4 Evaluation and Medical Management of Vertebral Osteoporosis: Preventing the Next Fracture

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Introduction

Osteoporosis is a frequently silent, systemic disease defined by both low bone mineral density and changes in the microstructure of the skeleton, both of which lead to an increased risk for fragility fractures. A fragility fracture is defined by a fracture sustained from a fall from a standing height or less, or a fall out of bed. Additionally, a fragility fracture is one that occurs when a fracture otherwise would not have been expected, such as resulting from a slip on ice. Osteoporosis is the most common bone disease in humans and is a major public health concern. Vertebral compression fractures (VCFs) are the most common types of osteoporotic fractures. These fractures are often asymptomatic making them challenging to diagnose and are associated with increased risk of subsequent fracture as well as increased morbidity and mortality. This chapter both discusses the societal impact of and provides guidance for the evaluation and medical management of vertebral osteoporosis.

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Epidemiology

In the USA, ten million people over the age of 50 years carry a diagnosis of osteoporosis, and 34 million additional people have low bone mass [1, 2]. In those affected by osteoporosis, 1.5 million annual fragility fractures have been noted; half of these are VCFs – this is twice the rate of hip fractures [1, 2]. It is estimated that VCFs occur in up to 50% of people over the age of 50 years, and the incidence increases with age [3, 4]. It is difficult to estimate the true incidence of vertebral fractures, particularly as compared to other fragility fractures. Limitations in these estimates are affected by several factors including the fact that two-thirds to three-fourths of VCFs are asymptomatic, and <10% of patients are hospitalized related to the fracture [4–7]. Access to healthcare and the specific definition of a VCF also play a role in the reliability of this estimate. Vertebral fractures are diagnosed clinically, as when a patient presents with a painful spine fracture, or radiographically (the latter is termed a "morphometric" fracture), and this relationship is not well-defined, as few studies have prospectively compared the agreement between an incident radiographic VCF and an incident clinically recognized, radiographically confirmed VCF in the same person at the same vertebral level [6]. Spinal fractures may remain under-recognized as based on morphometric diagnosis: (1) they may be overlooked on imaging, (2) they may be recorded as "age indeterminate," or (3) they may

A. E. Razi, S. H. Hershman (eds.), *Vertebral Compression Fractures in Osteoporotic and Pathologic Bone*, https://doi.org/10.1007/978-3-030-33861-9_4

not be recorded in the patient's medical record – all three of scenarios likely result in treatment not being initiated at that time [4, 7].

A recent study provides a robust analysis of the worldwide prevalence and incidence of vertebral insufficiency fractures while acknowledging the paucity of quality data on this most common osteoporotic fracture, mostly due to its silent presentation in many [4]. Ballane and colleagues report that the assessment of vertebral fracture incidence and prevalence between distinct countries and areas is most reliable when vertebral fractures are defined morphometrically [4]. They found the prevalence of morphometric fractures in Europe to be lowest in Eastern Europe and highest in Scandinavia (18% vs. 26%, respectively), and in North America the prevalence rates are 20–24% in Caucasian women ≥50 years of age, with a Caucasian/African American ratio of 1.6 [4]. Prevalence rates in women ≥50 years old in Latin America are 11–19% and are lower than in North America and Europe. In Asia, rates in women ≥65 years old are lowest in Indonesia and highest in Japan (9% and 24%, respectively) [4]. Incidence data are scarce and heterogeneous, but these authors report that age-standardized incidence rates in studies that combine ambulatory and hospitalized VCFs are highest in Hong Kong, the USA, and South Korea and lowest in the UK [4]. In the USA, incidence rates in Caucasian patients are ~ fourfold higher than in African American patients [4].

The European Vertebral Osteoporosis Study (EVOS) is a multinational, multicenter population survey of vertebral osteoporosis, whose aim was to determine the prevalence of radiographically (morphometrically) defined "vertebral deformity" as a marker of vertebral osteoporosis by age and sex in different areas and populations of Europe [8]. EVOS revealed an overall increased prevalence of vertebral deformity in women compared with men, and this increased with age (from 5% at 50 years of age to 25% at 75 years of age in women compared with 10% at 50 years of age to 18% at 75 years of age in men) [8]. Notably the prevalence of vertebral deformity was higher in the younger age groups of men than women possibly due to a higher incidence of traumatic injury in men and is therefore less likely to be representative of a fragility fracture in men. It is also noted that men have higher bone density and after age 50 have a slower rate of bone loss compared with women, thereby corroborating the lower prevalence of vertebral deformity in men with increasing age [8].

Risk Factors for Vertebral Fracture

Bone remodeling is a continuous process whereby a healthy skeleton is preserved by removing older bone (resorption), and replacing it with new bone (formation). When this balance is altered, and more bone is removed than replaced, bone loss occurs. In older adults, bone mass equals the peak bone mass achieved by age 18–25 years minus the amount of bone subsequently lost [9]. The attainment of peak bone mass is determined by genetics as well as influences by multiple factors, including physical activity, nutrition, medication use, and endocrine status [9, 10]. With advancing age, and in women with menopause, the rate of bone remodeling increases, and an imbalance occurs leading to changes in skeletal architecture and an increased risk for fracture [9]. Cancellous bone, as is found in the vertebrae, undergoes changes with loss of individual plates of trabecular bone resulting in a weakened structure with diminished bone mass. There is an associated increased fracture risk related to the microarchitecture changes which is compounded by other age associated declines in function including but not limited to visual impairment, increased frailty, sarcopenia, and falls [9]. There are numerous risk factors and conditions (see Table 4.1) associated with an increased risk of osteoporotic fractures, and these can be categorized into areas such as endocrine, gastrointestinal, hematologic, neurologic and rheumatic diseases, as well as lifestyle factors, and medications [9, 11].

Table 4.1 Selected risk factors for osteoporosis and related fractures

Medications	Glucocorticoids Selective serotonin reuptake inhibitors Aromatase inhibitors Hypoglycemic agents: thiazolidinediones Proton pump inhibitors Antiepileptics Anticoagulants: heparin and oral agents Loop diuretics Antiretroviral agents Calcineurin inhibitors Androgen deprivation therapy Depot medroxyprogesterone acetate
Lifestyle	Tobacco use Excessive alcohol use Inadequate exercise Low calcium intake Immobilization Thin body habitus High salt intake
Gastrointestinal disease	Gastric bypass Malabsorption Inflammatory bowel disease Celiac disease
Endocrine disease	Thyrotoxicosis Diabetes mellitus (Type 1 and 2) Hyperparathyroidism Cushing's disease
Hematologic disease	Multiple myeloma Sickle cell disease Leukemia and lymphoma
Hypogonadal states	Anorexia nervosa Athletic amenorrhea Premature menopause (<40 years); Early menopause (<45 years) Panhypopituitarism
Rheumatologic disease	Rheumatoid arthritis Ankylosing spondylitis Systemic lupus erythematosus
Neurologic disease	Epilepsy Multiple sclerosis Parkinson's disease Muscular dystrophy
Genetic disease	Porphyria Hemochromatosis Parental history of hip fracture Osteogenesis imperfecta
Miscellaneous	Sarcoidosis Posttransplant bone disease Weight loss Amyloidosis Hypercalciuria AIDS/HIV

Adapted from Cosman et al. [9] and The Surgeon General's Report [11]

Societal Impact of Osteoporosis and Vertebral Fractures

As the most common bone disease in humans, osteoporosis and its fracture consequences carry a significant economic burden and profoundly affect individual morbidity and mortality. The Surgeon General Report reveals that in the USA, each year, two million fractures are related to osteoporosis leading to 2.5 million medical office outpatient visits, 432,000 hospital admissions, and ~ 180,000 nursing home admissions [11]. It is projected that between the years 2000 and 2025, the US population of 50 years of age and older will increase by 60% (to 121.3 million) [12].

A study designed to predict the US burden of osteoporosis-related fractures and costs yielded interesting results for clinicians, healthcare organizations, and policy makers and demonstrated the importance of interventions to reduce the burdens of this disease [13]. This study estimated, using a validated model, incident fractures and costs by age, race/ethnicity, sex, and skeletal site for the US population ≥50 years of age for 2005 through 2025. In 2005, there were more than two million incident fractures at an economic cost of $17 billion; this amount rose to more than $19 billion if costs of prevalent fractures were included [13]. The study predicted that by 2025, the healthcare burden of fragility fractures in the USA is anticipated to grow by approximately 50% to >three million fractures and equate to $25.3 billion annual in healthcare expenditures [13]. In addition, by race/ethnicity, the model estimated a 2.7-fold increase in fracture costs and incidence for Hispanic and other nonwhite populations [13]. The combined cumulative cost of both incident and prevalent fractures is projected to increase from $215 billion from 2006 to 2015 to $259 billion in the next decade, 2016–2025 [13]. Interestingly, men accounted for 25% of these costs and represented 29% of these fractures, recognizing that osteoporosis is not only a "woman's disease" [13]. The authors note that in 2005, the model predicts total incident fractures by skeletal site were vertebral (27%), wrist (19%), hip (14%), pelvis (7%), and other sites (33%), and that total costs by fracture type were

vertebral (6%), wrist (3%), hip (72%), pelvis (5%), and other sites (14%) [13]. Thus, non-vertebral fractures accounted for 73% of the fractures and 94% of the costs [13]. Although there is a lower proportion of vertebral fractures estimated with lower cost burden, vertebral fractures remain the most common type of fracture, are under-detected, and are predictive of frailty, morbidity, and future fractures, thus vertebral fractures are an important fracture burden with high impact.

Diagnostic Approach

In 2015, the International Society for Clinical Densitometry (ISCD) released its official position for indications for BMD testing as a guide to clinicians, and these are summarized in Table 4.2 [14]. The dual-energy x-ray absorptiometry (DXA) scan provides the gold standard for assessment of bone mineral density (BMD). The DXA scan measures BMD at the lumbar spine, hip, and/or forearm. The World Health Organization (WHO) defines osteoporosis as a T-score at the lumbar spine, forearm, or hip which is less than or equal to −2.5, and this equates to at least 2.5 standard deviations below the mean BMD of a young-adult reference population. Severe osteoporosis is represented by a T-score less than or equal to −2.5 in the presence of an established fragility fracture. Osteopenia or low bone mass is defined by a T-score between −1.0 and −2.5, and normal BMD is a T-score of −1.0 or above (Table 4.3). Although the risk for osteoporosis is highest when there is a lower BMD, the majority of fragility fractures occur in patients with low bone mass/osteopenia rather than in those with T-scores in the osteoporosis range [9, 15].

In addition to the bone density definition of osteoporosis, the presence of a vertebral insufficiency fracture or a hip fragility fracture defines the presence of osteoporosis, and hence increased subsequent fracture risk. Asymptomatic VCFs require proactive imaging to diagnose, as their presence would change a patient's diagnostic bone health classification, affect treatment decisions,

Table 4.2 Indications for testing bone mineral density

1. Women age 65 years and older
2. Men age 70 years and older
3. Adults with a fragility fracture
4. Adults with a condition/disease known to be associated with bone loss or low bone mass
5. Adults taking a medication associated with bone loss or low bone mass
6. Postmenopausal women <65 years old with risk factors for low bone mass such as:
Prior fracture
High risk medication
Low body weight
Disease/condition associated with bone loss
7. Men <70 years old with risk factors for low bone mass such as:
Prior fracture
High risk medication
Low body weight
Disease/condition associated with bone loss
8. Perimenopausal women with clinical risk factors for fracture such as:
Prior fracture
High risk medication
Low body weight
9. Anyone being considered for pharmacologic therapy
10. Anyone being treated to monitor treatment effect
11. Anyone not receiving therapy in whom bone loss would lead to starting treatment
12. Women discontinuing estrogen

Adapted from The International Society for Clinical Densitometry (ISCD) [14]

Table 4.3 WHO definitions based on bone mineral density (BMD)

Classification	BMD	T-Score
Normal	Within 1 SD of the mean level for a young-adult reference population	T-score at −1.0 and above
Low bone mass (osteopenia)	Between 1.0 and 2.5 SD below that of the mean level for a young-adult reference population	T-score between −1.0 and −2.5
Osteoporosis	2.5 SD or more below that of the mean level for a young-adult reference population	T-score ≤ −2.5
Severe or established osteoporosis	2.5 SD or more below that of the mean level for a young-adult reference population with fractures	T-score ≤ −2.5 with one or more fractures

Adapted from Cosman et al. [9]

and impact future fracture risk [9, 16]. Independent of age, BMD, and other clinical risk factors, radiographically established vertebral fragility fractures define poor underlying bone strength and bone quality in addition to predicting increased risk for both subsequent vertebral and non-vertebral fractures [9].

Having a single VCF increases the risk of subsequent fractures fivefold and the risk for hip and other fractures two to threefold [9, 17]. After a vertebral fracture, the risk for subsequent vertebral fractures begins in the first year following the incident fracture. Vertebral imaging can be achieved using traditional diagnostic lateral (thoracic and lumbar) spine radiographs or, alternatively, the vertebral fracture assessment (VFA) software on the DXA scan. The VFA provides a lateral image of the thoracic and lumbar spine as a separate image on the DXA scan report. The ISCD, in its position paper, recommends use of VFA at the time of densitometric spine imaging to assist with the detection of vertebral fractures, acknowledging that VFA was designed to detect vertebral fractures and not other spinal abnormalities [14]. As VCFs are highly prevalent in the elderly and are most often asymptomatic (vide supra), there are recommendations for vertebral imaging (by standard radiography or VFA) listed in Table 4.4 that should be utilized in clinical practice [9, 14].

In an effort to determine the fracture probability in individuals with osteopenia (T-score between −1.0 and −2.4), the fracture risk assessment tool (FRAX®) was developed by the WHO Collaborating Centre for Metabolic Bone Disease at Sheffield, UK, and introduced in 2008 [15, 18]. The FRAX® tool estimates the 10-year probability of a hip fracture and of a major osteoporotic fracture (defined as a hip, forearm, proximal humerus, or vertebral fracture) and includes important clinical risk factors shown in Table 4.5, with or without the femoral neck BMD in the model [15]. The thresholds for treatment vary by country, and in the USA, treatment is recommended if the FRAX score for a 10-year probability of a hip fracture is ≥3% and/or a 10-year probability of a major osteoporosis-related fracture is ≥20% [15].

Table 4.4 Recommendations for vertebral imaging

[a]*Consider vertebral imaging tests for the following groups:*
1. All women 70 years and older and all men 80 years and older if BMD T-score is ≤ −1.0 at the spine, total hip, or femoral neck
2. Women 65–69 years old and men 70–79 years old, if BMD T-score is ≤ −1.5 at the spine, total hip or femoral neck
3. Postmenopausal women and men ≥50 years old with one of the following risk factors:
Historical height loss of 1.5 inches/4 cm or more[b]
Prospective height loss of 0.8 inches/2 cm or more[c]
Low-trauma fracture as an adult (age ≥ 50 years old)
Recent or ongoing long-term glucocorticoid treatment [equivalent to ≥5 mg of prednisone or equivalent per day for ≥3 months

Adapted from Cosman et al. [9] and The International Society for Clinical Densitometry (ISCD) [14]

[a]In the absence of BMD, vertebral imaging may be considered based solely on age

[b]Historical height is defined as current height compared to peak height during young adulthood

[c]Prospective height is defined as height loss measured during serial interval medical assessments

Table 4.5 Clinical risk factors utilized in the FRAX® calculation tool [18]

1. Current age
2. Gender
3. Prior osteoporotic fracture (includes asymptomatic VCFs and clinical fractures)
4. Weight
5. Height
6. Rheumatoid arthritis
7. Current smoking
8. Alcohol intake (3 or more units of alcohol daily)
9. Parental history of hip fracture
10. Use of oral glucocorticoids
Current exposure to oral glucocorticoids or ever exposure to oral glucocorticoids for more than 3 months at a dose of prednisone of 5 mg daily or more (or equivalent doses of other glucocorticoids)
11. Femoral neck BMD
12. Secondary causes of osteoporosis
Type I (insulin dependent) diabetes, chronic malnutrition, osteogenesis imperfecta in adults, hypogonadism or premature menopause (<45 years), untreated long-standing hyperthyroidism, malabsorption, and chronic liver disease)

The FRAX algorithm can be applied using different modalities including newer DXA machines, DXA software upgrades (provide the

FRAX® scores on the bone density report), or can be calculated by the clinician, with the FRAX calculator being found at the National Osteoporosis Foundation website (www.nof.org) or online at www.shef.ac.uk/FRAX. The FRAX tool is specific to a country and takes into account outcomes for fractures and associated morbidity and mortality [9]. This tool has been shown to improve fracture risk assessment compared to BMD alone [9, 19]. It is also important to note the application of FRAX® in the USA is intended for use in specific situations: in postmenopausal women and in men age ≥ 50; it is not meant to be used in patients currently or recently treated (within the last 2 years) with pharmacotherapy for osteoporosis [20]. Application of the BMD (femoral neck BMD) is preferred to use over the reported T-score in calculation [9, 18].

There are limitations to use of the FRAX® tool. Most importantly, the therapeutic thresholds are meant for clinical guidance and are not absolute "guidelines." This leaves treatment decisions to the provider emphasizing the importance of taking into consideration clinical judgment, individual patient factors, other risk factors not captured in FRAX® (such as falls, frailty, lumbar BMD), recent decline in BMD, and other factors that overestimate or underestimate fracture risk [9]. In addition, FRAX® underestimates fracture risk in patients with multiple osteoporotic fractures, those with recent fractures, and those at high risk for falls; it is most useful in those with low femoral neck BMD [9]. The use of FRAX® in patients with normal or low femoral neck BMD and lower lumbar spine BMD will underestimate the risk of fracture, as FRAX® is not validated for incorporation and does not utilize lumbar BMD in its calculation [9].

Risk Factor Modification

Risk factors that affect a person's underlying bone health should be assessed and modified as appropriate.

Regular weight-bearing and muscle strengthening exercise should be recommended to all patients to prevent falls as these can improve strength, posture, agility, and balance [9, 21–24]. Weight-bearing exercise refers to "exercise where the bones and muscles work against gravity as the lower extremities bear the body's weight," and the National Osteoporosis Foundation (NOF) strongly advocates for physical activity at all ages for overall health and osteoporosis prevention and recognizes that when exercise is stopped, its benefits are lost [9]. Examples of weight-bearing exercise recommendations include, but are not limited to, walking, hiking, dancing, stair climbing, tennis, and jogging. Examples of muscle strengthening exercises include, but are not limited to, weight training and resistive exercise such as pilates, use of resistive bands, yoga, and boot camp programs [9]. It is imperative to avoid a "one-size-fits-all" approach and to counsel patients individually about the most appropriate exercise programs to meet their needs based on their comorbidities and abilities.

Many patients with osteoporosis may benefit from physical and/or occupational therapy evaluations to assess balance and fall risk, to assist with walking aids and other assistive devices, and to provide balance and core strengthening programs. These modalities are discussed in more detail in other chapters.

Home environment assessment for fall prevention is an important intervention as more than 50% of falls in community-dwelling older adults occur in or around the home [25, 26]. A home health nursing visit can identify common environmental hazards whose modification may significantly reduce the risk for falling. These include, but are not limited to, improving dim lighting or glare with use of night lights and motion lighting, placement of handrails on the stairs and grab bars in the bathroom near toilets and showers, reviewing obstacles, removing clutter and tripping hazards, and improving slippery or uneven surfaces by placement of bathtub non-skid mats and removal of throw rugs and other non-stick floor coverings [27]. Additional research is needed in the areas of high-risk populations such as people who live in long-term care facilities, as these residents fall more frequently than community-dwelling individuals [28]. The astute clinician should also be aware of the many factors that put patients

at risk for falls including but not limited to medications, poor vision, deconditioning, balance impairment, and environmental risk factors such as clutter and low level lighting and make appropriate modifications if possible [29].

Tobacco and alcohol represent other modifiable risk factors, and targeted counselling in patient encounters is important. The deleterious effects of tobacco on skeletal metabolism via hormonal changes and direct toxicity on bone are well-known, and BMD is lower in current and ever smokers than in never smokers, regardless of gender [30, 31]. The NOF strongly encourages an active smoking cessation program as part of a comprehensive osteoporosis management program [9]. Ethanol has both direct and indirect effects on bone cells. It decreases BMD and bone mass directly in both cortical and trabecular bone mainly via a decrease in bone formation as well as indirectly, through malnutrition leading to weight loss, decreased fat and lean mass, and hormonal alterations that may change bone cell activity [32]. Recommendations from work by Maurel and colleagues include counselling patients with excessive alcohol as defined by greater than two drinks a day for women and three drinks for men. The detrimental effects of alcohol on bone health include increased fall risk; for patients with recurrent falls, inquiry into the possibility of excessive alcohol use should be approached to improve safety [32].

In summary, the following recommendations should be made to the general public in an effort to preserve bone strength, and these include lifelong muscle-strengthening and weight-bearing exercise, tobacco cessation, treatment of excessive alcohol use, fall risk reduction, and sufficient intake of calcium and vitamin D.

Diet, Calcium and Vitamin D Intake

Adequate lifelong calcium intake is vital to attaining peak bone mass and maintaining bone health; a balanced diet rich in fruits, vegetables, and low-fat dairy products is fundamental [9].

Approximately 99% of the body's calcium stores are in the skeleton, and when the exogenous supply is limited, bone resorption occurs to maintain a steady level of serum calcium. Consumption of calcium and vitamin D is a safe and cost-effective way to reduce fracture risk in patients with osteoporosis with controlled trials demonstrating that this combination reduces the risk of fracture [9, 33]. Interestingly, while there are strong data to support the benefit of calcium and vitamin D supplementation in the management of osteoporosis, a meta-analysis performed by Zhao and colleagues revealed no fracture risk reduction with calcium and vitamin D supplementation in community-dwelling adults over the age of 50 years [34]. While of interest, these data should not be extrapolated to a population of patients with known osteoporosis requiring treatment or to a population of elderly subjects in an institution with increased fracture risk.

The NOF and the National Academy of Medicine recommend that men 50–70 years of age consume 1000 mg/day of calcium and that men ≥71 years old and women ≥51 years old consume 1200 mg/day of calcium [9, 35]. There is no evidence that higher doses are advantageous in regard to bone health, and doses above 1200–1500 mg/day may increase the risk for the development of cardiovascular disease, stroke, and renal stones, although this remains an area of debate [9, 36–39]. A study by Xiao et al. found that calcium supplementation of 1500 mg daily or higher was associated with increased cardiovascular risk in men; however this was not found in women, and additionally, lower supplementation doses were not associated with increased cardiovascular disease or strokes in men or women [40]. Sufficient dietary calcium intake is recommended first line, with judicious use of supplements added when adequate dietary consumption cannot be accomplished. Calcium supplementation can be provided with the use of calcium citrate or calcium carbonate and should be taken in divided doses throughout the day. Calcium citrate can be taken with or without food, not requiring an acidic environment, and is thus the supplement of choice in patients using proton pump inhibitors, while calcium carbonate requires food intake for adequate absorption.

Vitamin D also plays an essential role in bone health by enhancing calcium absorption, balance,

and muscle performance and by reducing fall risk. The NOF recommendations are vitamin D 800–1000 IU daily in adults ≥50 years of age [9]. The National Academy of Medicine recommends vitamin D in a dose of 600 IU daily for adults to the age of 70 and 800 IU daily for adults ≥71 years of age [35]. The sun is a good source of vitamin D; dietary sources include salt water fish, liver, fortified milk (400 IU/quart), and some fortified cereals and juices (~40–50 IU/serving) [9]. Those at risk for vitamin D deficiency are patients with limited sun exposure, such as housebound and chronically ill patients, those with malabsorption or other gastrointestinal (GI) diseases (i.e., inflammatory bowel disease, celiac sprue, gastric bypass surgery), patients with renal insufficiency, dark skin pigmented individuals, and the obese [9]. Measurement of serum 25-OH-vitamin D should be undertaken in all patients at risk for deficiency and in those patients with osteopenia/osteoporosis, with supplementation recommended in amounts adequate to bring the serum 25-OH-vitamin D level to greater than 30 ng/ml (75 nmol/L) and a daily dose to maintain this level, especially in patients with osteoporosis [9].

It should be noted that many patients with osteoporosis will need more supplementation than the 800–1000 IU daily, and the National Academy of Medicine recommends the safe upper limit for vitamin D intake for the general adult population as 4000 IU daily [35]. If adults are noted to be vitamin D deficient, treatment with higher daily doses of Vitamin D3 supplementation are recommended, such as 4000–5000 IU daily, for 8–12 to achieve a 25-OH-vitamin D level of 30 ng/ml or higher, followed by a maintenance does of vitamin D3, 1500–2000 IU daily or a dose appropriate to maintain the target blood level [9, 41, 42].

Studies to date looking at high-dose vitamin D to reduce fall risk are inconclusive and warrant further study, with a recent study showing that a high-dose bolus vitamin D supplementation of 100,000 IU of vitamin D3/cholecalciferol monthly over 2.5–4.2 years did not prevent falls or fractures in a healthy, ambulatory, adult population [43]. Another study among older community-dwelling women, a single annual oral dose of 500,000 IU of vitamin D3/cholecalciferol resulted in an increased risk of falls and fractures [44].

Medical Management

When patients suffer from a VCF, treatment goals should be twofold: (1) to provide pain relief and (2) to assess and manage the underlying osteoporosis with appropriate pharmacologic therapies [2].

The acute pain arising from a new VCF usually improves over the course of 6–12 weeks, and throughout this interval, analgesics should be prescribed to decrease pain and to encourage movement [2, 45]. First-line analgesics should include acetaminophen or salicylates and nonsteroidal anti-inflammatory drugs (NSAIDs) [46]. Salicylates and NSAIDs should be used with caution in elderly patients with comorbidities due to the risk of gastric and/or renal adverse effects. Patients who fail initial management with these agents could be considered for opioid therapy; however these have considerable side effects especially in the elderly population, such as reduced GI motility and respiratory drive, urinary retention, and cognitive depressive effects. Opiate use in the elderly can lead to loss of balance and increased fall risk [47]. Short-term use of muscle relaxants for the first 1–2 weeks after vertebral fracture may be helpful to alleviate paravertebral muscle spasm associated with a VCF although side effects such as dizziness and drowsiness are potential concerns [2, 48]. In addition, the use of calcitonin agents for patients with acute pain from recent osteoporotic vertebral fractures is supported as an effective analgesic based on several randomized double-blind placebo-controlled trials, likely relating to an endorphin effect from this agent [2, 49].

Use of bracing remains largely opinion-based but can play a conservative role in many patients with VCFs. The main role of bracing in the management of osteoporosis-related VCFs is to prevent pain from movement by stabilizing the spine, and in addition, it leads to less back fatigue

and allows for decreased bed rest with early mobilization following an acute fracture [2, 50, 51]. Ideally, if warranted based on the patient's clinical status, braces should be easy to put on, comfortable and lightweight, and prevent abdominal compression and respiratory effects [2]. Long-term use of back bracing may lead to core muscle weakness and further deconditioning [9]. Specific types of braces (corset, back brace, posture training support devices, etc.) used for VCFs will be covered in other chapters within this textbook.

After a short period of bed rest, patients should begin an early mobilization process with rehabilitation exercises with the goals of fall prevention, reduction of the development of kyphosis, corrective spinal alignment, and axial muscle strengthening [2]. It has been shown that spinal extensor strengthening and dynamic proprioceptive programs result in increased bone density and reduce the risk of VCFs [52–54]. Back extensor exercises improve spinal strength leading to reduction in kyphotic deformity and better dynamic-static posturing; the correction in kyphosis increases mobility, improves pain, and improves quality of life [55]. Physical therapy including core strengthening exercises as well as balance, gait analysis, fall risk evaluation, and spine protective practices (such as how to avoid leaning over to perform activities) have an important role in the medical management of these patients leading to pain relief and improvement in physical function [56].

Patients with painful, recent VCFs that fail the aforementioned conservative therapy may be candidates for intervention with kyphoplasty or vertebroplasty. Considerations for use of these procedures will be discussed in a different chapter in this textbook.

Pharmacologic Management

The following patients, postmenopausal women and men ≥50 years old, should be considered for pharmacologic treatment with a (1) history of hip or vertebral fracture (clinically or morphometric VCF); (2) T-score ≤ −2.5 at the total hip, femoral neck, or lumbar spine (or 1/3 radius if hip or spine BMD is unavailable or unreliable due to instrumentation or spinal deformity); and (3) low bone mass (T-score between −1.0 and −2.5 at the femoral neck or lumbar spine) and increased calculated FRAX® risk [9].

All patients who have had a vertebral insufficiency fracture should be counselled on risk factor reduction, the importance of calcium and vitamin D intake, fall prevention, and exercise as part of a comprehensive treatment strategy. Prior to starting pharmacologic treatment, an individual's risk factors and comorbidities should be addressed, and, as appropriate, patients should undergo a metabolic evaluation for secondary causes of bone loss. Although not requisite to determine the need for osteoporosis treatment, a patient with a VCF should undergo BMD measurement via DXA scanning to determine baseline BMD which can be used for assessing treatment response.

The available FDA-approved drugs for the prevention and treatment of postmenopausal osteoporosis include antiresorptive agents such as bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid), estrogens (estrogen and other hormonal therapy), estrogen agonist/antagonist (raloxifene), the receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL) inhibitor (denosumab), and anabolic agents such as parathyroid hormone (PTH), teriparatide, and abaloparatide [1–34]. These agents are summarized in Table 4.6 [9]. Calcitonin does not reduce the risk of fractures but may assist with pain associated with vertebral fracture, and thus it may be utilized accordingly. The FDA-approved treatments have been shown to decrease fracture risk in patients with osteoporosis including those with and without prior fragility fractures [9]. The NOF does not endorse the use of non-FDA-approved therapies to prevent or treat osteoporosis such as calcitriol, sodium fluoride, tibolone, strontium ranelate, and genistein, among others [9]. Genistein is an isoflavone phytoestrogen which is a main ingredient in a prescription "medical food" product Fosteum® and

Table 4.6 Selected FDA-approved treatment for the prevention and treatment of osteoporosis

Agent	Mechanism of action	Dosage
Oral bisphosphonates 1. Alendronate/ Fosamax® 2. Risedronate/ Actonel® 3. Ibandronate/ Boniva®	Antiresorptive Inhibitor of osteoclast-mediated bone resorption	1. Prevention 5 mg daily/35 mg weekly 1. Treatment 10 mg daily/70 mg weekly 2. Prevention and treatment 5 mg daily/35 mg weekly 150 mg monthly 3. Treatment 150 mg monthly
IV bisphosphonate 1. Ibandronate/ Boniva® 2. Zoledronic acid/ Reclast®	Antiresorptive Inhibitor of osteoclast-mediated bone resorption	1. Treatment 3 mg IV every 3 months 2. Prevention 5 mg every 2 years 2. Treatment 5 mg yearly
RANKL/RANKL inhibitor Denosumab/ Prolia®	Antiresorptive Prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption	60 mg SQ every 6 months
SERM Raloxifene/ Evista®	Acts as an estrogen agonist in bone. Decreases bone resorption and bone turnover	Prevention and treatment 60 mg oral daily
PTH (1–34) 1. Teriparatide/ Forteo® 2. Abaloparatide/ Tymlos®	Anabolic Stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity	Treatment 1. 20 mcg SQ daily 2. 80 mcg SQ daily

IV intravenous, *SQ* subcutaneous

may benefit bone health in postmenopausal women; however more data from well-designed randomized-controlled trials are needed to fully understand its effects on bone health and fracture risk [9, 57]. Although there are strong data on the benefits of pharmacologic therapy for patients with osteoporosis with or without prior fractures, the evidence for overall anti-fracture benefit in patients with osteopenia who are not at high risk for fracture is not as compelling [9]. Use of the FRAX tool has helped to identify those patients with osteopenia who are at predictably high risk for fracture who may benefit from treatment; however there are limited data confirming fracture risk reduction with pharmacologic therapy in this group of patients [9]. Each provider must review with each patient the risks and benefits of osteoporosis pharmacotherapies to optimize management and compliance with the goal of risk reduction for vertebral and non-vertebral fractures [9].

Oral Bisphosphonates

Alendronate sodium (Fosamax®, Fosamax Plus D, Binosto™ and generic alendronate), risedronate sodium (Actonel®, Atelvia™), and zoledronic acid (Reclast®) are FDA approved to prevent and treat osteoporosis in postmenopausal women, to increase bone mass in men with osteoporosis, and for the treatment of glucocorticoid-induced osteoporosis (GIOP) in women and men [9, 58–63]. Alendronate, an oral medication, reduces the incidence of hip and vertebral fractures by about 50% over 3 years in patients with osteoporosis as defined by T-score or a prior vertebral fracture and reduces the incidence of vertebral fractures by 50% over 3 years in patients without a previous vertebral fracture [9, 59, 64, 65]. Risedronate sodium (Actonel®, Atelvia™), an oral medication, has been shown to reduce the incidence of non-vertebral fractures by 36% and vertebral fractures by 41–49% over 3 years with significantly

reduced risk within 1 year of treatment in patients with a history of a prior vertebral fracture [60, 66]. Ibandronate sodium (Boniva®) is FDA approved for the prevention and treatment of postmenopausal osteoporosis [9]. This medication was shown to reduce the incidence of vertebral fractures by ~ 50% at 3 years, but risk reduction of non-vertebral fractures was not specifically addressed prior to FDA approval of ibandronate [9, 67].

Zoledronic acid (Reclast®), an annual infusion medication, is also indicated for the prevention of new clinical fractures in women and men with a history of a recent hip fragility fracture [9, 68]. This medication reduces the incidence of vertebral fractures by 70% (with significant reduction at 1 year), non-vertebral fractures by 25%, and hip fractures by 41% over 3 years in patients with osteoporosis (defined by BMD in osteoporotic range at the hip and prevalent vertebral fractures) [9, 62]. When receiving zoledronic acid, patients should remain adequately hydrated and may receive premedication with acetaminophen to decrease the risk for an "acute phase reaction" or "flu-like syndrome" (fever, headache, arthralgia, myalgia) which has been reported in up to 32% of patients after the first dose, 7% after the second dose, and 3% after the third dose [9].

All bisphosphonates require adequate renal function prior to administration and have not been studied in patients with an estimated GFR <35 mL/min; zoledronic acid is not advised in patients with GFR <35 mL/min or evidence of acute renal insufficiency. Renal function should be assessed prior to administration of zoledronic acid [9, 69].

Two rare but noteworthy complications that have been reported with bisphosphonate use are osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF).

ONJ is a condition in which there is decreased metabolic support to the bony tissue of the mandible and maxilla resulting in bone necrosis and poor healing. ONJ can occur spontaneously or more commonly occurs after invasive dental work such as tooth extractions or dental implants, and thus all patients should be encouraged to have all dental procedures completed prior to starting therapy, as instrumentation appears to heighten the risk for this condition. The FDA has voiced precautions regarding the occurrence of ONJ seen in patients on bisphosphonates, with risks for developing ONJ higher in patients taking the drug intravenously and related to an underlying malignancy [9, 70]. AFF are rare, low trauma fractures that may be associated with long-term (>5 years) use of bisphosphonates and may be preceded by a prodrome of anterior thigh or groin pain which may be unilateral or bilateral [9, 71]. In the presence of a new AFF, bilateral femur x-rays should be obtained. If clinical suspicion remains high even in the presence of negative contralateral plain films, then MRI or radionuclide bone scan should be considered [9, 71]. The risk of atypical femoral fracture, but not osteonecrosis of the jaw, clearly increases with bisphosphonate therapy duration; however the risk of these rare events is outweighed by vertebral fracture risk reduction in high-risk patients [72]. Discontinuation of antiresorptive agents is imperative with the occurrence of ONJ or an AFF.

Rank Ligand Inhibition

Denosumab (Prolia®) is FDA approved for the treatment of osteoporosis in postmenopausal women at high risk for fracture, to increase bone mass in men with osteoporosis, to treat bone loss in women with breast cancer on aromatase inhibitors and men receiving gonadotropin-reducing hormone treatment for prostate cancer who are at high risk for fracture [9]. It is a monoclonal antibody that potently blocks the binding of receptor activator of nuclear factor kappa-B ligand (RANKL) to its osteoclast-derived receptor (RANK), thereby inhibiting osteoclast-mediated bone resorption [73]. It reduces, over 3 years, the incidence of vertebral fractures by~ 68%, non-vertebral fractures by ~ 20%, and hip fractures by ~40% [9, 74]. Denosumab can lead to hypocalcemia and has also rarely been associated with ONJ and AFF. Once treatment with this agent is stopped, bone loss may be rapid, and alternative agents should be considered to maintain BMD.

In addition, recent data suggest discontinuing denosumab may increase the risk of multiple vertebral fractures due to a rebound increase in bone resorption, thus clinicians and patients must be aware of this potential risk [9, 75].

Estrogen Agonist/Antagonist (Formerly Known as SERMs)

Raloxifene (Evista®) is FDA approved for the prevention and treatment of osteoporosis in postmenopausal women. It has been shown to reduce the risk of vertebral fractures by ~ 30% in patients with prior vertebral fracture and by ~ 55% in patients without a prior vertebral fracture over 3 years, though it does not have a demonstrated benefit for non-vertebral fracture risk reduction [76].

Anabolic Agents

Parathyroid hormone (PTH 1–34) teriparatide (Forteo®) is FDA approved for the treatment of postmenopausal women and men at high risk for fracture, and in those with osteoporosis associated with sustained use of systemic glucocorticoid therapy [9, 77]. A similar agent abaloparatide (Tymlos®) (PTH 1–34) is similarly FDA approved for the treatment of postmenopausal women with osteoporosis at high risk for fracture [78]. Teriparatide reduces the risk of vertebral fractures by ~ 65% and non-vertebral fragility fractures by ~ 53% after an average of 18 months of treatment [79]. Abaloparatide (Tymlos) compared with placebo also reduces the risk of new vertebral and non-vertebral fractures and results in higher BMD gains over 18 months [78]. These agents carry a black box warning of osteosarcoma risk, although there has not been an observed increased occurrence in humans clinically. Patients at high risk for osteosarcoma at baseline should not receive these agents such as those with Paget's disease of bone, unexplained increase in alkaline phosphatase, hypercalcemia, history of skeletal malignancy, history of bony metastases, or a history of prior skeletal radiation [9]. Other potential adverse effects from these agents are: leg cramps, dizziness, and orthostatic hypotension. Following treatment with an anabolic agent, an antiresorptive agent should be started to maintain skeletal benefits [9].

Another agent being studied for treatment of osteoporosis is romosozumab, a potent humanized monoclonal antibody that binds to sclerostin, an inhibitor of the Wnt signaling pathway, a major pathway in skeletal development, bone remodeling and adult skeletal homeostasis [80]. Romosozumab is a potent anabolic agent which activates the Wnt signaling pathway and leads to bone formation and an increase in BMD. In the Phase III placebo-controlled FRActure study in postmenopausal woMen with ostEoporosis (FRAME) trial comparing romosozumab to placebo, vertebral fractures were reduced by 73% after 1 year of treatment [80, 81] . Treatment with romosozumab for 1 year, followed by denosumab in the second year, reduced vertebral fractures by 75% compared to the group receiving placebo for 1 year followed by denosumab for 1 year [80, 81].

Treatment for osteoporosis should not be considered indefinite in duration with the realization that all non-bisphosphonate therapies produce temporary effects that fade with stopping the medication, and when these therapies are stopped, the benefits gained will quickly disperse [9]. Bisphosphonates often allow for residual effects even after their discontinuation, and thus it is possible to stop bisphosphonate therapy and retain lingering benefits against fracture for years [9]. Treatment duration must be tailored to individual patients, and after 3–5 years of therapy, a risk assessment should be conducted with assessment of clinical fracture history, BMD testing, new medications and medical illnesses, height loss, and consideration of vertebral imaging [9]. As evidence of efficacy beyond 5 years of treatment is limited, it is reasonable to stop bisphosphonates after 3–5 years in patients with modest risk after the initial treatment timeframe; however in those at high risk for fracture, continued treatment should be considered [9, 82, 83].

The appropriate duration of therapy to treat osteoporosis with medications remains an area of

uncertainty and several studies have attempted to clarify this. The Fracture Intervention Trial Long-term Extension (FLEX) evaluated the effects of stopping alendronate/Fosamax® therapy after 5 years versus continuing therapy for 10 years [84]. In this trial, 1099 postmenopausal women who had been randomized to alendronate in FIT (Fracture Intervention Trial), with a mean of 5 years of prior alendronate treatment, were randomized to one of two doses of alendronate or placebo for 5 years [84]. After 5 years, the cumulative risk of non-vertebral fractures (RR, 1.00; 95% CI, 0.76–1.32) was not significantly different between those continuing on (19%) and stopping (18.9%) alendronate. Among those who remained on drug for 10 years, there was a significantly lower risk of clinically recognized vertebral fractures (5.3% for placebo and 2.4% for alendronate; RR, 0.45; 95% CI, 0.24–0.85) but no significant reduction in morphometric vertebral fractures (11.3% for placebo and 9.8% for alendronate; RR, 0.86; 95% CI, 0.60–1.22) [84]. The study concluded that for many postmenopausal women, discontinuation of alendronate after 5 years of therapy does not appear to significantly increase fracture risk but that women at very high risk of vertebral fractures may benefit by remaining on therapy for a total course of 10 years [84]. Based on these data, many authorities recommend therapy with oral bisphosphonates for 5 years followed by consideration for a "drug holiday" while continuing to monitor the patient clinically with DXA scan, assessment of clinical and morphometric fractures, and risk factor assessment.

Another trial, a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT), looked at the effect of 3 years versus 6 years of zoledronic acid treatment for osteoporosis [85]. To investigate the long-term effects of zoledronic acid on BMD and fracture risk, in this extension trial, 1233 postmenopausal women who received zoledronic acid for 3 years in the core study were randomized to 3 additional years of zoledronic acid (Z6, n = 616) versus placebo (Z3P3, n = 617) [85]. They found that new morphometric vertebral fractures were lower in those patients who received 6 years of zoledronic acid compared to those patients receiving zoledronic acid for 3 years followed by placebo infusions for 3 years (odds ratio = 0.51; p = 0.035), but other fractures were not noted to be different [85]. Small differences in bone density and bone turnover markers in those who continued versus those who stopped zoledronic acid suggest residual effects, and it was concluded that after 3 years of annual zoledronic acid infusions, many patients can discontinue therapy for up to 3 years [85]. However, vertebral fracture reductions in this trial suggested that those at high risk of fracture and particularly vertebral fractures may benefit from continued treatment for more than 3 years [85].

Summary

Despite available treatments, many patients are not being given the tools for prevention of osteoporosis and related fractures, and many are not undergoing the testing to diagnose or establish their underlying bone health risk. In addition, many patients who have suffered osteoporotic-related fractures are not receiving any of the very effective FDA-approved pharmacologic therapies for the treatment of osteoporosis [9].

Many of the same principles related to primary prevention, risk assessment, and screening should be implemented once a fracture has occurred to help avoid further fractures.

Primary prevention of osteoporosis includes risk assessment, BMD testing, and pharmacotherapy if indicated. These same principles in patient management apply to those patients who have sustained a fragility fracture (secondary prevention). Many patients who have sustained a fragility fracture do not receive treatment and thus remain at very high risk for subsequent fracture, increased morbidity and mortality. The medical management of osteoporotic fractures is well-supported by data demonstrating medication efficacy. Treatment regimens should be individualized for patient needs including medication selection and duration of therapy. Risk factor assessment, including fall risk, remains an essential part of the management plan.

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