Bone Mineral Density: Clinical Relevance and Quantitative Assessment

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Learning Objectives: On successful completion of this activity, participants should be able to describe (1) the benefits and limitations of evaluating bone mineral density by dual-energy x-ray absorptiometry and FRAX to assess fracture risk; (2) the uses of various pharmacologic therapies available for the treatment of osteoporosis; and (3) the process of monitoring and ensuring patient response to osteoporosis therapy.

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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 U.S. National Osteoporosis Foundation guidelines, postmenopausal women and men at least 50 y old with osteopenic BMD warrant pharmacologic treatment if they have a FRAX-calculated 10-y probability of at least 3% for hip fracture or at least 20% for major osteoporotic fracture. 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. Although 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 who have an incident fragility fracture on therapy, secondary causes of osteoporosis or non-compliance with medical therapy should be considered.

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

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Osteoporosis is highly prevalent but underdiagnosed and undertreated, partly because it is often clinically undetected until a fragility fracture occurs. Among adults aged greater than 50 y, 1 of 3 women and 1 of 5 men will experience a fragility fracture (*1*). Hip fractures are associated with more than a 20% mortality rate at 1 y (*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 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 noncollagenous 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 ratio of the internal surface area to the mineralized bone matrix volume determines the accessibility of remodeling the mineralized bone matrix and its vulnerability to deterioration when remodeling becomes unbalanced (*6*). The surface area–to–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 (Fig. 2) (*8*).

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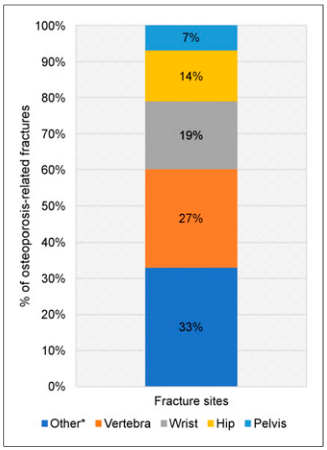

FIGURE 1. Sites of fractures caused by osteoporosis in United States in 2005. There were ~2 million osteoporosis-related fractures in 2005 in United States: 29% in men, 14% in nonwhite Americans, and 73% at nonvertebral sites. *Radius, humerus, clavicle, hands/fingers, patella, and tibia/fibula. (Adapted with permission (5).)

BMD measurement by dual-energy x-ray absorptiometry (DXA), since its approval by the U.S. Food and Drug Administration (FDA) in 1988, has become the main method by which fracture risk is assessed in the United States. 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 2 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 2 different energies (*12*). Before the advent of current DXA systems, the earliest attempts to measure BMD comprised plain radiographs for quantitative and qualitative morphometry (*13*). Nuclear medicine would play a role in early BMD measurement with single-photon absorptiometry and dual-photon absorptiometry. Although current systems use an x-ray tube as the radiation source, the earliest forms of photon absorptiometry used radionuclides as the photon-emitting source. ^{125}I (27.3 keV) was most commonly used to generate the single photon beam, whereas dual-photon absorptiometry used ^{153}Gd with its 2 distinct photoelectric peaks (44/100 keV). These radionuclide-based techniques have led to current DXA systems using x-ray photons.

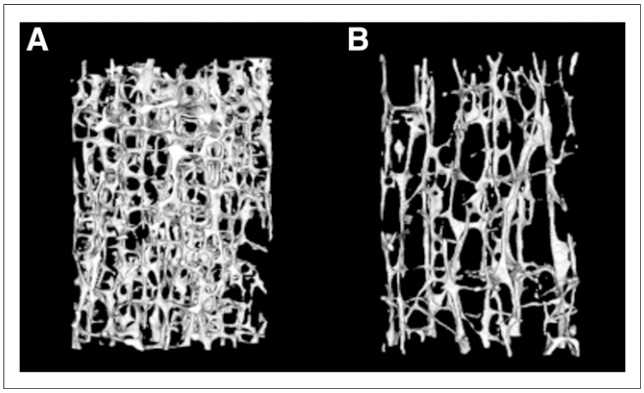

FIGURE 2. Three-dimensional micro-CT. Loss of horizontal trabeculae in osteoporosis is seen in 52-y-old woman (A) and 84-y-old woman (B) with vertebral fracture. (Reprinted with permission of (*8*).)

DXA is a 2-dimensional measurement of bone mass, or a measurement of area. Since bone depth is not a factor, bone size can affect apparent BMD. Essentially, 2 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. Although DXA is still considered the gold standard for assessing fracture risk, other modalities can offer potential value in the assessment of bone mass. Quantitative CT is a volumetric measurement of bone density. Quantitative CT 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 is possible with DXA (*13*). Although quantitative CT and DXA have the same ability to predict vertebral fractures in postmenopausal women, there is lack of evidence to support this position for men (*14*). For both men and women, the International Society for Clinical Densitometry (ISCD) does not recommend spine quantitative CT 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 ^{99m}Tc-MDP was found to be a viable tool for clinical quantification of bone metabolism in patients with osteoporosis (*15*). On the other hand, using 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 μSv), comparable to natural background radiation received each day (7 μSv) (*16*). Full-table DXA systems can obtain BMD measurements at several sites (e.g., lumbar spine, hip, forearm), whereas 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, uses a software program and evaluation by the semiquantitative method of Genant et al. (Fig. 3) (*12,17,18*).

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 SDs that the patient's score is below the control value. Osteoporosis is defined by a T-score of no more than −2.5 (*19*). Like vertebral fracture assessment, DXA has also been adapted to semiquantitatively assess skeletal microstructure. Using a software program that determines the extent to which the lumbar vertebra is homogeneous or heterogeneous, a noninvasive assessment of skeletal microstructure is possible. This adaptation, known as the trabecular bone score (TBS), was approved by the FDA in 2012 (*20*). TBS, an independent predictor of fracture risk, adds to information obtained by the T-score and the fracture risk assessment tool (FRAX; Centre for Metabolic Bone Diseases, University of Sheffield). The Medimaps Group, which produced the TBS iNsight (Osteo) software, proposes the following interpretation of TBS values. For postmenopausal women, a TBS of at least 1.350 is normal; 1.2–1.350 indicates partially degraded bone; and 1.2 or less indicates the lowest tertile of skeletal microstructure (*21*). TBS is not used alone for treatment

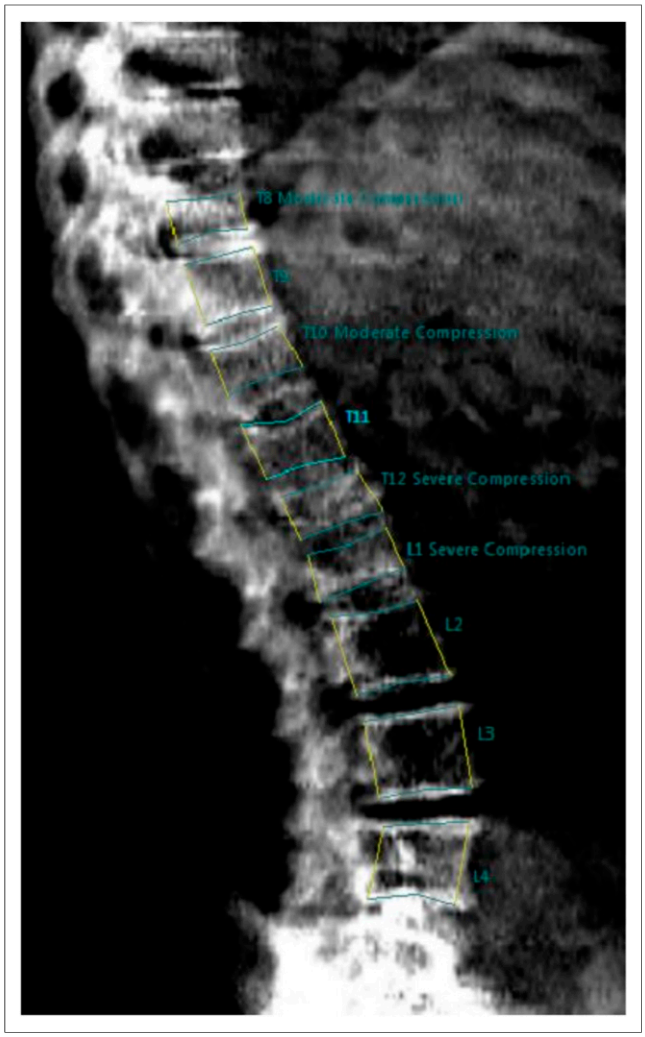

FIGURE 3. Vertebral fracture assessment depicting multiple compression deformities.

decision making, but it is helpful as an adjunct to the 2 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 ISCD (*22,23*). The semiquantitative assessment is now incorporated into the FRAX software (*24*), adding to its predictive power. ISCD suggests using the TBS-adjusted World Health Organization FRAX in treatment decision making (*22*), as described in the "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 (*25,26*). Nonetheless, abdominal obesity can potentially introduce an artifact in the TBS measurement (*27,28*).

Recommendations for DXA Screening

DXA screening for osteoporosis is important because osteoporosis is asymptomatic until a fracture occurs. The National Osteoporosis Foundation, American Society for Bone and Mineral Research, and ISCD recommend BMD testing by DXA for women aged at least 65 y and men aged at least 70 y, as well as, according to risk factor profile, postmenopausal women and men aged at least 50 y (*29*). 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 (*5,30*).

DXA SCANNING IN SPECIAL POPULATIONS

Patients Treated with Chronic Glucocorticoid Therapy

The 2017 American College of Rheumatology guidelines on glucocorticoid-induced osteoporosis prevention and treatment recommend BMD testing for fracture risk assessment in all adults receiving chronic glucocorticoid therapy (≥3 mo) aged at least 40 y or those younger than 40 y whose fracture risk is high because of a previous fracture or other significant osteoporotic risk factors (*31*).

Recipients of Solid-Organ Transplants

Recipients of solid-organ transplants experience rapid bone loss in the first 6–12 mo after transplantation (*32*), a time when fractures are most common (*33,34*). There is no consensus on prevention of bone loss and fractures through medical management in patients undergoing solid-organ transplantation. The American College of Rheumatology recommends treatment, following the same age guidelines mentioned above for glucocorticoid-induced osteoporosis prevention and treatment in this population (*31*).

Women with Premature Menopause

Premature menopause is defined as menopause in women younger than 40 y. Etiologies of premature menopause include chemotherapy, oophorectomy, 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 (*35*), 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 mo, as demonstrated in men starting androgen deprivation therapy for prostate cancer. Men who are found to be hypogonadal should have a baseline DXA measurement, as well as intermittent follow-up (*36*).

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. A complete laboratory work-up, including calcium, phosphate, alkaline phosphatase, and vitamin D levels, is vital for the clinician to make the correct diagnosis (*37*). Successful treatment of this condition causes remineralization of the skeleton and often produces a 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 nonadherence to ISCD guidelines on serial DXA measurements (Figs. 4 and 5). These issues may adversely affect the calculation of BMD and should be considered when

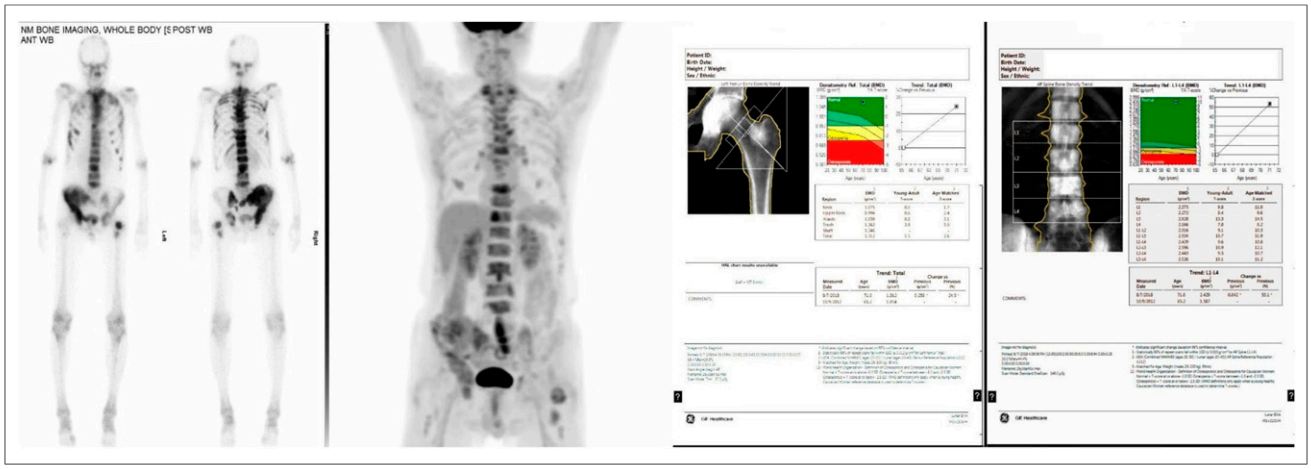

FIGURE 4. Osteoblastic metastases limiting assessment. ISCD recommended imaging techniques to include nondominant forearm to avoid inaccurate measurement.

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 the utmost importance. Another pitfall is the administration of oral contrast or radionuclides preceding the DXA scan. Failure to recognize the oral contrast medium overlying the lumbar spine could lead to reporting a falsely high BMD.

The effect of radionuclide administration before DXA studies has been debated for years. On GE Healthcare Lunar systems, the effect on BMD varies between patients and is dependent on the site scanned and dose administered (*38*). To avoid the radionuclide effect on BMD, DXA can be performed before the administration of the radiopharmaceutical. If this is not possible, it is recommended that the DXA study be postponed for 24–48 h after the nuclear medicine study (*38*).

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 (*39*). The ISCD recommends calculating the least significant change (LSC) at each center performing DXA (*30*). 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 as was used for their prior measurement for proper serial BMD measurement.

A 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 or further assessment. Notably, substantial weight loss can lead to reduced BMD, despite effective therapy.

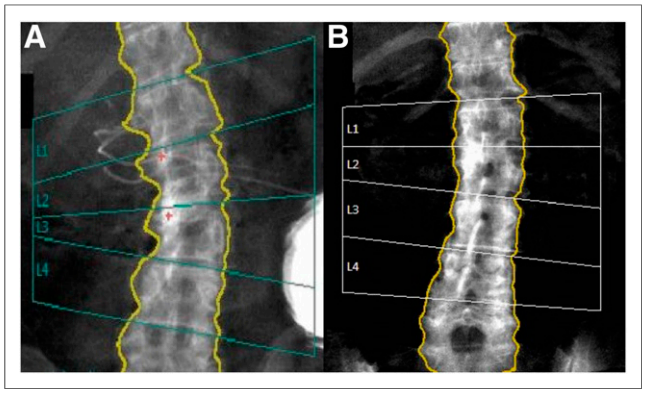

FIGURE 5. Cases of entities that confound DXA. (A) Scoliotic spine with hepatic arterial infusion pump limiting assessment. (B) Degenerative spine with multilevel sclerotic artifacts falsely increasing BMD.

INDICATIONS FOR TREATMENT BASED ON BMD

Guidelines from the National Osteoporosis Foundation and other societies recommend that, after hip or vertebral fractures, patients should receive pharmacotherapy as described in the "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). The Genant semiquantitative grading system is a useful method to evaluate subclinical osteoporotic vertebral fractures (*18*). 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 2-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

TABLE 1
Indications for Treatment to Reduce Osteoporosis or Osteopenia in Postmenopausal Women and Men Aged ≥50 Years with Elevated Fracture Risk

Indication	Description
Hip or vertebral fracture	Clinically apparent hip or vertebral fracture
Vertebral fracture	Vertebral fracture detected on imaging
T-score	
≤−2.5	T-score of ≤ −2.5 at femoral neck, total hip, or lumbar spine
−1 to −2.5	T-score of −1 to −2.5 and 10-y probability of ≥3% for hip fracture or of ≥20% for major osteoporotic fracture* estimated with FRAX

*Hip, clinical spine, humerus, or wrist.

ISCD states that at least 2 evaluable vertebrae must be present for a lumbar spine measurement to be reportable.

There are 2 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 no more than −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. Although patients with osteopenia have a lower fracture risk than patients with osteoporosis, the incidence of osteopenia is much higher than that of osteoporosis; therefore, most patients with fractures do not have preexisting 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 helpful. If these patients meet treatment thresholds by FRAX, they are candidates for pharmacologic treatment (Table 1). The FRAX score is calculated using a computer-based algorithm that estimates the 10-y probability of both a major osteoporotic fracture (hip, clinical spine, humerus, or wrist) and a hip fracture (*44*). FRAX calculations integrate a patient's age, sex, race, weight, height, family medical history, tobacco use, glucocorticoid use, history of rheumatoid arthritis, 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-y period, the lower the risk of sustaining a fracture for the same risk factors.

The values 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 (*24*). FRAX-based indications for therapy depend on high risk as determined by country-specific FRAX scores of at least 3% or at least 20% for hip or major osteoporotic fractures, respectively (Table 1) (*44,46*).

Diabetes mellitus 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, diabetes mellitus is associated with greater risk. Although patients with diabetes mellitus do not have rheumatoid arthritis, many clinicians will adjust the FRAX score by selecting the box labeled "rheumatoid arthritis" (*24*) to account for the additional risk of having diabetes mellitus. 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, antiresorptive agents reduce osteoblast activity and bone formation. The generalized reduction in bone turnover is beneficial in 2 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 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 y of therapy because of reported rare adverse effects with long-term bisphosphonate use (*48*) and evidence of persistent antifracture effects. Resumption of bisphosphonate therapy after a drug holiday may be indicated in

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 analog)	Transient increase	Eventual increase
Anabolic therapy (e.g., sclerostin antibody)	Transient increase	Decrease

PTH = parathyroid hormone.

patients who experience a fracture or show significant BMD loss (*7*). According to the American Society for Bone and Mineral Research 2015 guidelines, a drug holiday should be considered after 5 y for postmenopausal women treated with oral bisphosphonates and after 3 y for those treated intravenously (*49*).

Denosumab, a monoclonal antibody that targets the bone-resorbing ligand known as RANKL, 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 RANKL, denosumab binds to and inactivates RANKL. Loss of RANKL leads to a profound reduction in osteoclast activity. The approved dose (60 mg) by subcutaneous injection lasts for approximately 6 mo, 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 increased to values higher than baseline by 12 mo after the discontinuation of a 2-y 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 because of concerns of increased cancer risk and its weak therapeutic benefit (*51,52*). Although 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 $\leq$–3.5 in the absence of a fracture or a T-score of $\leq$–2.5 in the presence of a fragility fracture); patients with contraindications to oral bisphosphonates (e.g., esophageal emptying disorders or esophageal strictures); and patients for whom other therapies have failed (e.g., the patient sustained a fracture or had significant BMD loss while receiving other therapy).

Two human parathyroid hormone analogs, teriparatide and abaloparatide, are anabolic agents that produce a quick increase in bone-formation markers and, later, an increase in bone-resorption markers; this interval is described as an anabolic window (Fig. 6) (*55*). These agents are contraindicated in patients with a history of external-beam radiation therapy because of a theoretic risk of osteosarcoma, and in patients with active bone metastases. However, with teriparatide now approved for almost 2 decades, no oncogenic signals have emerged. Both teriparatide and abaloparatide are administered subcutaneously as a daily dose for no more than 2 y.

A recently introduced anabolic agent and monoclonal antibody, romosozumab, binds the osteocyte-derived protein sclerostin,

TABLE 3
FDA-Approved Antiresorptive and Anabolic Therapies Used in Randomized Clinical Trials (*53,54*)

Drug	Name of study	No. of patients	RR% of vertebral Fx	RR% of hip Fx
Antiresorptive therapies				
Calcitonin	PROOF	1,255	36	NS
Raloxifene	MORE	7,704	30–55	NS
HRT/ERT	WHI	16,608	34	34–39
Alendronate	FIT-1	2,027	47	51
Risedronate	VERT	2,458	41–49	NA
Risedronate	HIP-OP	5,445	NA	40
Ibandronate	BONE	2,946	52	NS
Zoledronic acid	HORIZON	7,765	70	41
Denosumab	FREEDOM	7,868	68	40
Anabolic therapies				
Teriparatide	NCT00670501*	1,637	84	NA
Abaloparatide	ACTIVE	2,463	86	43 (NV Fx)
Romosozumab	FRAME	7,180	83	NS

*ClinicalTrials.gov identifier.

RR = relative risk reduction; Fx = fracture; HRT/ERT = hormone replacement therapy/estrogen replacement therapy; NS = not significant; NA = not available; NV Fx = nonvertebral fracture.

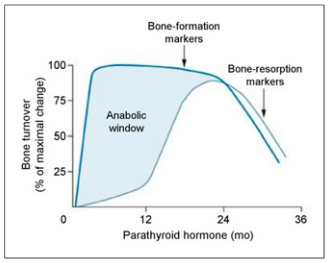

FIGURE 6. Anabolic window. With 2 anabolic agents that have mechanism of action similar to that of parathyroid hormone analogs, there are rapid increases in bone-formation markers followed by increases in bone-resorption markers. (Reprinted with permission of (*55*).)

which inhibits bone formation. Compared with other pharmacotherapy, romosozumab results in the largest increases in BMD at both the lumbar spine and the hip (*56*) over the shortest period. Patients treated with romosozumab followed by alendronate had fewer spinal fractures than patients receiving the alendronate regimen alone (*56,57*). Romosozumab has an interesting property of rapidly transitioning from an anabolic to an antiresorptive after 6 mo of use. By 12 mo, 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 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 myocardial infarction or stroke in the past year and should be discontinued for patients who develop a myocardial infarction 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 a motor vehicle accident or homicide (*59*). Largely because of fear of adverse effects, the percentage of patients who received an approved therapy for

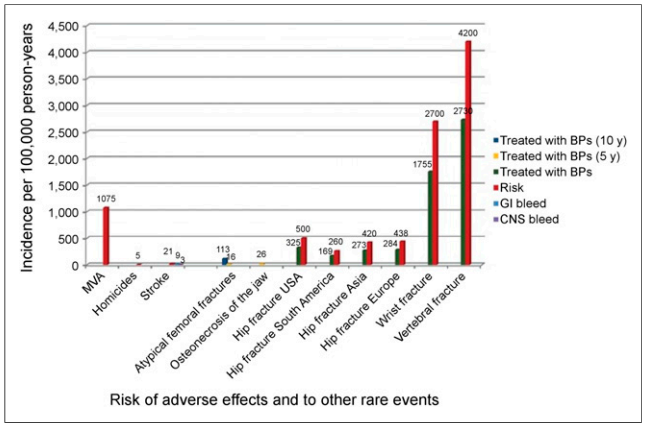

FIGURE 7. Risks associated with bisphosphonate use relative to both adverse effects and other rare events. BPs = bisphosphonates; CNS = central nervous system; GI = gastrointestinal; MVA = motor vehicle accident. (Reprinted with permission of (*59*).)

osteoporosis declined in the United States 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 more than 2 cm in height, vertebral imaging is recommended to evaluate for the occurrence of a new vertebral fracture (*29*).

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 mo 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 y is reasonable. Yearly monitoring of BMD can be extremely helpful since the drugs can show changes, although these are 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 or a compliance issue. In specific situations such as ongoing glucocorticoid therapy, aromatase inhibitors, 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 full-length femur imaging, which uses DXA for the detection of atypical femur fractures, a rare adverse effect of these therapies. On imaging, atypical femur fracture starts as a stress reaction in the 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 rheumatoid arthritis, hyperparathyroidism, untreated longstanding hyperthyroidism, male hypogonadism, premature menopause, malnutrition, multiple myeloma, celiac disease, other malabsorptive disorders, Cushing syndrome, hyperprolactinemia, chronic immobilization, chronic liver disease, osteogenesis imperfecta, type 1 diabetes mellitus, and treatment with certain medications (e.g., antiepileptic, aromatase inhibitor, and glucocorticoid therapies) (*5*). Obvious secondary causes should have been ruled out before 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 ensured. No drug therapy is perfect; fractures are going to occur despite effective drugs and therapeutic compliance. However, patients understandably often interpret the intercurrent 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 (romosozumab) 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 in 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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