beam, while DPA utilized Gadolinium-153 with its two distinct photoelectric peaks (44/100 keV). These radionuclide-based techniques have led to current DXA systems utilizing x-ray photons.

DXA is an areal or two-dimensional measurement of bone mass. Since bone “depth” is not a factor, bone size can affect apparent BMD. Essentially, two vertebrae with identical volumetric densities can have different areal densities based on size (13). As a result, the larger the bone the higher the apparent BMD. While DXA is still considered the gold standard for assessing fracture risk, other modalities can offer potential value in the assessment of bone mass. Quantitative computed tomography (QCT) is a volumetric measurement of bone density. QCT of the spine spatially isolates trabecular bone, which is metabolically more active than cortical bone, allowing changes in bone mass to be observed at a greater rate than DXA (13). While QCT has the same ability to predict vertebral fractures in postmenopausal women as that of DXA, there is lack of evidence to support this position for men (14). For both men and women, the ISCD does not recommend spine QCT for the prediction of hip fractures.

Recent data suggest that modern nuclear medicine departments can assess bone mass. In a study by Huang et al., quantitative bone SPECT/CT with Tc99m MDP was found to be a viable tool for clinical quantification of bone metabolism in patients with osteoporosis (15). On the other hand, utilizing the CT component of SPECT/CT and PET/CT can offer the nuclear medicine physician the opportunity to analyze CT Hounsfield units, which can provide useful information on bone mass and the need for further imaging.

DXA has an extremely low radiation dose (1-10 μ Sv), comparable to natural background radiation received each day (7 μ Sv) (16). Full-table DXA systems can obtain BMD

measurements at several sites (e.g., lumbar spine, hip, forearm) while peripheral DXA systems measure only the peripheral skeleton such as the forearm. Full-table systems are used widely in clinical practice and research for osteoporosis assessment, with the lumbar spine and hip serving as principal sites for diagnosis and therapeutic decision-making (12). Vertebral fractures can be identified with good sensitivity and specificity by DXA. This adaptation, known as vertebral fracture assessment (VFA), utilizes a software program and evaluation by the semiquantitative method of Genant et al. (Figure 3) (12,17).

The standard BMD measurement is by T-score, which is a comparison between the patient's BMD and the mean BMD of a healthy young adult. The T-score unitage is most simply described as the number of standard deviations of the patient's score that is below the control value. Osteoporosis is defined by a T-score of ≤ -2.5 (18). Like VFA, DXA has also been adapted to semi-quantitatively assess skeletal microstructure. Using a software program that determines the extent to which the lumbar vertebra is homogenous or heterogeneous, a non-invasive assessment of skeletal microstructure is possible. This adaptation, known as the trabecular bone score (TBS), was approved by the FDA in 2012 (19). TBS, an independent predictor of fracture risk, adds to information obtained by the T-score and Fracture Risk Assessment Tool (FRAX[®]; Centre for Metabolic Bone Diseases, University of Sheffield, UK). The Medimaps Group, which produced the TBS iNsite™ (Osteo) software, proposes the following interpretation of TBS values. For postmenopausal women, a TBS ≥ 1.350 is normal; 1.2-1.350 indicates partially degraded bone; ≤ 1.2 indicates the lowest tertile of skeletal microstructure (20). TBS is not used alone for treatment decision-making, but it is very helpful as an adjunct to the two modalities that are used for clinical decision-making, namely BMD and FRAX[®]. Guidelines on the use of TBS in clinical practice have been published by the International Society for Clinical

Densitometry (ISCD) (21,22). The semiquantitative assessment is now incorporated into the FRAX[®] software (23), adding to its predictive power. ISCD suggests using the TBS-adjusted World Health Organization FRAX[®] in treatment decision-making (21) (see “Evaluating Fracture Risk Using FRAX[®]” section). An advantage of TBS is that it is not affected by osteophytes or other ectopic skeletal calcifications unlike DXA (24,25). Nonetheless, abdominal obesity can potentially introduce an artifact of the TBS measurement (26,27).

Recommendations for DXA Screening

DXA screening for osteoporosis is important because osteoporosis is asymptomatic until a fracture occurs. The National Osteoporosis Foundation (NOF), American Society for Bone and Mineral Research (ASBMR), and ISCD recommend BMD testing by DXA for women aged ≥ 65 years and men aged ≥ 70 years, as well as, according to risk factor profile, postmenopausal women and men aged ≥ 50 years (28). Risk factors for fragility fractures include advancing age, low body weight, excessive alcohol consumption, current smoking, family history of osteoporosis, early menopause, hyperthyroidism, hyperparathyroidism, hypogonadism, history of organ transplantation, malabsorption, and treatment with certain medications, such as long-term glucocorticoids, aromatase inhibitors, or androgen deprivation therapies (5,29).

DXA Scanning in Special Populations

Patients treated with chronic glucocorticoid therapy

The 2017 American College of Rheumatology (ACR) guidelines on glucocorticoid-induced osteoporosis prevention and treatment recommend BMD testing for fracture risk assessment in all adults receiving chronic glucocorticoid therapy (≥ 3 months) aged ≥ 40 years or

those <40 years whose fracture risk is high due to a previous fracture or other significant osteoporotic risk factors (30).

Recipients of solid organ transplant

Recipients of solid organ transplants experience rapid bone loss in the first 6-12 months after transplantation (31), a time when fractures are most common (32,33). There is no consensus on prevention of bone loss and fractures through medical management in patients undergoing solid organ transplantation. The ACR recommends treatment, following the same age guidelines mentioned above for glucocorticoid-induced osteoporosis prevention and treatment in this population (30).

Women with premature menopause

Premature menopause is defined as menopause in women aged <40 years. Etiologies of premature menopause include chemotherapy, oophorectomy, and/or medical conditions (e.g., autoimmune diseases). Women who experience premature menopause after chemotherapy have more rapid bone loss than their counterparts who maintain menses (34), suggesting that it is reasonable to screen for osteoporosis and fragility fractures by DXA in this population.

Men with hypogonadism

Men with primary hypogonadism, secondary hypogonadism, or androgen insensitivity have increased bone turnover and decreased bone density. Significant loss of BMD can occur in as little as 6 months, as demonstrated in men starting androgen deprivation therapy for prostate cancer. Men who are found to be hypogonadal should have baseline DXA measurement, as well as intermittent follow up (35).

Osteomalacia

Osteomalacia, a condition distinct from osteoporosis in which large amounts of unmineralized bone (osteoid) are present, is most commonly caused by severe vitamin D deficiency. In these patients, DXA may show decreased BMD at the spine, hip, and forearm, generally indistinguishable from osteoporosis on DXA alone. Complete laboratory work-up, including calcium, phosphate, alkaline phosphatase, and vitamin D levels are vital in order for the clinician to make the correct diagnosis (36). Successful treatment of this condition causes remineralization of the skeleton and often produces dramatic increase in BMD.

DXA Interpretation and Positioning

DXA results may be confounded by several issues, including positioning errors, artifacts, vertebral fractures, vertebral osteoarthritis, scoliosis, and non-adherence to ISCD guidelines on serial DXA measurements (Figures 4 and 5). These issues may adversely affect the calculation of BMD and should be considered when interpreting DXA images. Suboptimal internal hip rotation is a common pitfall adversely affecting the BMD of the femoral neck and total hip. Continuous technologist training to ensure adherence to ISCD positioning guidelines is of utmost importance. Another pitfall is the administration of oral contrast or radionuclides preceding the DXA scan. Failure to recognize the oral contrast medium overlaying the lumbar spine could lead to reporting a falsely high BMD.

The effect of radionuclide administration prior to DXA studies has been debated for years. On GE-Lunar systems, the effect on BMD varies between patients and is dependent on the site scanned and dose administered (37). To avoid the radionuclide effect on BMD, DXA can be performed prior to the administration of the radiopharmaceutical. If this is not possible, it is

recommended that the DXA study be postponed for 24-48 hours after the nuclear medicine study (37).

Discrepancies among BMD measurements also can be observed when different DXA machines are used. Each manufacturer uses a different reference population database to calculate the T-score at several sites (38). The ISCD recommends calculating the least significant change (LSC) at each center performing DXA (29). For centers with more than 1 technologist, the LSC is measured at each skeletal site by each technologist and is calculated by multiplying 2.77 times the precision error; it is best expressed as an absolute value (g/cm^2). The provided DXA manufacturer-specific default precision error value should not be used in lieu of a center-specific calculated LSC.

Discrepancies among BMD measurements can also be observed between DXA machines of the same manufacturer. The ISCD currently provides instructions on cross-calibration of hardware or scanners across different centers. It is not currently possible to quantitatively compare BMD values or to calculate the LSC between centers without cross-calibration (14). Therefore, patients are encouraged to return to the same DXA scanner that was used for their prior measurement for proper serial BMD measurement.

Stable or increased BMD correlates with the antifracture efficacy of pharmacotherapy. When DXA follow-up testing shows BMD deterioration despite pharmacotherapy, collaboration between readers of the DXA scans and physicians treating osteoporosis is particularly important, because substantial loss of BMD (greater than the LSC) may require therapy adjustment and/or further assessment. Notably, substantial weight loss can lead to reduced BMD, despite effective therapy.

INDICATIONS FOR TREATMENT BASED ON BMD

Guidelines from the NOF and other societies recommend that, after hip or vertebral fractures, patients should receive pharmacotherapy (see “Treatment Options” section). Both symptomatic and asymptomatic spine fractures (detected on vertebral imaging modalities, as shown through loss of vertebral height) warrant pharmacotherapy (Table 1). Genant’s semiquantitative grading system is a useful method to evaluate subclinical osteoporotic vertebral fractures (39). These morphometric fractures are as predictive of future fractures as are clinically overt events (40,41). Notably, both compression fractures of the spine and osteophyte formation may artificially elevate the calculated two-dimensional BMD measurement on a DXA scan, resulting in false reassurance of normal BMD when in fact the patient may have osteoporosis. Typically, the experienced reader of DXA scan will rather quickly identify and exclude the artifact in a given vertebra from the analysis. The ISCD states that ≥ 2 evaluable vertebrae must be present for a lumbar spine measurement to be reportable.

There are two ways to establish the diagnosis of osteoporosis. The first is in patients with no history or evidence of a fragility fracture. In this population, osteoporosis can be diagnosed if the T-score is ≤ -2.5 (42). The second is the fragility fracture event, which supersedes DXA measurement. In other words, BMD might be in the osteopenic range (T-score between -1.0 and -2.5), but if a fragility fracture is present, the correct clinical diagnosis is osteoporosis. While patients with osteopenia have lower fracture risk compared to patients with osteoporosis, the incidence of osteopenia is much higher than that of osteoporosis, so most patients with fractures do not have pre-existing osteoporosis based on DXA measurement. Treatment is effective in both situations (43).

Evaluating Fracture Risk Using FRAX[®]

Another indication for treatment relates to those who have not sustained a fragility fracture and whose T-score is in the osteopenic range. In this setting, the FRAX[®] calculation can be very helpful. If they meet treatment thresholds by FRAX[®], they are candidates for pharmacological treatment (Table 1). The FRAX[®] score is calculated using a computer-based algorithm that estimates the 10-year probability of both a major osteoporotic fracture (hip, clinical spine, humerus, or wrist fracture) and hip fracture (44). FRAX[®] calculations integrate a patient's age, gender, race, weight, height, family medical history, tobacco use, glucocorticoid use, history of rheumatoid arthritis (RA), evidence of secondary osteoporosis, and excessive alcohol use, in addition to femoral neck BMD. FRAX[®] is a well-validated tool with over a million person-years of observation (45). The FRAX[®] score takes into account the risk of death, because the greater the risk of death in a 10-year period, the lower the risk of sustaining a fracture for the same risk factors.

The value of individual risk factors for an osteoporotic fracture and mortality data are country specific. Thus, FRAX[®] scores necessarily vary from country-to-country for individuals who may present with the same risk profile (23). FRAX-based indications for therapy depend upon high risk as determined by country-specific FRAX[®] scores of $\geq 3\%$ or $\geq 20\%$ for hip or major osteoporotic fractures, respectively (Table 1) (44,46).

Diabetes mellitus (DM) is known to confer an additional increased fracture risk but is not integrated as an associated clinical risk factor in the FRAX[®] calculator (47). For a given T-score, DM is associated with greater risk. Although patients with DM do not have RA, many clinicians will adjust the FRAX[®] score by selecting the box labeled "rheumatoid arthritis" (23) to account

for the additional risk of having DM. Notably, there are other risk factors not considered by FRAX[®], such as risk of falls and rate of bone loss.

TREATMENT OPTIONS

Antiresorptive Agents

Antiresorptive agents reduce bone turnover, improve BMD, and reduce fracture risk. They represent the mainstay of therapy for osteoporosis. Antiresorptive agents (Table 2) inhibit osteoclast activity, which causes decreased bone resorption, and, because bone turnover is a tightly coupled process, reduce osteoblast activity and bone formation. The generalized reduction in bone turnover leads to benefit in two ways. General bone remodeling is reduced and the balance between bone resorption and bone formation becomes positive because resorption is inhibited to a greater extent than bone formation.

Bisphosphonates bind to bone mineral with variable strength and studies evaluating discontinuation suggest a persistent antifracture effect, at least in the short term. The FDA recommends bisphosphonate drug “holidays” after 3-5 years of therapy because of reported rare adverse effects with long-term bisphosphonate usage (48) and evidence of persistent antifracture effects. Resumption of bisphosphonate therapy after a ‘drug holiday’ may be indicated in patients who experience a fracture or show significant BMD loss (7). According to the ASBMR 2015 guidelines, a drug holiday should be considered for postmenopausal women treated with oral bisphosphonates after 5 years, and for those treated intravenously after 3 years (49).

Denosumab, a monoclonal antibody that targets the bone resorbing ligand known as RANK, is another common antiresorptive treatment. Unlike bisphosphonates, denosumab does

not bind to bone mineral. It circulates as all antibodies do. Because of its specific affinity for RANK L, denosumab binds to and inactivates RANK L. Loss of RANK L leads to a profound reduction in osteoclast activity. The approved dose (60 mg) by subcutaneous injection lasts for ~6 months, at which time another dose is administered. The effects of denosumab are rapidly reversible. If a dose is missed, the antiresorptive effect dissipates. This rebound effect has been demonstrated in a study showing that BMD decreased to baseline values and bone turnover markers (BTMs) increased to values higher than baseline by 12 months following the discontinuation of a 2-year treatment period with denosumab (7). Cases of multiple spine fractures have been observed in high-risk patients who discontinued denosumab. If denosumab is stopped, a bisphosphonate should be prescribed to prevent BMD loss (46). For denosumab, a drug holiday is not recommended.

Other antiresorptive agents include calcitonin, raloxifene, and hormone or estrogen replacement therapies. All of these treatments allow more time for secondary mineralization in the existing bone tissue mass, which increases BMD and the mechanical resistance of bone to loading (50).

Calcitonin, a weak antiresorptive agent, is no longer used to treat osteoporosis due to concerns of increased cancer risk and its weak therapeutic benefit (51,52). While maintaining the function of osteoblasts and osteocytes, bone remodeling is suppressed to the premenopausal range by estrogens and raloxifene (a selective estrogen receptor modulator that acts as an estrogen agonist in bone) (50). Raloxifene also has been shown to reduce the incidence of breast cancer (50). It has not been found to reduce the risk of hip fracture, however, possibly because of its relatively weaker antiresorptive potency. Randomized controlled trials of FDA-approved antiresorptive and anabolic therapies are compared in Table 3 (53,54).

Anabolic Agents

In contrast to antiresorptive agents, anabolic agents promote bone formation and activate bone remodeling (Table 2). Generally, anabolic agents are given to men or postmenopausal women who have a very high risk of subsequent fractures, or “severe osteoporosis” (generally defined as either a T-score of ≤ -3.5 in the absence of a fracture or a T-score of ≤ -2.5 in the presence of a fragility fracture); patients with contraindications to oral bisphosphonates (e.g., esophageal emptying disorders, esophageal strictures); and patients who have “failed” other therapies (e.g., sustaining a fracture and/or with significant BMD loss while receiving other therapy).

Two human parathyroid hormone analogues, teriparatide and abaloparatide, are anabolic agents that produce a quick increase in bone-formation markers and, later, an increase in bone-resorption markers; this is described as an anabolic window (Figure 6) (55). These agents are contraindicated with a history of external beam radiation therapy because of a theoretical risk of osteosarcoma and contraindicated in patients with active bone metastases. However, with the use of teriparatide now for almost two decades, no oncogenic signals have emerged. Both teriparatide and abaloparatide are administered subcutaneously as a daily dose for ≤ 2 years.

A recently introduced anabolic agent and monoclonal antibody, romosozumab, binds the osteocyte-derived protein sclerostin, which inhibits bone formation. Compared with other pharmacotherapy, romosozumab results in the largest increases in BMD at both the lumbar spine and hip (56) over the shortest period. Patients treated with romosozumab followed by alendronate had fewer spinal fractures compared with patients receiving the alendronate regimen alone (56,57). Romosozumab has an interesting property of rapidly transitioning from an

anabolic to an antiresorptive after 6 months of use. By 12 months, both bone formation and bone resorption markers are below baseline.

One trial of romosozumab versus alendronate (no placebo control) noted an increased risk of myocardial infarction (MI) and stroke. In other trials of romosozumab with placebo controls, this imbalance was not seen (56-58). The FDA has issued a black box warning stating that romosozumab is contraindicated for patients with a history of MI or stroke in the past year and should be discontinued for patients who develop an MI or stroke on treatment.

Risks of Treatments for Osteoporosis

It is important to balance a discussion of benefits with risks especially when discussing treatments for osteoporosis, because several classes have been associated with rare but serious side effects. Unfortunately, media reports have disproportionately magnified these risks and have not effectively communicated the benefits that most patients gain by taking these therapies. Figure 7 exemplifies this point by describing, for example, the benefits of bisphosphonates relative to the risks of its adverse effects and of other rare events, such as motor vehicle accident or homicide (59). Largely due to fear of adverse effects, the percentage of patients who received an approved therapy for osteoporosis has declined in the US from 41% in 2001 to 21% in 2011 (60).

RESPONSE TO THERAPY

Patients receiving antiosteoporosis therapy should be monitored for compliance, not only with the prescribed drug, but also with regard to sufficient calcium and vitamin D. Annual height

measurements in this population will not necessarily identify year-to-year changes but can become important over years of assessments. If a patient loses >2 cm in height, vertebral imaging is recommended to evaluate for the occurrence of a new vertebral fracture (28).

BTMs can be used to track not only compliance but also responsiveness (61). These markers include those that reflect bone formation and bone resorption and thus, bone turnover. In contrast to BMD which takes several years to change, these dynamic assays can change within 3-6 months of pharmacotherapy and generally correlate with later changes in BMD (62). For antiresorptive therapies, a reduction of 50% in BTMs is typically seen in a compliant patient (50). Compliance can be enhanced when patients are aware of their response through demonstrated measures of responsivity, such as BTMs and BMD (63).

Serial DXA testing is also important when monitoring response to osteoporosis therapy. The optimal interval for DXA testing varies and depends on the clinical situation. If one goes strictly by the 'LSC' and expected rate of improvement with most of the therapies available for osteoporosis, an interval of 2 years is reasonable. Yearly monitoring of BMD can be extremely helpful since the drugs used can show changes, although not always significant within the first year. An observed positive change can also encourage therapeutic compliance (7). Also, a significant reduction in BMD within a year can alert the clinician to an intervening process that is interfering with therapy and/or a compliance issue. In specific situations such as ongoing glucocorticoid therapy, aromatase inhibitor, or androgen deprivation therapy, yearly measurement of BMD is generally recommended because of the potential for rapid bone loss. For patients receiving long-term antiresorptive treatment with bisphosphonates or denosumab, the ISCD recently recommended considering the use of FFI (full-length femur imaging) which utilizes DXA for the detection of atypical femur fractures (AFF), a rare adverse effect of these

therapies. On imaging, AFF starts as a stress reaction in subtrochanteric region of the lateral femur (64).

Clinicians may be prompted to investigate possible secondary causes for bone loss if patients are not responding as expected to antiosteoporosis medications. There are many secondary causes of osteoporosis, including RA, hyperparathyroidism, untreated longstanding hyperthyroidism, male hypogonadism, premature menopause, malnutrition, multiple myeloma, celiac disease, other malabsorptive disorders, Cushing's syndrome, hyperprolactinemia, chronic immobilization, chronic liver disease, osteogenesis imperfecta, type 1 DM, and treatment with certain medications (e.g., anti-epileptic, aromatase inhibitor, glucocorticoid therapies) (5). Obvious secondary causes should have been ruled out prior to instituting therapy for osteoporosis. This differential diagnosis is a useful reference even if these disorders were not apparent when therapy was instituted.

Drug failure can be considered if a patient has a new fracture on therapy and compliance has been assured. No drug therapy is perfect; fractures are going to occur despite effective drugs and therapeutic compliance. However, patients understandably often interpret the inter-current fracture as evidence for drug failure. Significantly worsening BMD is a clearer reflection of drug failure assuming good compliance. If the patient is receiving oral therapy, these situations often call for a switch to parenteral therapy, such as denosumab or zoledronic acid. Another option in patients who have "failed" antiresorptive therapy by sustaining a fracture is to switch to an anabolic agent, such as teriparatide, abaloparatide, or romosozumab. Limiting factors for the use of anabolic agents for many patients include administration of daily (teriparatide or abaloparatide) or monthly (romosuzumab) injection, as well as the cost for treatment.

CONCLUSION

DXA is a safe and cost-effective method of bone density measurement, both in assessing fracture risk and monitoring response to therapy. Given the high prevalence of osteoporosis and the morbidity and mortality associated with fragility fractures, BMD measurement remains an important public health intervention.

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FIGURES AND FIGURE LEGENDS

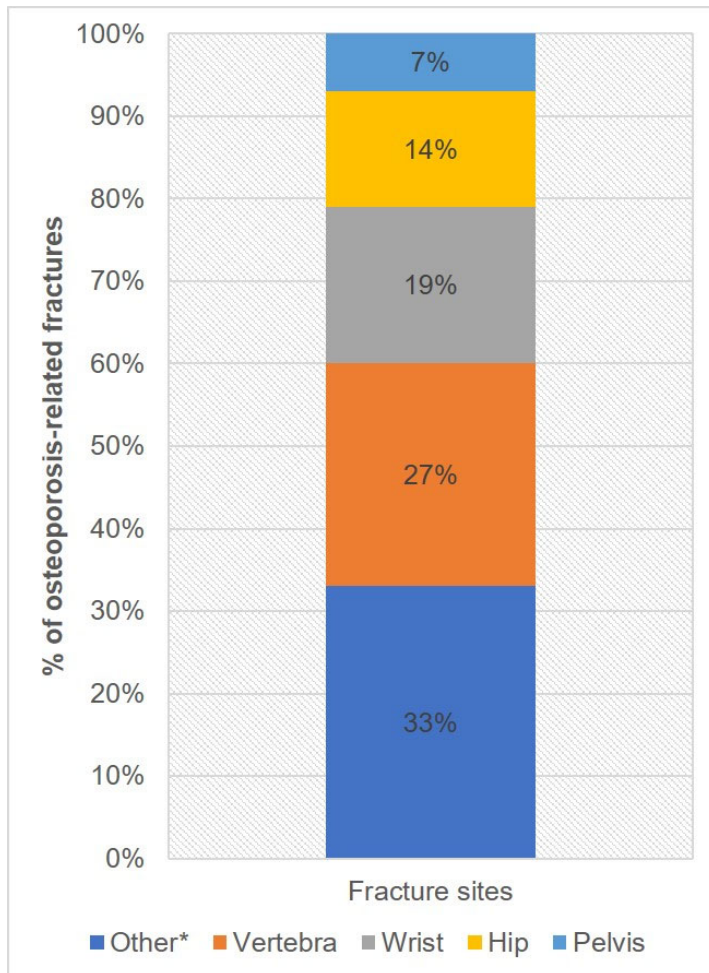


FIGURE 1. Sites of fractures caused by osteoporosis in the United States in 2005. There were ~2 million osteoporosis-related fractures in 2005 in the US: 29% occurring in men, 14% occurring in non-white Americans, and 73% occurring at nonvertebral sites. *Other fracture sites include the radius, humerus, clavicle, hands/fingers, patella, and tibia/fibula. (Reprinted and adapted with permission from American Association of Clinical Endocrinologists © 2016 AACE, Ref. (5): Pauline M. Camacho, Steven M. Petak, Neil Binkley, et al. AACE/ACE Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016. *Endocr Pract.*2016;22(4): 1-42.)

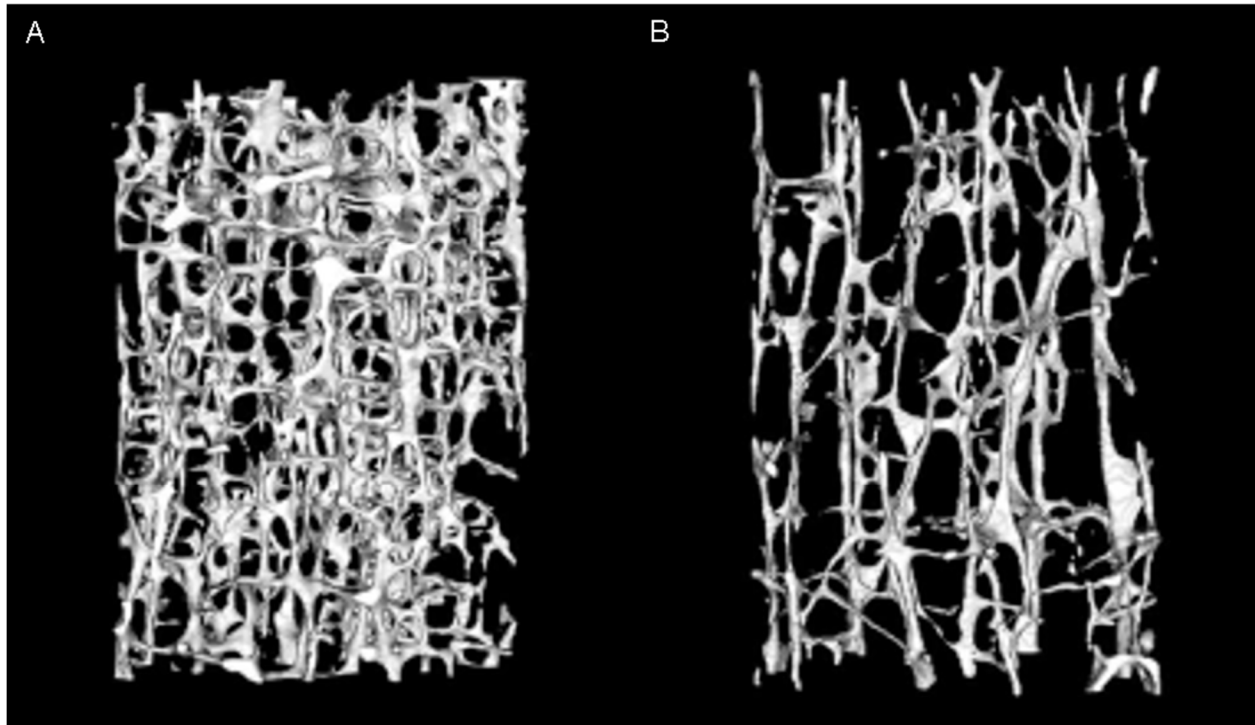


FIGURE 2. Three-dimensional micro-computed tomography. Loss of horizontal trabeculae in osteoporosis from (A) a 52-year-old female and (B) an 84-year-old female with a vertebral fracture. (Reprinted with permission of Ref. (8).)



FIGURE 3. Vertebral fracture assessment depicting multiple compression deformities.

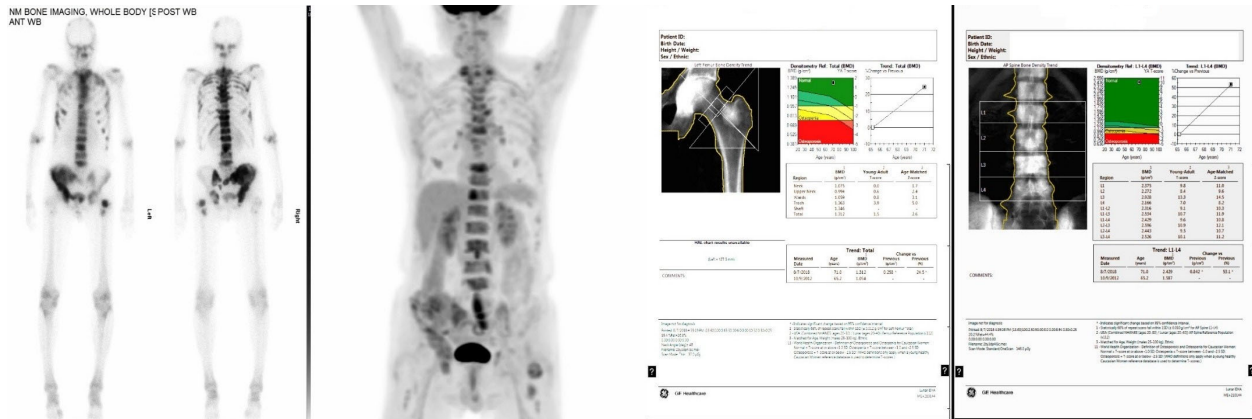


FIGURE 4. Osteoblastic metastases limiting assessment. The International Society For Clinical Densitometry recommended imaging techniques to include the non-dominant forearm to avoid inaccurate measurement.

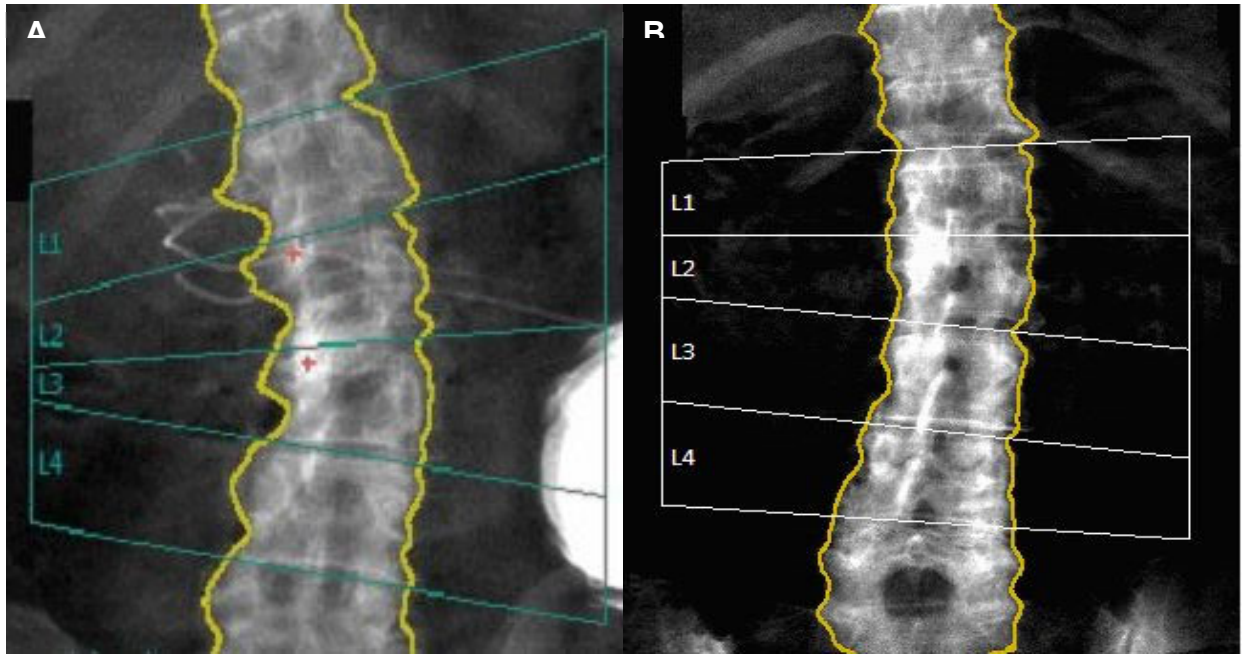


FIGURE 5. Cases of entities that confound dual-energy x-ray absorptiometry (DXA). (A) Scoliotic spine with hepatic arterial infusion pump limiting assessment. **(B)** Degenerative spine with multi-level sclerotic artifacts falsely increasing bone mineral density.

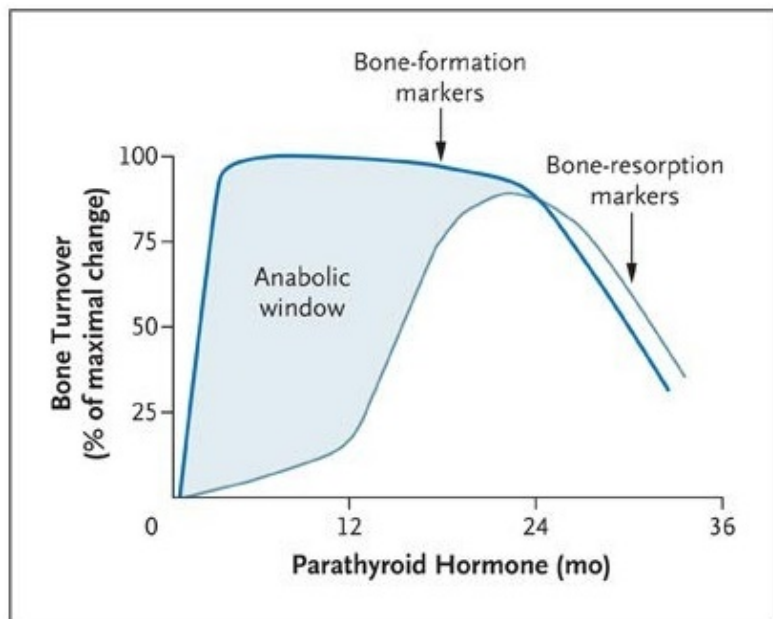
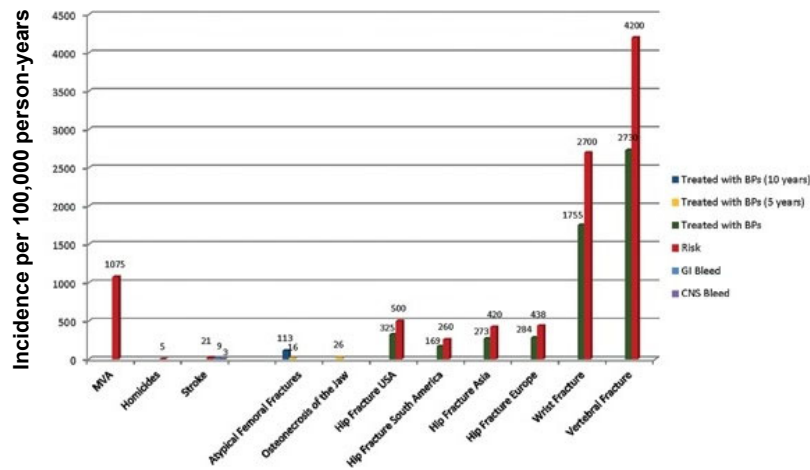


FIGURE 6. The anabolic window. The observation of rapid increases in bone-formation markers, and later, increases in bone-resorption markers with two anabolic agents that share a similar mechanism of action as parathyroid hormone analogues. (Reprinted with permission from Massachusetts Medical Society, Ref. (55): from *The New England Journal of Medicine*, Ernesto Canalis, Andrea Giustina, John P. Bilezikian, Mechanisms of Anabolic Therapies for Osteoporosis, 357: 905-916, © 2007 Massachusetts Medical Society.)



Risk of adverse effects and to other rare events

FIGURE 7. Risks associated with bisphosphonate use relative to both the risk of adverse effects and to other rare events. *Abbreviations:* BPs, bisphosphonates; CNS, central nervous system; GI, gastrointestinal; MVA, motor vehicle accident. (Reprinted with permission of Ref. (59).)

TABLES

TABLE 1. Indications for treatment to reduce osteoporosis or osteopenia in postmenopausal women and men age ≥ 50 years with elevated fracture risk.

Indications
Clinically apparent hip or vertebral fracture
Vertebral fracture detected on imaging
T-score of ≤ -2.5 at the femoral neck, total hip, or lumbar spine
T-score between -1 and -2.5 AND 10-year probability of hip fracture at $\geq 3\%$ estimated with FRAX [®]
T-score between -1 and -2.5 AND 10-year probability of major osteoporotic fracture* at $\geq 20\%$ estimated with FRAX [®]

* A major osteoporotic fracture includes hip, clinical spine, humerus, or wrist fracture.

Abbreviation: FRAX[®], fracture risk assessment tool.

TABLE 2. Mechanism of action with antiresorptive and anabolic therapies.

Type of Drug	Bone Formation	Bone Resorption
Antiresorptive therapy	Decrease	Decrease
Anabolic therapy (e.g., PTH analogue)	Transient increase	Eventual increase
Anabolic therapy (e.g., sclerostin Ab)	Transient increase	Decrease

Abbreviations: Ab, antibody; PTH, parathyroid hormone.

TABLE 3. FDA-approved antiresorptive and anabolic therapies used in randomized clinical trials (53,54).

<i>Drug</i>	<i>Name of Study</i>	<i>No. of patients</i>	<i>RR% of Vertebral Fx</i>	<i>RR% of Hip Fx</i>
Antiresorptive therapies				
Calcitonin	PROOF	1255	36	NS
Raloxifene	MORE	7704	30-55	NS
HRT/ERT	WHI	16608	34	34-39
Alendronate	FIT-1	2027	47	51
Risedronate	VERT	2458	41-49	NA
Risedronate	HIP-OP	5445	NA	40
Ibandronate	BONE	2946	52	NS
Zoledronic acid	HORIZON	7765	70	41
Denosumab	FREEDOM	7868	68	40
Anabolic therapies				
Teriparatide	ClinicalTrials.gov identifier: NCT00670501	1637	84	NA
Abaloparatide	ACTIVE	2463	86	43 (NV Fx)
Romozosumab	FRAME	7180	83	NS

Abbreviations: FDA, US Food and Drug Administration; Fx, fracture; HRT/ERT, hormone replacement therapy/estrogen replacement therapy; NA, not available; No., number; NS, not significant; NV Fx, non-vertebral fracture; RR, relative risk.