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Review

Management of Osteoporosis and Spinal Fractures: Contemporary Guidelines and Evolving Paradigms

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Physicians involved in treating spine fractures secondary to osteopenia and osteoporosis should know the pathogenesis and current guidelines on managing the underlying diminished bone mineral density, as worldwide fracture prevention campaigns are trailing behind in meeting their goals. This is a narrative review exploring the various imaging and laboratory tests used to diagnose osteoporotic fractures and a comprehensive compilation of contemporary medical and surgical management. We have incorporated salient recommendations from the Endocrine Society, the American Association of Clinical Endocrinology (AACE), and the American Society for Bone and Mineral Research (ASBMR). The use of modern scoring systems such as Fracture Risk Assessment Tool (FRAX®) for evaluating fracture risk in osteoporosis with a 10-year probability of hip fracture and major fractures in the spine, forearm, hip, or shoulder is highlighted. This osteoporosis risk assessment tool can be easily incorporated into the preoperative bone health optimization strategies, especially before elective spine surgery in osteoporotic patients. The role of primary surgical intervention for vertebral compression fracture and secondary fracture prevention with pharmacological therapy is described, with randomized clinical trial-based wisdom on its timing and dosage, drug holiday, adverse effects, and relevant evidence-based literature. We also aim to present an evidence-based clinical management algorithm for treating osteoporotic vertebral body compression fractures, tumor-induced osteoporosis, or hardware stabilization in elderly trauma patients in the setting of their impaired bone health. The recent guidelines and recommendations on surgical intervention by various medical societies are covered, along with outcome studies that reveal the efficacy of cement augmentation of vertebral compression fractures via vertebroplasty and balloon kyphoplasty versus conservative medical management in the elderly population.

Keywords: Cement augmentation; bone density; Kyphoplasty; Osteoporosis; Postmenopausal; Spinal fractures

Osteoporosis is a systemic disease characterized by low bone mass, micro-architectural deterioration of bone tissue, and skeletal fragility. Osteoporosis is linked to socioeconomic burden, morbidity, and mortality.[1,2,3] Fractures of the hip, spine, and distal forearm are regarded as typical osteoporotic fractures. The presence of a single spine fracture increases the risk of subsequent vertebral compression fractures (VCFs) by five-fold and the risk of hip and other fractures two to three-fold.[4] Significant gaps still exist around various aspects of knowledge dissemination related to bone health and osteoporosis. This is causing us to face unmet goals of fracture prevention strategies across the globe. We aim to provide an updated narrative review on the epidemiology, pathogenesis, diagnosis, and management of

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osteoporosis and spine fractures. This narrative review was conducted between March and May 2021 involving six authors independently reviewing the latest evidence. A consensus was reached amongst authors about presenting only high-quality evidence supporting the statements mentioned in the article.

Pathogenesis of Osteoporosis

The pathogenesis of primary osteoporosis is complex and multifactorial.[5] Many people fail to attain peak bone mass and subsequently develop osteoporosis.[6] Bone fragility is affected by bone remodeling, bone turnover, bone mineral density (BMD), and bone quality. The maintenance of adult mass is affected by nutrition, lifestyle, physical activity, hormone status, systemic illnesses, genetic predisposition,

Table 1. Drugs precipitating bone loss

Drug	Mechanism	Comments
Heparin	Decreases bone formation and increases resorption	Studies were mainly done in pregnant women (Enoxaparin may have lesser effect; not enough data)
Cyclosporine	Increase in both bone resorption and bone loss	As bone loss is a co-existing risk factor with diseases treated with cyclosporine, a univariate risk analysis is difficult.
Medroxyprogesterone acetate	Increases bone loss due to induction of estrogen deficiency	Only found with higher doses by inducing estrogen deficiency. No effect with low dose combination therapy with estrogen.
Vitamin A and synthetic retinoid	Excess intake was found to Inhibit osteoblast activity and stimulate osteoclast production. Counteracts the ability of vitamin D to maintain normal serum calcium concentration	Vitamin A is required for normal bone growth. Adverse effect is associated with excess intake.
Methotrexate	High dose methotrexate regimens are associated with increase in bone resorption and an inhibition of bone formation.	This side effect has not been observed with methotrexate doses used for rheumatic disease.
Loop diuretics	Calcium loss through urine due to impaired absorption in the loop of Henle	Loop diuretic use has been shown to increase risk of hip fracture.
Anti-epileptic drugs	Induce cytochrome P450 system and thereby leading to increased catabolism of vitamin D to inactive metabolites and subsequent rise in PTH and mobilization of bone calcium resulting in increased bone turnover	Non-enzyme inducing drugs like valproate have also been associated with increased rates of bone loss and higher incidence of fracture.
Ifosfamide	Causes damage to renal proximal tubules, causing metabolic acidosis, hypercalciuria, and renal phosphate loss.	Hypophosphatemic rickets appears to be a sequelae in children treated with ifosfamide chemotherapy.
Proton pump inhibitors	Reduced stomach acid secretion leads to reduced calcium absorption as it needs an acid environment for optimal absorption	For patients on long term proton pump inhibitors or H2 blocker therapy, use calcium supplements like calcium citrate that do not require acid for absorption.
Antidepressants	Both tricyclic anti-depressants and selective serotonin reuptake inhibitors have been associated with increased risk of fragility fracture, although studies could not prove causality	Predominantly hip and non-vertebral fractures with use of SSRIs.
Thiazolidinediones (Pioglitazone, Rosiglitazone)	Thiazolidinediones have adverse effects on skeletal health (increased fracture risk) suggested by evidence	Alternative anti-hyperglycemic medications should be considered in patients with low bone density or other risk factors for fracture.

advancing age, and medications (Table 1). Various cytokines and hormones help stimulate bone growth.[6,7] Bone strength is a biomechanical property of bones, a function of both BMD and bone quality (Table 2).[8,9] Trabecular and cortical microarchitecture, bone turnover, micro-fractures, mineralization, and micro-damage can affect bone quality (Table 3).[10,11] Bone remodeling is a tightly coupled cycle of bone resorption and bone formation happening inside multicellular units composed of osteoclasts, osteoblasts, and osteocytes (Figure 1).[9,12,13] Under normal homeostasis, bone resorption is completed in 10 days and bone formation in 3 months. Osteocytes, due to their innate ability to sense mechanical stimuli and micro-damage, function as regulatory bodies in the dynamic milieu of the bone. Osteocytes initiate the remodeling cycle by recruiting osteoclasts.[14,15] This remodeled bone tissue is then replaced by an osteoid matrix formed by osteoblasts that eventually undergoes mineralization. Mature osteoblasts that survive are embedded in the new bone tissue as osteocytes, completing the cycle. Osteoblastic differentiation is mediated by Runt-related transcription factor 2, bone morphogenetic proteins, and Wnt/β-catenin. Sclerostin and Dickkopf-1 inhibit the Wnt/β-catenin pathway.[16,17] Osteoclasts are stimulated through activation of receptor activator of nuclear factor κB by its ligand (RANKL) produced by osteoblasts and osteocytes.[17] Towards completion of the remodeling cycle, osteocyte mediated sclerostin causes blockage of further Wnt signaling.

Diagnosis of Osteoporosis

Clinical Assessment

Fragility fracture, by definition, occurs spontaneously or after trauma such as a fall from standing height or less.[18,19] Craniofacial, hand, and foot fractures are not considered osteoporotic. History of sudden onset backache or height loss might signal presence of occult vertebral fractures.[20] Fall risk assessment is done using standardized questionnaires, and gait and balance should be assessed. Screening for vertebral fractures can be done by documenting kyphosis, prospective height loss of >2 cm in a year, rib to pelvis distance ≤2 fingers' breadth, and an occiput-to-wall distance of >5 cm. The "Get-Up-and-Go Test" is used to assess proximal muscle weakness, gait, and risk of falls.[21]

Diagnostic Imaging

BMD is measured by dual X-ray absorptiometry (DEXA), which is a surrogate measure of bone strength,[22] accounting for about 70% of bone strength.[23,24] Three major sites used are lumbar spine (L1 to L4), total hip, and femoral neck (Figure 2). Distal forearm is recommended only when hip and/or lumbar spine cannot be used, as in the case of obesity and hyperparathyroidism. A minimum of two vertebrae is necessary to generate an accurate report. Data generated by DEXA scan is analyzed to derive T and Z scores comparing BMD values to young healthy populations or age-matched controls, respectively. As per World Health Organization

Table 2. Determinants of bone health and anatomical hierarchy in bone

Bone strength			
Bone Volume	***Material Properties***	***Structure***	
Bone Mineral Density	Hydration Tissue density Osteocyte network integrity Cellular density Mineralization degree Mineral crystallinity Degree and type of collagen cross linking Non collagenous proteins	<u>Bone geometry</u> Size Shape Cortical thickness Moment of inertia Femoral neck geometry	<u>Internal architecture</u> Turnover Damage accumulation (micro cracks) Trabecular connectivity Trabecular shape Cortical porosity Tissue organization
Anatomical hierarchy of bone			
	Dimensions	***Descriptions***	
Nature	Nano scale	Organic phase: collagen fibers Mineral phase: hydroxyapatite crystals	
Texture	15-80 μm	Lamellar in mature bone or randomly packed collagen bundles in woven bone Polarization microscopy	
Structure	120-300 μm	Trabecular bone: Arch-like bone structural units in trabecular bone Cortical bone: osteons centered around haversian canal	
Microarchitecture	0.2-0.4 mm	Trabecular bone: rods and plates Cortical bone: compact osteons	

(WHO), osteoporosis is diagnosed in postmenopausal women and in men aged 50 and older if the T-score of the lumbar spine, total hip, or femoral neck is -2.5 or less. [24] In men younger than 50 years, osteoporosis cannot be diagnosed solely on the basis of BMD.

The main limitation of BMD is that it explains bone strength only to a certain extent.[25,26] DEXA is two-dimensional and does not differentiate between cortical and trabecular bone microarchitecture. False positive readings on spine BMD can be seen in patients with spinal degenerative changes, diffuse idiopathic skeletal hyperostosis, ankylosing spondylitis, and fractures. Trabecular bone score (TBS) is a bone texture parameter that can be generated from BMD images of the lumbar spine and is a measure of bone microarchitecture.[26,27] It can be used in situations where BMD value is false positive. Low lumbar spine TBS is associated with fracture risk independent of BMD. Further research on the validity and scope of TBS is ongoing. Vertebral fracture assessment is another DEXA-based technique used to detect spinal fractures. As this technique is based on DEXA, it is inexpensive with relatively low exposure to radiation. Computed tomographic (CT)-based techniques of the spine have good fracture predictability, but we are awaiting validated data on treatment intervention thresholds.[28,29] Quantitative CT of the spine and high-resolution peripheral quantitative CT of the radius and tibia can generate volumetric measurements of trabecular and cortical compartments of bone (Figure 2).[30,31] Thus, it is possible to identify whether bone loss and fractures are occurring due to cortical thinning, porosity or loss of trabecular structure. Finite element analysis (FEA) is another technique used to study bone fragility.

Artificial Intelligence is emerging as a diagnostic modality, with CT images of bones being studied through machine learning algorithms to predict osteoporosis.[31,32] Histomorphometry done using iliac crest biopsy specimens is the gold standard for assessing bone structure, bone formation, and resorption.[33,34] Limitations such as lack of data on load-bearing sites and vertebral bodies, invasiveness, and time-consumption prevent it from being used routinely.

Laboratory Tests

Bone turnover markers (BTMs) are molecular markers of bone remodeling used to assess bone turnover status in certain clinical situations.[35] They are classified as bone formation and bone resorption markers. Products of osteoblasts represent formation markers including byproducts of collagen synthesis such as propeptides of type 1 collagen: C-terminal propeptide of type I procollagen, N-terminal propeptide of type I procollagen, osteoblastic enzymes such as alkaline phosphatase (total and bone specific), and matrix proteins such as osteocalcin. N-terminal propeptide of type I procollagen is the most favored marker due to less variability. Serum C telopeptide crosslink (CTX)-1 is the most reliable marker for bone resorption. The main challenge in using BTMs is that the assays are highly sensitive to analytical variability as well as other factors such as meal intake, exercise, medication use, diurnal and seasonal changes, hormone status, recent fracture, and multiple myeloma. Assays should be performed in fasting samples. BTMs are measured to confirm the efficacy, oral absorption, and compliance to medications. Measurement of serum CTX or bone specific alkaline phosphatase (BSAP) at 3 months of starting treatment is another useful tool.

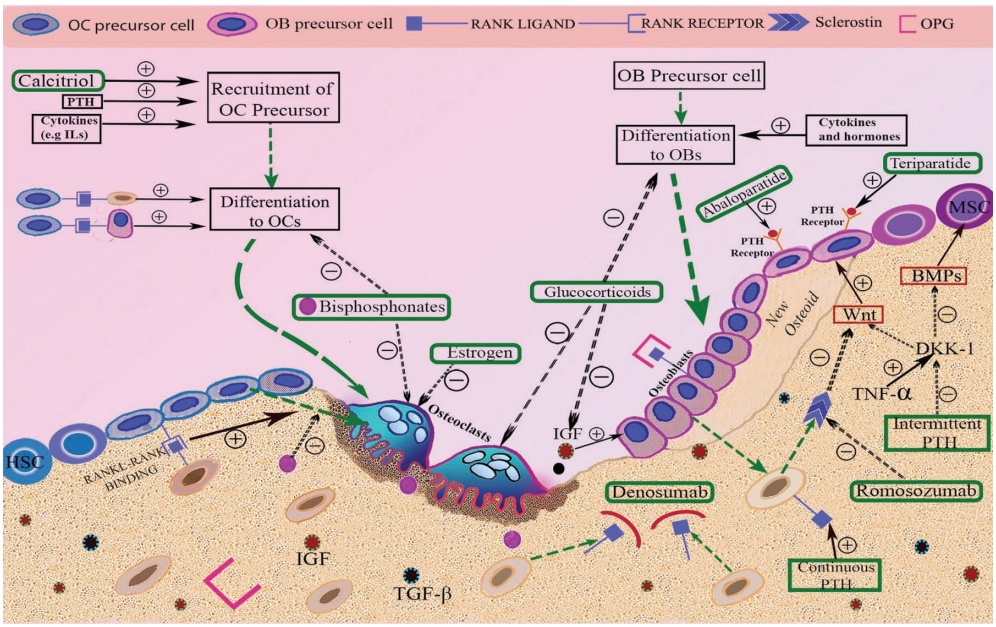

Figure 1. Physiology of bone formation and mechanism of action of drugs used for management of osteoporosis. Mineral deposition into new bone and resorption of old bone are interconnected. Osteocytes, osteoblasts and osteoclasts are key cells involved in bone remodeling. Treatment for osteoporosis are targeted at regulators of osteoclasts and osteoblasts, like RANKL and OPG.

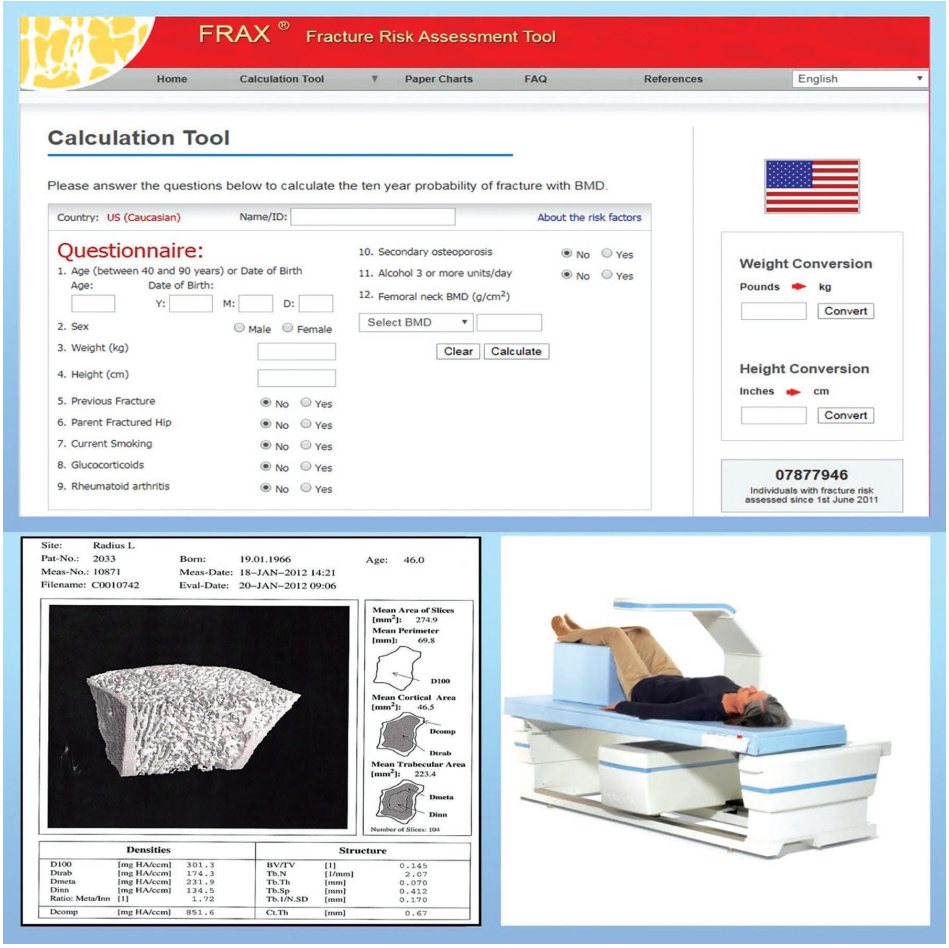

Figure 2. Modalities for diagnosis of osteoporosis and assessment of fractures. Top: Fracture Risk Assessment Tool (FRAX®) is an online questionnaire with 12 questions in estimating fracture risk. Bottom left: High resolution quantitative computed tomography. Bottom right: Dual-energy x-ray absorptiometry (DEXA) scan. Images courtesy of HOLOGIC, Inc and affiliates.

Management of Osteoporosis

Assessment of Fracture Risk and Treatment Using FRAX®

There has been a paradigm shift in the conceptual aspects around pharmacological management of osteoporosis and fractures. Treatment decisions are not made solely on BMD alone; rather, they are made based on a risk score categorization that predicts the future risk of fractures. WHO recommends using an interactive online calculator, Fracture Risk Assessment Tool (FRAX®), developed based on clinical risk factors (Figure 2). BMD and TBS can be put into this calculator to generate more information.[36,37] FRAX® has good predictability for the risk of osteoporotic fractures. Patients with two or more fragility fractures or major osteoporotic fractures are categorized as high risk regardless of BMD or FRAX®. Medical management of osteoporosis includes optimization of calcium, vitamin D, protein intake, fall prevention, ruling out secondary bone loss, lifestyle changes, and improved physical activity. Pharmacological management is mainly accomplished through anti-resorptive or anabolic agents.

All patients with high fracture risk score based on FRAX® will benefit from pharmacological measures. In others, serial BMD measurements and clinical assessment of fracture risk help determine the need for treatment. BTMs and TBS also aid in decision-making. Most patients without high fracture risk are managed by optimizing the intake of calcium, vitamin D, physical activity, correcting life style factors, and managing underlying secondary bone loss causes; although pharmacotherapy may be indicated in a certain subset. In such patients, a drug holiday from bisphosphonates should be considered. Duration of drug holiday is around 2-3 years for alendronate and 1-2 years for risedronate, but can be extended based on individual clinical scenarios. BMD needs to be monitored annually, and if there is a significant drop, treatment decisions should be readdressed. Secondary causes including recent exaggerated weight loss should be ruled out. Patients with high fracture risk require long-term treatment unless there are contraindications or side effects. Drug holiday is not advisable in this category of patients. Even high-risk patients can be treated with oral bisphosphonates as first line, but many of them might require treatment escalation to zoledronic acid, denosumab, or anabolic agents. Monitoring is done through annual BMD and, if stable, every 2-3 years.

Medical Management of Osteoporosis

Calcium and Vitamin D

Appropriate calcium intake is necessary to potentiate the action of anti-resorptive agents.[38] Maintaining a calcium intake of at least 1000-1200 mg/day through diet or supplements is recommended. There are concerns about cardiovascular safety based on meta-analyses suggesting a weak association with myocardial infarction and stroke, whereas others show no association. The Institute of Medicine recommends daily calcium intake of 1000-1200 mg of calcium per day from all

Table 3. An overview of contemporary therapeutic agents in osteoporosis

Agents	Mechanism of action	Effect on bone metabolism	Side effects
Calcium	Reduction of PTH release	Inhibition of bone resorption	Gastrointestinal disorders Hyperkalemia
Vitamin D	Modulation of calcium metabolism	Inhibition of bone resorption	Toxicity with excessive dose (> 4000 U/day). Symptoms of toxicity include nausea, vomiting, constipation, loss of appetite, fatigue, confusion, irritability)
Anti-resorptive agents			
Calcitonin	Regulation of osteoclast function	Inhibition of bone resorption	Gastrointestinal disorders
	Prevention of osteoclast precursors from maturing		Hypocalcemia Weak association with malignant neoplasms
SERM	Interaction with RANKL/RANK/OPG system	Inhibition of bone resorption	Thromboembolic events Pulmonary embolism Fatal strokes
Bisphosphonates	Inhibition of osteoclast apoptosis	Inhibition of bone resorption	Gastrointestinal disorders Osteonecrosis of jaw Atypical femur fractures Acute renal failure
Anti-RANKL antibody (Denosumab)	Prevention of the RANKL/RANK system	Inhibition of bone resorption	Osteonecrosis of the jaw Atypical femoral fracture Hypocalcemia
Anabolic agents			
PTH (Teriparatide)	Stimulation of osteoblast differentiation	Activation of bone formation (intermittent PTH)	Hypercalcemia Increasing risk of osteosarcoma
Sclerostin Inhbitors (Romosozumab)	Regulation of BMP and Wnt signaling	Activation of bone formation	Cardiac ischemic event (Do not start within a year of MI or stroke)
Novel Therapy			
Stem cells	Differentiation into osteoblasts directly Secretion of various growth factors	Supplementation of cell source for osteoblasts	Appear to be safe (limited data)

Abbreviations: SERM, selective estrogen receptor modulators; RANKL, receptor activator of nuclear factor-κB ligand; OPG, osteoprotegerin; PTH, parathyroid hormone; BMP, bone morphogenetic protein

sources. The Endocrine Society recommends a dietary and or supplemental intake of calcium to <1000 mg/d because of concerns with supplements, especially renal calculi. Calcium supplements need to be taken with food. It is recommended to avoid taking more than 500 mg elemental calcium through supplements at once. Safe limit of vitamin D supplementation is recommended as between 800-2000 IU per day. Higher doses might be necessary in patients with malabsorption, history of bariatric surgery, and obesity. Therapeutic target of vitamin D is maintained as at least 20-30 ng/mL, with higher doses being linked to hypercalciuria. In elderly people with osteoporosis, higher protein intake (≥0.8 g/kg body weight/day), unless contraindicated, is associated with increase in BMD, a slower bone loss, and lower risk of hip fracture. Exercise helps to increase BMD, improve posture and balance, and lower fall risk and fractures. Strength training, balance training, aerobic physical activity, posture and back extensor training, and spine-sparing strategies are recommended.

Other medical management options for treating osteoporosis include anti-resorptive and anabolic agents (Table 3).[38] Commonly used anti-resorptive agents include bisphosphonates, calcitonin, and denosumab. Bone formation agents available include teriparatide, abaloparatide, and romosozumab. Anabolic agents should be considered in patients with severe osteoporosis or high risk of fracture, failure of alternative agents while

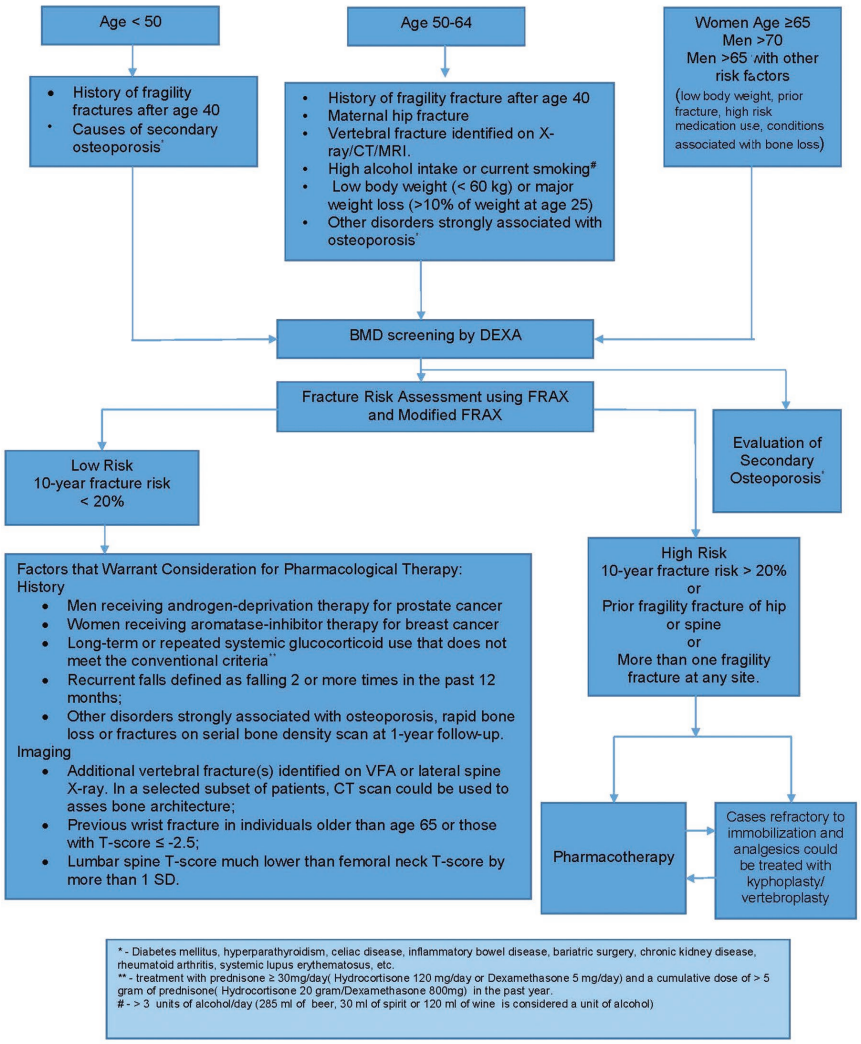

Figure 3. Algorithm for management of osteoporosis. We considered use of DEXA scan and FRAX® to determine osteoporosis. Low risk subjects (<20%) with risk factors could be considered for pharmacological treatment. Subjects with high risk (>20%), prior fragility fracture or more than one fragility fracture should be considered for pharmacotherapy or kyphoplasty/vertebroplasty.

adherent to treatment (fracture or loss of BMD), intolerability or contraindications to other agents, and glucocorticoid-induced osteoporosis. Patients with FRAX® based 10-year probability of hip fracture ≥3 % or the 10-year probability of major osteoporotic fracture ≥20 % should be considered for pharmacotherapy. An algorithm to summarize the diagnostic and therapeutic aspects in all patients with osteoporosis are shown in Figure 3.

Anti-Resorptive Medications

Bisphosphonates

Bisphosphonates such as alendronate, risedronate, ibandronate, and zoledronic acid are recommended as initial treatment (Table 3). Rare side effects of bisphosphonates include osteonecrosis of the jaw, atypical femoral fractures (AFFs), atrial fibrillation, and acute renal failure. AFFs are low trauma or insufficiency stress fractures of the femoral shaft occurring after prolonged bisphosphonate use. Patients often present with pain in the thigh or groin. These are bilateral in 60% of cases and have specific radiology-based definitions proposed by the American Society for Bone and Mineral Research (ASBMR). AFFs have been linked to the use of denosumab and romosozumab. Osteonecrosis of the jaw, by definition, is a non-healing wound in the oral mucosa with exposed bone lasting for more than 8 weeks. This usually occurs after invasive dental procedure such as extraction or implantation. As per the American Dental Association, if a tooth extraction or implant is planned or ongoing, initiation of potent anti-resorptive therapy could be deferred until the area is healed. The American Association of Oral and Maxillofacial Surgeons recommend a 2-month drug holiday apart from a routine dental care.

Denosumab

Denosumab is indicated in high-risk patients and in those with inadequate response to treatment with oral bisphosphonates in the form of lack of BMD improvement or the occurrence of new fractures. It is administered as 60 mg dose subcutaneously every 6 months. The beneficial effects of denosumab reverses after 6 months and, hence, a drug holiday or treatment interruption is not recommended. If treatment is to be discontinued, other anti-resorptive agents should be administered to prevent a rebound increase in bone turnover and vertebral fractures.

Calcitonin

Calcitonin nasal spray and injection (intramuscular or subcutaneous) is approved for treatment of osteoporosis in postmenopausal women when first line treatment agents are not tolerated or not considered appropriate. Due to the possible association between malignancy and calcitonin use, the need for continued therapy should be re-evaluated periodically.[39]

Anabolic Agents

Teriparatide (PTH1-34) is an anabolic agent (Table 3). It is a recombinant parathyroid hormone identical to the 34 N-terminal amino acids of human parathyroid hormone (PTH). The

Table 4. A synopsis of published official guidelines and recommendations by major academic organizations in USA on cement augmentation in osteoporotic VCF during 2010-2020	
American Association of Clinical Endocrinology (2010)	Vertebroplasty and kyphoplasty are indicated for relief of pain.
	Kyphoplasty has been suggested to provide at least partial reversal of the vertebral deformity[62]
American Academy of Orthopedic Surgeons (2011)	Strong recommendation against the use of vertebroplasty for patients who present with an acute osteoporotic VCF and are neurologically intact
	Weak recommendations for kyphoplasty in patients presenting with an osteoporotic spinal compression fracture on imaging correlating clinical signs and symptoms and those who are neurologically intact[44].
National Institute for Health and Care Excellence (2013)	Percutaneous vertebroplasty and percutaneous balloon kyphoplasty without stenting, are recommended for treating osteoporotic VCF only in people who have severe ongoing pain after a recent, unhealed vertebral fracture despite optimal pain management and in whom the pain has been confirmed to be at the level of the fracture by physical examination and imaging[3].
Society of Interventional Radiology (SIR), American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), American College of Radiology (ACR), American Society of Neuroradiology (ASNR), American Society of Spine Radiology (ASSR), Canadian Interventional Radiology Association (CIRA), and the Society of Neuro Interventional Surgery (2014)	Percutaneous vertebral augmentation (PVA) with the use of vertebroplasty or kyphoplasty is a safe, efficacious, and durable procedure in appropriate patients with symptomatic osteoporotic and neoplastic fractures[6].
American Academy of Family Physicians (2016)	Percutaneous vertebral augmentation can be considered in patients who have inadequate pain relief with nonsurgical care of when persistent pain substantially affects quality of life [43]

VCF, verterbral compression fracture

continuous use of PTH or PTH-related peptide (PTHrP) results in increased bone resorption, whereas intermittent administration stimulates bone formation. Intermittent use of PTH causes expression of interleukin-11, suppresses Dickkopf-1, and eventually, activates Wnt signaling and bone formation. It is approved for the treatment of postmenopausal women and men with severe osteoporosis and steroid induced osteoporosis. Dosing of 20 µg daily subcutaneous injection has been demonstrated to lower the risk of vertebral and non-vertebral fractures.[40]

Abaloparatide (PTHrP 1-34) is a 34-amino acid synthetic analog of PTHrP with more potency than teriparatide and fewer side-effects of bone resorption and hypercalcemia[41] (Table 3). Abaloparatide comes in 80 µg daily subcutaneous injection. Patients on anabolic agents need to be monitored for the development of hypercalcemia. Vitamin D deficiency should be treated before starting anabolic agent therapy. BMD needs to be performed at baseline and monitored after 1–2 years of treatment. Ideal duration of anabolic agents should be up to 24 months. After discontinuation, the beneficial effects should be maintained by using anti-resorptive agents. Contraindications for the use of teriparatide and abaloparatide include hypercalcemic disorders, primary or secondary hyperparathyroidism, or increased risk for osteosarcoma (eg., history of Paget disease, skeletal radiation, and bone metastases). Hypercalciuria and renal stones are relative contraindications.

Romosozumab, a monoclonal humanized antibody to sclerostin, is a treatment option for high-risk individuals. Sclerostin inhibits the Wnt/β-catenin pathway in osteoblasts via competitive binding of lipopolysaccharide *binding* protein-5/6, and thus, inhibits osteoblast differentiation.[42] Sclerostin inhibition can induce osteoblast activation and promote bone formation. Romosozumab is a unique agent that has beneficial effects on both bone resorption and bone formation.[43] Dosing is 210 mg monthly as a subcutaneous injection. Women at high risk of cardiovascular disease and stroke should not be considered for romosozumab until more safety data are available on cardiovascular risks.[44]

Bisphosphonate Drug Holiday

Women who are at high risk of fractures should continue therapy, but those with low-to-moderate risk of fractures should be considered for a "bisphosphonate holiday". The concept of "drug holiday" is based on previous data of existence of residual effect of bisphosphonates after discontinuation of treatment. Drug holiday helps to minimize prolonged drug exposure and prevent adverse events. Patients will continue to benefit from some degree of anti-fracture protection due to the residual anti-resorptive effect of retained bisphosphonates in the bone tissue; however, for all other therapies, as described above, benefits are quickly lost after discontinuation. Thus, these therapies must be continued indefinitely or followed with bisphosphonates or another type of therapy to retain the gains achieved.

Monitoring Patients

Monitoring is done mainly using BMD. For high risk patients on pharmacotherapy, serial BMD is necessary to ensure compliance with medications and to assess response to treatment. Annual BMD is required for patients with ongoing bone loss, on pharmacotherapy, on drug holiday, or changing medications. Longer intervals are appropriate if BMD is maintained and treatment is established. VCFs would be evaluated by spine surgeons.

Surgical Management of Osteoporotic VCF

Evidence from the prior randomized clinical trials for the efficacy of vertebral augmentation in VCF has been mixed and controversial.[45] There has been debate on increased fracture risk after augmentation, wide range of complications from cement augmentation, and no consensus on the long-term pain relief or patient satisfaction over nonsurgical management.[46] These were all based on two initial randomized clinical trials (INVEST and Australian Trial) and a subsequent Cochrane review of six trials where the effect of augmentation on disability, mortality, or quality of life were inconsistent. Beall et al[47] published a meta-analysis in 2018 where kyphoplasty had significantly better outcomes in terms of pain reduction compared with nonsurgical management based on Level I and II studies.

Hoyt et al[48] in 2020 reported deconditioning that affects patients with VCFs leads to mortality at a far higher rate than age-matched controls. Evidence based on level I and II studies showed that balloon kyphoplasty resulted in significantly better pain reduction compared to non-surgical management. Another recent claims-based analyses from national registries or insurance datasets by Hirsch et al[45] in 2020 showed a significant mortality benefit for patients from US Medicare registry with VCF treated with vertebral augmentation with a low number needed to treat. This 10-year sample of 100% US Medicare data showed a low number needed to treat to save one life at 1 year and at 5 years. The adjusted number needed to treat to save one life for nonsurgical management versus kyphoplasty ranged from 14.8 at year 1 to 11.9 at year 5, while the adjusted number needed to treat for nonsurgical management versus vertebroplasty ranged from 22.8 at year 1 to 23.8 at year 5.

Another study in 2020 by Hinde et al,[49] in a meta-analysis of more than 2 million patients, those with osteoporotic VCFs who underwent vertebral augmentation were 22% less likely to die at up to 10 years after treatment than those who received nonsurgical treatment. There is mounting evidence that balloon kyphoplasty offers a short procedure, fast and sustained pain relief, early return to ambulation, and reduced need for pain medications with increased physical quality of life, amounting to improved patient satisfaction over nonsurgical treatment.[19,50-52] This is reflected in the formulation of recent Society Guidelines and Recommendations of cement augmentation in VCF (Table 4).

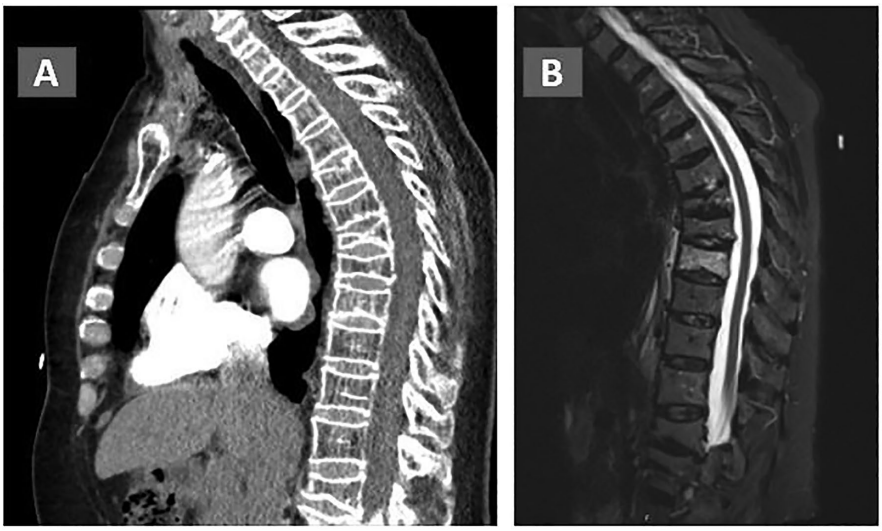

Figure 4. Demonstration of MRI STIR sequences in identifying the acuity of fracture, in patients with multiple vertebral body compression fractures. The acute fracture with bone marrow edema will be bright on STIR while chronic or remote fractures will remain isointense with adjacent normal vertebral bodies (Figures A and B).

A retrospective radiographic study published in 2020 by Lu X et al[53] in 112 acute VCFs (72 treated with kyphoplasty and 40 with non-operative treatments) in 101 subjects followed for mean 21.5 months found that vertebral augmentation may be associated with increased creep deformity of the adjacent vertebra and the progression of segmental kyphosis. However, Momomura et al[46] in 2020 reported no significant differences in incidence of severe posterior wall injury,

pedicle fracture, or flattened vertebral body in post kyphoplasty patients. Disease duration emerged as a possible risk factor for developing adjacent vertebral fracture, whereas other characteristics were not risk factors for complications after kyphoplasty.[46]

While controversies exist on new non-contiguous fracture versus adjacent fracture after cement augmentation in osteoporotic VCF, most agree on a re-fracture presumably due to shifting of the normal load transmission through the already weak osteoporotic spine. In Figure 4A, a CT scan of the thoracic spine shows multiple age indeterminate fractures with concurrent magnetic resonance imaging short tau inversion recovery (STIR) sequence showing single level of acute fracture which had a positive clinical correlation with clinical symptoms (Figure 4B).

In recent years, there have been many trailblazing innovations in interventional and surgical treatment of osteoporosis outside the realms of conventional kyphoplasty and vertebroplasty. Akin to developments in non-cement technologies in kyphoplasty (to prevent complications due to cement embolism), there are also advancing technologies in fusion of osteoporotic spines, where cement augmented pedicle screws (cannulated and fenestrated) and expandable pedicle screws with varying locations and lengths of expansion zones are being introduced. Likewise, there is steady progress in exploring stem cell therapy in treating refractory osteoporosis, with success reported in early animal studies.[54] However, an extensive discussion of modern interventional therapeutics is beyond the scope of this paper.

Conclusion

Timely medical management of poor bone mineralization can reduce the fracture risk in patients diagnosed with osteoporotic fractures. We have highlighted the clinical use of FRAX® along with BMD testing as a reliable tool to determine the need for pharmacotherapy. The role of newer drugs such as denosumab, abaloparatide, and romosozumab has been elaborated with mechanisms of action. Given the limitations of our narrative approach, we have presented the evidence, which is relevant high quality and contemporary, that would aid physicians to guide their treatment. Emerging literature on the advantages of cement augmentation over non-surgical management has been presented along with various society guidelines and recommendations from academic/professional organizations across the world for cement augmentation of VCF and future directions of managing osteoporotic spinal fractures surgically.

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