Chapter 1
Osteoporosis

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Case Presentation and Discussion

A 58-year-old woman has a screening bone density test with dual-energy X-ray absorptiometry (DXA) that shows a T-score of −2.9 at the left femoral neck. She is generally healthy except for episodic diarrhea and constipation, which has been attributed to irritable bowel syndrome and treated with a high-fiber diet. She has a family history osteoporosis (mother with hip fracture at age 82 years). She has no known fracture and has never received pharmacological therapy to reduce fracture risk. A diagnosis of osteoporosis is made, and she is started on treatment with a generic oral bisphosphonate. Eighteen months later she has a repeat bone density test at the same facility using the same instrument. She is reported to have a decrease in bone mineral density (BMD) compared with the baseline study. Detailed discussion suggests she is taking medication regularly and correctly with no recognizable adverse effects. What should be done now?

Before starting treatment for osteoporosis, every patient should have a laboratory evaluation for factors contributing to skeletal fragility, to guide the management plan, and assure the safety of proceeding with treatment. As examples, a finding of severe chronic kidney disease would lead to avoidance of bisphosphonates for treatment, and a finding of a monoclonal antibody might necessitate referral to an oncologist. In this patient, a thorough baseline evaluation was not done. Laboratory studies now revealed several abnormalities of importance. A 24-h urine collection showed low calcium of 35 mg while having an adequate calcium intake and normal renal function. Subsequently testing show high levels of celiac antibodies. A diagnosis of celiac disease was confirmed by small bowel biopsy. She was placed on a gluten-free diet and maintained on the same oral bisphosphonate. A follow-up bone density test 1 year later showed substantial improvement in BMD consistent with a beneficial effect of therapy.

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Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone strength leading to an increased risk of fracture. Bone strength is determined by BMD and other skeletal properties that include bone architecture, remodeling, mineralization, and damage accumulation. A 2004 report of the US Surgeon General on bone health in America identified osteoporosis as a major public health problem that affected about 10 million Americans over the age of 50 years [1]. Worldwide, about 200 million individuals are afflicted with osteoporosis, with 1 in 3 women and 1 in 5 men over the age of 50 years expected to experience an osteoporotic fracture in their remaining lifetimes [2]. The consequences of osteoporotic fractures are serious, including disability, loss of independence, and death. After a hip fracture, 40% of patients cannot walk independently, and 10–20% require permanent nursing home care [2]. The economic burden is high, with healthcare costs of about €37 billion per year in the EU and $19 billion USD per year in the USA [2].

Excellent clinical tools are now available to diagnose osteoporosis and assess fracture risk. A wide range of pharmacological agents have been tested and approved for treatment of to reduce fracture risk. Clinical practice guidelines to assist clinicians in managing osteoporosis patients have been developed. And yet, osteoporosis remains a disease that is underdiagnosed and undertreated. The osteoporosis treatment gap, the difference between those who could benefit from treatment but do not receive it, has reached crisis proportions [3]. This is an update of our current understanding of osteoporosis, opportunities to reduce fracture risk, and challenges in managing patients with this disease.

Diagnosis

BMD is classified as osteoporosis, osteopenia (low bone mass), or normal according to criteria established by the World Health Organization (WHO) [4] and refined for use in clinical practice by the International Society for Clinical Densitometry (ISCD) [5]. A DXA T-score of −2.5 or below (i.e., BMD at least 2.5 standard deviations (SD) less than the mean BMD of a young-adult reference population) is consistent with a diagnosis of osteoporosis (Table 1.1). However, the finding of a T-score ≤ -2.5 can also be due to other disorders, such as osteomalacia. It is the responsibility of the clinician to evaluate the patient for all factors that might be responsible for the low T-score and address those that are relevant. Recent guidance from the ISCD states that femoral neck and total hip T-scores calculated from two-dimensional (2-D) projections of quantitative computed tomography (QCT) data are equivalent to the corresponding DXA T-scores for diagnosis of osteoporosis using the WHO criteria [5].

A diagnosis of osteoporosis may also be made in the presence of a fragility fracture, independently of BMD. The US National Bone Health Alliance (NBHA) has

Table 1.1 The World Health Organization classification of bone mineral density measured by dual-energy X-ray absorptiometry [4]

Classification	T-score
Normal	−1.0 and above
Osteopenia (low bone mass)	Between −1.0 and −2.5
Osteoporosis	−2.5 and below
Severe osteoporosis	−2.5 and below and fragility fracture

Table 1.2 Criteria for the diagnosis of osteoporosis from NBHA and AACE/ACE [6, 7]

Method of diagnosis	Criteria	Applicability
Bone density	T-score ≤−2.5 at lumbar spine, total hip, femoral neck, or 33% radius	Worldwide
Fracture	Low trauma hip fracture regardless of BMD; low trauma vertebral, proximal humerus, pelvis, or some distal forearm fractures with T-score between −1.0 and −2.5	USA
Fracture risk	FRAX 10-year probability of major osteoporotic fracture ≥20% or hip fracture ≥3% (corresponds to thresholds for treatment with the guidelines of the National Osteoporosis Foundation)	USA

identified types of fractures leading to a diagnosis of osteoporosis and also recommended that a high fracture probability by the WHO fracture risk algorithm (FRAX) is sufficient for a diagnosis of osteoporosis [6]. Table 1.2 summarizes the recommendations of the NBHA for a clinical diagnosis of osteoporosis, which are supported by the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) and other professional societies.

BMD Measurement

DXA measurements of BMD are used to diagnose osteoporosis, monitor changes in BMD, and estimate fracture risk. DXA utilizes ionizing radiation with photon beams of two different energy levels, resulting in a 2-D projection of the bone and soft tissue that is visualized on a computer monitor. The difference in attenuation of the photon beams passing through body tissues with variable composition provides a quantitative measurement of areal BMD in grams per square centimeter (g/cm^2). A "central" DXA system consists of a table supporting the patient, a radiation source below the table, a radiation detector above the table, and a computer to acquire and analyze the data (Fig. 1.1). DXA is the standard technology for measuring BMD in clinical practice because of BMD by DXA is strongly correlated with bone strength in biomechanical studies, epidemiological studies show a strong relationship with fracture risk, WHO classification of BMD is based primarily on

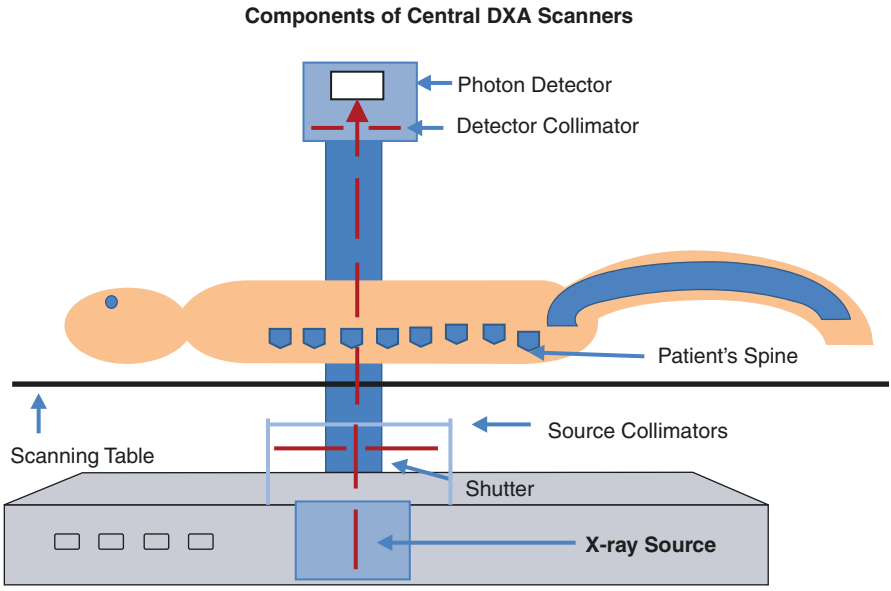

Fig. 1.1 Components of central DXA scanners. (Image courtesy of S. Bobo Tanner, MD. Used with permission)

reference data obtained by DXA, and enrollment of subjects in registration clinical trials is based entirely or partly on DXA measurements. In addition, precision and accuracy of DXA is excellent and the radiation dose is low. DXA measurements have non-BMD applications, including vertebral fracture assessment (VFA), analysis of body composition, hip structural analysis (HSA), and trabecular bone score (TBS) determination. Quantitative ultrasound (QUS) can be used to measure properties of bone that correlate well with fracture risk, although QUS cannot be used to diagnose osteoporosis and parameters measured by QUS respond poorly and/or slowly to treatment [8].

The clinical utility of BMD testing is highly dependent on the quality of the measurement, especially for serial BMD measurements with quantitative comparisons. When BMD measurements are correct and interpretation is consistent with well-established standards, clinicians are best equipped to make proper clinical decision. Poor quality acquisition, analysis, or interpretation of DXA data can mislead healthcare providers. This may be followed by unnecessary tests, failure to do needed tests, inappropriate treatment, or failure to treat. Best use of limited healthcare resources and appropriate patient management is optimized when DXA facilities follow recommended procedures for instrument calibration, acquisition, analysis, interpretation, and reporting of results. For these reasons, the ISCD has developed Official Positions [5] and DXA best practices [9]. Strict adherence to these standards assures referring clinicians that the DXA results are a reliable source of information to aid in making treatment decisions. Indications for BMD testing from the US National Osteoporosis Foundation (NOF) are provided in Table 1.3.

Table 1.3 Indications for bone density testing from the US National Osteoporosis Foundation [10]

Women age 65 and older and men age 70 and older
Postmenopausal women and men above age 50–69, based on risk factor profile
Postmenopausal women and men age 50 and older who have had an adult age fracture, to diagnose and determine degree of osteoporosis

Fracture Risk Assessment

Measurement of BMD is a powerful tool for estimating fracture risk. The lower the BMD, the greater is the risk of fracture. For every SD decrease in BMD at the hip measured by DXA, there is about a 2.6-fold increase in hip fracture risk and a 1.6-fold increase in the risk of any fracture [11]. However, BMD combined with clinical risk factors (CRFs) predicts fracture risk better than BMD or CRFs alone [12]. FRAX is a computer-based algorithm that estimates 10-year fracture probability in untreated men and women from age 40 to 90 years by combining CRFs and femoral neck BMD, when available. CRFs included in the FRAX algorithm are previous fracture, parent with hip fracture, current smoking, glucocorticoid therapy, rheumatoid arthritis, secondary osteoporosis, and alcohol intake of three or more units per day. A "yes" or "no" response is allowed for each of these CRFs, not allowing for gradation of risk according to dose, severity, or duration of the risk. Secondary osteoporosis is a "dummy" risk factor that does not change the risk estimation unless femoral neck BMD is not entered. A FRAX calculator is included in current DXA software, available online at http://www.shef.uk/FRAX, and can be purchased for use with handheld electronic devices. FRAX provides a quantitative estimate of the 10-year probability of major osteoporotic fracture (clinical spine, forearm, hip, shoulder fracture) and the 10-year probability of hip fracture. When BMD is not available, FRAX can be used without BMD, and in some countries, it is used to determine which patients qualify for DXA. Since many or most patients with a hip fracture do not have T-scores in the osteoporosis range [13], the use of T-scores alone will lead to missed opportunities for interventions to reduce fracture risk.

Evaluation

Osteoporosis is often classified as primary (i.e., due to postmenopausal estrogen deficiency or aging in women and men), secondary (i.e., due to factors such nutritional deficiencies and medications with harmful skeletal effects), or idiopathic (osteoporosis in children or young adults without identifiable cause). A patient may have both primary and secondary osteoporosis. It is essential for all patients at risk for fracture to be evaluated for secondary osteoporosis prior to starting treatment. Previously unrecognized causes of osteoporosis are common. The prevalence of

Table 1.4 Laboratory tests to consider in the evaluation for secondary causes of osteoporosis

For all patients
Complete blood count (CBC)
Chemistry levels (including calcium, phosphorus, renal function, liver function, alkaline phosphatase)
25-OH-vitamin D
24-h urine for calcium
For selected patients
Thyroid test for patients on thyroid medication or with symptoms or signs of thyroid disease
Parathyroid hormone (PTH) when abnormalities are suspected
Total testosterone and gonadotropin in younger men
Bone turnover markers
Serum protein electrophoresis (SPEP) or serum immunofixation electrophoresis
Serum kappa/lambda free light chains
Celiac antibodies
Homocysteine
Prolactin
Tryptase
Urinary free cortisol level
Urinary histamine

Adapted from Cosman et al. [10]

secondary osteoporosis also varies according to the extent of evaluation and the cutoffs for distinguishing normal from abnormal. Evaluation of a patient with osteoporosis includes a thorough bone-related medical history, physical exam with accurate height measurement and falls assessment, laboratory tests (Table 1.4), and sometimes imaging studies [14]. The benefits of such an evaluation include the identification of previously unrecognized conditions affecting skeletal health that may require different or additional therapy and assessment of factors that could influence treatment decisions. The case presented at the opening of this chapter is an example of a disease (celiac disease) that requires additional treatment with a gluten-free diet. A history of esophageal stricture should lead to avoidance of oral bisphosphonates, and a history of a clotting disorder suggests that raloxifene and estrogen should not be prescribed. Historical loss of height (height measured with a wall-mounted stadiometer >1.5 in. less than historical maximum height) suggests possible vertebral fracture and usually warrants spine imaging for further evaluation.

The finding of a previously unrecognized vertebral fracture could lead to a change in diagnostic classification, enhance fracture risk stratification, and possibly lead to a change in treatment decisions [15]. The ISCD has developed recommendations for vertebral imaging with VFA by DXA or conventional radiography (Table 1.5). VFA is lateral spine imaging by DXA that offers an opportunity for point-of-service care done at the same visit as for BMD testing by DXA, with lower cost and less radiation than spine X-rays. Image resolution is not as good as with X-ray, but some vertebral fractures are more easily identified due to less parallax effect.

Table 1.5 Indications for spine imaging to identify vertebral fractures from the International Society for Clinical Densitometry [5]

Lateral spine imaging with standard radiography or densitometric VFA is indicated when T-score is <−1.0 and one or more of the following is present:
Women age ≥70 years or men ≥ age 80 years,
Historical height loss >4 cm (>1.5 in.),
Self-reported but undocumented prior vertebral fracture,
Glucocorticoid therapy equivalent to ≥5 mg of prednisone or equivalent per day for ≥3 months

Table 1.6 Indications (US-specific) for pharmacological therapy to reduce fracture risk from the US National Osteoporosis Foundation [10]

Treatment recommendation may vary by country depending on healthcare priorities, cost, and availability of healthcare resources
In those with hip or vertebral (clinical or asymptomatic) fractures
In those with T-scores ≤−2.5 at the femoral neck, total hip, or lumbar spine by DXA
In postmenopausal women and men age 50 and older with low bone mass (T-score between −1.0 and −2.5) at the femoral neck, total hip, or lumbar spine by DXA and a 10-year hip fracture probability ≥3% or a 10-year major osteoporosis-related fracture probability ≥20% based on the USA-adapted WHO absolute fracture risk model (FRAX)

Treatment

Advances in understanding the pathophysiology of osteoporosis have led to the development of a broad range of medications (e.g., bisphosphonates [alendronate, risedronate, ibandronate, zoledronic acid], raloxifene, denosumab, salmon calcitonin, teriparatide and abaloparatide) that strengthen bone and reduce fracture risk [16]. The cost of some of these, especially the oral bisphosphonates, is very low. Clinical trials have shown that the balance of benefits and risks is highly favorable in appropriately selected patients. Abaloparatide [17], a synthetic analog of parathyroid hormone related peptide (PTHrP[1–34]) with skeletal anabolic effects, received regulatory approval in 2017 for the treatment of postmenopausal women with osteoporosis at high risk of fracture. Romosozumab [18] is a humanized monoclonal protein that blocks the action of sclerostin, a naturally occurring inhibitor of osteoblastic bone formation. Phase 3 clinical trials with romosozumab have been completed. It appears to be a promising agent for the treatment of women with postmenopausal osteoporosis, but it has not received regulatory approval at the time of this writing.

Table 1.6 shows indications for pharmacological therapy in the USA. Treatment decisions must be individualized considering all available clinical information, including patient preference. AACE/ACE has recommendations for choosing initial medication (Table 1.7). After any treatment is started, patients should be monitored to assess tolerance and adherence to therapy. Patients who are suboptimal respond-

Table 1.7 Recommendations for initial treatment of osteoporosis from AACE/ACE [7]

Approved agents with efficacy to reduce hip, nonvertebral, and spine fractures including alendronate, risedronate, zoledronic acid, and denosumab are appropriate as initial therapy for most patients at high risk of fracture
Teriparatide, denosumab, or zoledronic acid should be considered for patients unable to use oral therapy and as initial therapy for patients at especially high fracture risk
Raloxifene or ibandronate may be appropriate initial therapy in some cases where patients requiring drugs with spine-specific efficacy

ers to therapy, by virtue of having a decline in BMD, failure of bone turnover markers to respond as expected, or multiple fractures on therapy, should be reevaluated to identify contributing factors. Suboptimal response to therapy could be due to circumstances such as poor absorption of an oral bisphosphonate, even when taken regularly and correctly, or development of a new disease or condition, such as multiple myeloma or vitamin D deficiency.

Osteoporosis Treatment Gap

Despite the availability of medications to reduce fracture risk, most patients who could benefit from these medications are not taking them [19]. Of those who are prescribed a medication, some do not fill the prescription, do not take medication regularly or correctly (proper administration is especially important with oral bisphosphonates), or do not take it long enough to achieve the desired reduction of fracture risk [20]. The net result is a large osteoporosis treatment gap, resulting in a high personal and economic burden from fractures that might have been prevented by treatment. Many factors contribute to the osteoporosis treatment gap. For some, it is the misperception that osteoporosis is a normal part of aging and not a treatable disease. Others may believe that osteoporosis only affects women. BMD testing is not universally available or affordable. Clinical practice guidelines for osteoporosis treatment are sometimes confusing or conflicting. Physicians and their patients sometimes have a poor understanding of the balance of benefits and risks with osteoporosis treatment. There is often limited time during encounters with patients to address osteoporosis issues. Patients who have had a fracture may not appreciate the high risk of future fractures. There are few osteoporosis specialists with advanced levels of expertise in managing patients with osteoporosis.

Many patients are afraid to take drugs that might help them. Fear of osteoporosis drugs was assessed in a recent study conducted by the NOF with their "online community" of about 28,000 individuals, with 853 (3%) responding [21]. Thirty-eight percent of responders had been prescribed a medication they did not take, with 79% of these stating that fear of side effects was the reason for not taking it. Forty-three percent felt that the risk of side effects with osteoporosis treatment was greater than the benefit. The findings of the NOF survey are consistent with the clinical experience that many patients who might benefit from an osteoporosis medication are afraid to take it.

The osteoporosis treatment gap appears to be worsening, with concern that more hip fractures than expected have been occurring in the USA in recent years [22]. The gap has been termed as crisis by the American Society for Bone and Mineral Research (ASBMR) [3], with a call to action to find ways to reduce the treatment gap.

New Concepts in Osteoporosis Care

How Long to Treat Long-term bisphosphonate therapy has been associated with rare adverse effects such as osteonecrosis of the jaw [23] and atypical femur fractures [24]. Discontinuing treatment appears to reduce the risk of these very unlikely events. Since bisphosphonates have a long skeletal retention time with persistence of antiresorptive effects and perhaps anti-fracture effects when long-term therapy is stopped, the concept of a bisphosphonate "holiday" has emerged. The rationale is that for patients no longer at high risk of fracture who have taken a bisphosphonate for 3–5 years, temporarily withholding treatment will allow continuing benefit while reducing the risk of adverse events. Although there is little evidence to guide clinical decisions, the evidence that is available has been carefully reviewed by an ASBMR task force that recently reported their findings (Table 1.8), which are similar to recommendations from AACE/ACE. Drug holidays apply only to bisphosphonates, as other osteoporosis medications, such as denosumab, rapidly lose their beneficial effects with discontinuation [26]. Patients who are started on a drug holiday should be monitored periodically with the thought of resuming treatment when fracture risk is once again high.

Table 1.8 Managing patients on long-term bisphosphonate therapy from an ASBMR task force [25]. AACE/ACE guidelines are similar with a slightly different terminology: consider a "bisphosphonate holiday" after 5 years of stability with oral bisphosphonate therapy in moderate-risk patients and after 6–10 years of stability in higher-risk patients; for intravenous (IV) zoledronic acid, consider a drug holiday after three annual doses in moderate-risk patients and after six annual doses in higher-risk patients [7]

For postmenopausal women treated with an oral bisphosphonate for ≥5 years or an intravenous bisphosphonate for ≥3 years, consider treatment decisions based on fracture risk stratification, as follows:
Low fracture risk
Definition: hip T-score >−2.5 and no hip, spine, or multiple osteoporotic fracture before or during therapy
Suggestion: consider drug holiday of 2–3 years
High fracture risk
Definition: hip T-score ≤−2.5 or hip, spine, or multiple osteoporotic fracture before or during therapy
Suggestion: consider continuing oral bisphosphonate up to 10 years and intravenous bisphosphonate up to 6 years

Treat-to-Target The concept of treat-to-target is based on the premise that a response to therapy is not necessarily the same as achieving an acceptable level of fracture risk [27, 28]. While a response to therapy is necessary in order to reduce fracture risk, it is not always sufficient to bring fracture risk to a level that is desirable. Since treatment targets are common clinical practice for some other chronic diseases, such as diabetes mellitus and hypertension, and might be useful in the care of patients with osteoporosis, an ASBMR-NOF working group was formed with the charge of exploring the feasibility of treat-to-target for osteoporosis. The findings were recently reported [29]. It was suggested that baseline risk stratification be performed and that a treatment target be identified before treatment is started. The choice of initial treatment should be one that is likely to reach the target. When treatment is started according to a T-score ≤ -2.5, then the target should be at least a T-score > 2.5, above the threshold for starting treatment with the NOF guidelines. A target T-score > -2.0 allows for the variability of DXA measurements and the LSC. These suggestions were primarily based on expert opinion, recognizing the need for more data to confirm or reject the clinical utility of osteoporosis treatment targets.

Fracture Liaison Service Secondary fracture prevention by coordinator-based systematic identification and management of patients with fractures may help to close the osteoporosis treatment gap [30–32]. The concept of a fracture liaison service (FLS) has been emerging worldwide. Uptake of FLS seems to be best in countries with a national healthcare system and in the USA for large integrated health systems that have financial incentives to reduce healthcare costs. With fee-for-service medical care, the adoption of FLS has been slower. A study with a Markov state-transition computer simulation model nevertheless found potential economic benefit with FLS in the USA [33]. This may encourage further use of FLS in the USA.

Education by Teleconferencing The idea that every primary care provider would be willing and able to manage the vast majority of patients with osteoporosis has not been successful, thereby contributing to the osteoporosis treatment gap. An alternative strategy is to find a single healthcare provider or a small group in each community with a special interest in osteoporosis and then elevate their level of knowledge to near-expert level through the use of teleconferencing technology. Project ECHO (Extension for Community Healthcare Outcomes), developed at the University of New Mexico in Albuquerque, New Mexico, USA, has been shown to improve the care of chronic hepatitis C in rural New Mexico [34]. The same concept has been applied to Bone Health TeleECHO to improve the care of osteoporosis in underserved communities [35, 36]. Weekly videoconferences are held to link faculty and learners anywhere that an electronic link is available. Learning is primarily through case-based discussions with brief weekly didactic presentations. Preliminary results have been favorable, with a very large effect size for self-confidence in osteoporosis patient care responsibilities.

Summary

Osteoporosis is a common disease that weakens bones and increases the risk of fractures. The consequences of osteoporotic fractures include disability, loss of independence, and death. Effective and safe medications have been proven effective at reducing fracture risk, but are currently underutilized, resulting in a large osteoporosis treatment gap. New strategies with the potential of reducing the treatment gap are being developed.

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