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Osteoporosis: An Update on Screening, Diagnosis, Evaluation, and Treatment

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Abstract

Osteoporosis screening, diagnosis, and treatment have gained much attention in the health care community over the past two decades. During this time, creation of multispecialty awareness programs [e.g., “Own the Bone,” American Orthopedic Association (AOA), “Capture the Fracture,” International Osteoporosis Foundation (IOF), etc.], and improvements in diagnostic protocols have been evident. Significant advances in technology have elucidated elements of genetic predisposition for decreased bone mineral density in the aging population. Additionally, several novel drug therapies have entered the market and provide more options for primary care and osteoporosis specialists to medically manage patients at risk for fragility fractures. Despite this, adherence to osteoporosis screening and treatment protocols has been surprisingly low by health care practitioners, including orthopedic surgeons. Continued awareness and education of this skeletal disorder is crucial to effectively care for our aging population.

Introduction:

Over a person’s lifespan, bone is acquired during growth, reaches peak bone mineral density (BMD) in early adulthood and is lost with advancing age. Osteoporosis is defined as a low BMD with deterioration in the microarchitectural structure of bone tissue resulting in skeletal fragility and increased risk of fracture [1, 2]. Previous studies estimated a 10.3% prevalence of osteoporosis in the United States amongst individuals 50 years of age or greater [3]. In 2017, Wright et al demonstrated approximately 16.9% of men and 29.9% of women 50 years or older meet the updated diagnostic criteria for osteoporosis as defined by the National Bone Health Alliance (NBHA). This prevalence increases to 46.3% in men and 77.1% in women 80 years or older [4].

The most obvious clinical sign of osteoporosis is a fragility fracture. When considering fracture risk, Strom et al estimated a lifetime risk of developing a major osteoporotic fracture (spine, hip, forearm, humerus) at 46.4% for women and 22.4% for men [5]. In 2000, the worldwide incidence of fragility fractures was estimated to be 9.0 million and projections

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show a total of 3 million fragility fractures in the United States alone by 2025 [6, 7]. Osteoporotic fractures have been shown to account for loss of more Disability Adjusted Life Years (DALYs), than most common cancers and a fragility hip fracture has almost a 30% 1-year mortality rate [6, 8]. This underscores the importance of recognizing and treating osteoporosis as well as advancing our understanding of the disease to develop newer therapeutics with fewer side effects.

Osteoporosis and Genetics:

While fracture is the clinical event of most importance in osteoporosis, this phenotype can be challenging to study genetically [9]. Parental osteoporotic fracture is predictive of future risk of fracture in their children, highlighting the existence of a genetic contribution to this disease [16, 17]. There are a large number of rare monogenic diseases that can impact bone mass and strength, but these disease alleles contribute very little to the variation observed in BMD in the population as a whole [10, 11]. Rather, BMD is a complex trait with multiple alleles dictating the genetic proportion of peak BMD in any one person [12]. The proportion of heritable genetic influence on peak BMD has been estimated to be as high as 85% and equally high heritabilities have been noted for bone architectural phenotypes that are predictive of fracture [13–16].

Historically, linkage analysis and candidate gene testing were used to find associations between regions of the genome and a phenotype of interest, but these have not been successful in finding the actual genes associated with BMD [17, 18]. There are many types of genetic changes that can cause differences in phenotype and/or lead to disease. While mutations can involve multiple base pairs, such as is seen with genomic duplications and deletions, mutations may be as a small as a single base pair (SNP). Genome wide association studies (GWAS) are now much more frequently used for genetic mapping. In short, a GWAS is an approach by which the whole genome is examined for associations between genotype and phenotype (reviewed in [18]). A population ranging in size from a few hundred to several thousand persons is phenotyped for a trait of interest. Then arrays are used to find associations between phenotypes of interest and SNP variants. Across the human population, approximately 10 million SNPs have been found and on average there is a SNP every 300 base pairs [19]. Genetic variants may alter the amino acid composition and potentially the function of a protein product of a gene [9]. However, in complexly inherited diseases such as osteoporosis, the causative variant is often located outside of the protein coding region of the gene and may affect the expression of a single gene or multiple genes in a region [20].

What has GWAS taught us about osteoporosis?

The first GWAS for BMD was conducted on data from ~1000 people from the Framingham Osteoporosis Study and established the principle that BMD could be investigated using GWAS [21]. In 2009, Rivadeneira identified twenty GWAS loci for BMD that met the accepted significance cut off [22]. In the intervening decade, a large number of GWAS studies have been conducted in adults, yielding loci associated with BMD of the total hip, forearm, spine and more recently for whole body BMD sans the head (reviewed in [23]). A recent meta-analysis of GWAS for whole body BMD showed that when the data

was stratified by age, only 2 of the 80 identified loci were impacted by age. This means that the majority of genetic loci exert their effects by impacting peak BMD and that the consequences of these loci on peak BMD persist over the life of the individual. In essence, osteoporosis is a young person's disease wherein there is a failure to acquire adequate peak BMD, predisposing a person for fragility fracture in later life.

Osteoporosis is an exceedingly complex common disease. Historically, GWAS was conducted under the common variant hypothesis which roughly stated that common disease was caused by common variants [18]. The newest studies include rare variants in the analysis and show that the effect size of rare variants is often larger than that of common variants, but this explains only ~20% of the population variance in BMD [12]. Likely, some of this can be ascribed to gene by environment (G*E) and gene by gene (G*G) interactions that could not be accounted for in study design [18] An interpretation of these results is that "osteoporosis" is actually a collection of syndromes, but it is unknown at this time if parsing out the "kind" of osteoporosis a person has would be of clinical value.

There has been much interest in using these results to calculate risk scores to identify patients at high risk for developing disease [24]. In principle, these risk scores are not that different than risk assessment tools already available, such as the commonly used fracture risk assessment calculator, FRAX [25]. A polygenic risk score totals how many disease-associated variants a person has, weighs each variant based on how much of an effect that variant has on the phenotype and yields a mathematical calculation of the risk of developing a disease based on their genotypes [24]. There have been mixed results to date in the creation of polygenic risk scores for osteoporosis, but this is a quickly evolving and promising area of research [26]. A hope for this technology is these scores can be used to determine who might benefit most from costly medications that are not without serious side effects, such as romosozumab, which is effective in preventing fracture, but is associated with increased risk for stroke and heart attacks [26].

Diagnosis of Osteoporosis:

The diagnosis of osteoporosis is made when patients meet any of the following criteria [27, 28]:

1. Fragility fracture
2. T-score ≤−2.5 at the lumbar spine, femoral neck, total hip or distal 1/3 radius on DXA exam
3. T-score between −1.0 and −2.5 with elevated fracture risk as determined by country-specific thresholds using the online Fracture Risk Assessment Tool (FRAX) [29]. In the United States, the cutoffs for 10-year fracture risk estimates are ≥20% risk of major osteoporotic fracture and ≥3% risk of hip fracture.

The lowest T-score on an individual's DXA exam is used for diagnosis. For example, a postmenopausal 65 year old woman with a T-score of −2.6 at the lumbar spine and −2.0 at the left femoral neck and left total hip meets criteria for osteoporosis and should not be classified as having osteoporosis at the spine and osteopenia at the hip. The National

Osteoporosis Foundation recommends screening DXA to assess BMD at the lumbar spine and one or both hips (± distal radius under certain clinical circumstances such as primary hyperparathyroidism) in the following groups [27]:

- Women ≥65 years old
- Men ≥70 years old
- Postmenopausal women and men ≥50 years old with risk factors for osteoporosis (e.g., premature menopause, rheumatoid arthritis, use of bone harming medications) and those with a history of adult fracture

Clinical Evaluation of Osteoporosis and Secondary Causes of Osteoporosis

Primary osteoporosis is osteoporosis due to aging and/or post-menopausal status. An individual suspected of having osteoporosis, either due to fragility fracture and/or low BMD by DXA, should have an evaluation to rule out secondary causes (Table 1) [30–34]. A DXA machine cannot tell the difference between low BMD due to osteoporosis or low BMD due to osteomalacia. Therefore, the clinician should perform an appropriate evaluation and associated laboratory studies. Secondary causes are found in approximately 30% of post-menopausal women and 50-80% of men [32, 33], often in those with very low Z-scores[30]. Table 1 provides a list of common causes of secondary osteoporosis.

Evaluation for secondary causes of osteoporosis consists of a thorough History and Physical Exam (H&P) and preliminary laboratory evaluation. The H&P should be targeted at fracture history (particularly number, site, trauma vs. atraumatic, age of onset) and predisposing factors for low BMD including genetic (family history) or environmental exposures (tobacco use, excess alcohol/caffeine intake, exposure to steroids or other bone harming medications, malabsorption, or inadequate intake etc). For women, age at menarche, and menstrual, obstetric, and menopausal histories, including use of hormones, should be sought. It may also be important to determine if low BMD is due to low peak BMD or ongoing bone loss. For most Orthopedic Surgeons, this goes beyond the typical scope of practice and therefore, we recommend referral to either a patient's primary care provider or an endocrinologist. With that being said, these physicians often have a significant wait time for evaluation and all physicians should be able to initiate the initial work up for osteoporosis.

Table 2 contains a suggested laboratory evaluation to rule out secondary causes of osteoporosis in otherwise healthy individuals. The suggested panel should identify >90% of secondary causes of osteoporosis, if present [32, 36]. In particular, osteomalacia, due to inadequate calcium (often due to vitamin D deficiency) or phosphorous, must be ruled out or treated prior to initiating pharmacotherapy to avoid increased risk of side effects (e.g., hypocalcemia with anti-resorptive medications). Additional lab evaluation (SPEP/UPEP, celiac panel, magnesium, serum tryptase, 1mg dexamethasone suppression test, 1,25-dihydroxyvitamin D, bone turnover markers) should be performed as guided by H&P findings and co-morbidities. If height loss is reported or observed, imaging of the thoracic and lumbar spine should be performed to rule out vertebral compression fractures (Table

3). Recent chest x-rays and/or abdominal imaging can be used to evaluate the spine without additional cost or radiation exposure.

Updates in Osteoporosis Treatment

Once osteoporosis has been confirmed and any underlying abnormalities have been corrected (e.g., Vitamin D Deficiency, primary hyperparathyroidism), treatment should be considered in those individuals meeting appropriate criteria [30, 31, 37, 38] (Table 4). Diagnosis and treatment of osteoporosis has fallen over recent decades in part due to lack of recognition that fragility fractures are diagnostic of osteoporosis and fear of medication side effects [39]. Orthopedists are often the first providers involved in patient care when a fracture occurs and, therefore, are uniquely positioned to inform the patient who experienced a fragility fracture that they have osteoporosis and should have appropriate osteoporosis evaluation and treatment. Fracture Liaison Services (FLS, see below) can assist orthopedists with the evaluation and treatment of osteoporosis when patients present with fracture. Importantly, osteoporosis therapy consists of pharmacologic and NON-pharmacologic treatments.

Non-pharmacological therapy includes adequate calcium/vitamin D/protein intake, smoking cessation, fall prevention, avoiding bone-harming medications (if possible), maintaining a healthy weight, remaining active with weight-bearing exercise and avoiding excess alcohol and caffeine intake. The Institute of Medicine[40] and National Osteoporosis Foundation[31] recommend individuals over the age of 50 years target 1000-1200mg of calcium per day, including and preferably via dietary intake [37, 38]. If a supplement is needed to make up the difference in those unable to get the recommended amount exclusively via diet, calcium carbonate (40% elemental calcium, must be taken with food) or calcium citrate (21% elemental calcium, more expensive, can be taken with or without food, better absorbed in achlorhydria such as PPI use or gastric bypass) may be used. The Institute of Medicine[40] recommends 400-600 IU/day of Vitamin D for healthy adults 51 years of age or older whereas most osteoporosis guidelines recommend 800-2000IU/day to achieve adequate 25-hydroxyvitamin D levels [30, 31, 37, 38]. The appropriate vitamin D level is a matter of debate [40, 41]. Our practice is in line with the Endocrine Society Guidelines targeting a 25-hydroxyvitamin D level of 30 ng/mL [30, 41]. Vitamin D3 (aka cholecalciferol) is preferred to Vitamin D2 due to its longer half-life [42]. Calcium and vitamin D are “threshold” vitamins, meaning that adequate amounts are important for mineralization, maintaining BMD, and avoiding excess BMD loss but more (and particularly excessive amounts) are not necessarily better.

Osteoporosis pharmacotherapy (Table 5) is classically divided into two categories, anti-resorptive or anabolic. Societal guidelines are available that provide suggested treatment algorithms to help medical providers select the appropriate pharmacotherapy for their patients [28, 37, 38]. Anti-resorptive therapies (bisphosphonates, denosumab, raloxifene) target and block osteoclast activity to decrease bone resorption and BMD loss. All anti-resorptive therapies can cause hypocalcemia and are associated with osteonecrosis of the jaw (ONJ) and atypical femur fracture (AFF) which occur in less than 1% of patients[43–45]. Anabolic therapies (e.g., teriparatide, abaloparatide) transiently stimulate

the PTH receptor to stimulate osteoblasts and bone formation. The most recently FDA-approved osteoporosis medication, romosozumab, is a monoclonal antibody to sclerostin and therefore has both anti-resorptive and anabolic features. By inhibiting sclerostin (an inhibitor of bone formation), romosozumab stimulates bone formation and suppresses bone resorption [46]. In the FRAME study [47], romosozumab for 12 months followed by 12 months of denosumab significantly decreased the risk of vertebral in post-menopausal women with osteoporosis compared to placebo for 12 months followed by 12 months of denosumab (RR 0.25, $p < 0.001$). Although romosozumab resulted in significantly greater increases in BMD at the lumbar spine, total hip, and femoral neck, non-vertebral and hip fractures were not statistically significantly different between the romosozumab and placebo groups. Similar to other anti-resorptive medications, osteonecrosis of the jaw and atypical femur fractures have been reportedly rarely with romosozoumab [47]. Uniquely, romosozumab carries a black box warning for potentially increased risk of myocardial infarction, stroke, and cardiovascular death and should not be initiated in those who have had a cardiovascular event within the previous 12 months. Romosozumab is a subcutaneous injection administered in a healthcare facility monthly and is only approved for 12 months of use.

Assessment of Osteoporosis Management:

Despite the increasing prevalence of osteoporosis and expected increase in fragility fracture rate, there appears to be an overall poor adherence to osteoporosis screening and treatment protocols. Studies have found that <25% of patients for whom osteoporosis screening is recommended receive such screening [61]. A 2019 study demonstrated that in patients 50 year or older who presented to the emergency department with a vertebral fragility fracture, only 27% were receiving medical therapy for osteoporosis prior to their fracture [7]. While our knowledge of screening guidelines and adherence to their recommendations certainly lacks, as does our post-fragility fracture care of bone health. Studies demonstrate an almost 200% increased risk of subsequent fragility fracture and an almost 300% increased risk of hip fracture following a vertebral fragility fracture [62]. In 2016, Oertel et al evaluated osteoporosis management in 1375 geriatric patients following fragility fractures and found only 21% of patients were previously tested for bone mineral density or received osteoporosis treatment [63]. Similarly, another study found that one year after fragility fracture, over 90% of patients failed to receive a bone density scan or start empiric treatment for osteoporosis [7]. Ultimately, 38% of patients in this study went on to develop a second osteoporotic fracture within 2 years of their initial fragility fracture [7]. These results highlight the fact that we are slow to diagnose and treat osteoporosis before fragility fractures occur. Even more concerning, they demonstrate a generalized lack of understanding about the need for testing and treatment following fragility fractures in order to prevent future fractures.

Beyond the lack of understanding about the need for testing and treatment for osteoporosis, there are also significant patient factors to consider, especially non-compliance. While there are a variety of reasons for poor patient compliance, it has previously been shown that patient adherence to treatment correlates with decreased fragility fracture risk as well as improvement in BMD [64]. Therefore, it is incredibly important to discuss areas of

patient concern including their understanding of the diagnosis and treatment plan, as well as the potential consequences of untreated osteoporosis as well as the side effects of medications. While clinicians believe >67% of their patients are taking their prescribed osteoporosis medications, only 40% of patients are picking those medications and it is likely that even fewer are actually taking these medications as prescribed [65]. From a patient stand-point, the major reasons for non-compliance include side effect profile of medications, lack of education/awareness of benefits of treatment, as well as dosing/administration inconveniences [65]. It is our recommendation that practitioners treating osteoporosis have an in-depth discussion with their patient regarding the side effect profile of the medications they prescribe. They should also stress the significant morbidity/mortality associated with untreated osteoporosis and the benefits of treatment.

Areas of Improvement:

Initially implemented in the UK, a Fracture Liaison Service (FLS) is a coordinator based, post fracture model of care designed to close the gap between sentinel fragility fracture and secondary fracture [66]. The aim is to create a structured pathway to improve identification, evaluation, and implementation of appropriate treatment in patients at risk of a secondary fragility fracture. A successful FLS program generally consists of a core of three individuals. These include a physician leader, FLS coordinator, and nurse navigator. Outside the core, significant multispecialty assistance is necessary and includes orthopedic surgery, rheumatology, endocrinology, primary care, and nursing support [67]. The International Osteoporosis Foundation (IOF) launched their “Capture the Fracture” program in 2012 and provided guidance on development of FLS programs globally [68]. When comparing institutions with FLS programs in place versus non-FLS institutions, an approximate 30% reduction in any re-fracture and 40% reduction in major re-fractures have been reported [69]. Gupta et al described their institution’s unique FLS program supplemented with EMR based alerts. These alerts helped identify at-risk patients who were admitted to the hospital or evaluated in the emergency department. After implementation for 12 months, the authors reported their ability to identify “captured missed opportunities” in 73.1% of previously undiagnosed and 77.1% of previously untreated osteoporosis patients [70]. Although success of FLS may vary, key factors that influence effectiveness include a multidisciplinary involvement, dedicated case managers, regular assessment and follow up, multifaceted interventions, and patient education [71]. The authors of this paper recommend that an FLS be developed at each institution in order to improve diagnosis and treatment of individuals suffering from osteoporosis.

Summary

In 2004, The US Surgeon General report warned that in 2020, the prevalence of osteoporosis and low bone mass is expected to increase to 1 in 2 Americans over age 50. We have made significant progress in understanding the genetic etiology of osteoporosis and development of treatments [72]. As our understanding of this diseased has improved, a greater number of pharmacotherapy options have become available for treatment.

While we continue to make great strides in the understanding of the disease and development of treatment modalities, there is continued need for improvement in screening and implementation of treatment. Many age-appropriate patients do not receive screening or counselling on osteoporosis. Furthermore, patients with known fragility fractures do not consistently receive the osteoporosis care and treatment they most certainly need. With more than 53 million people in the US alone affected by this disease, a thorough understanding of the basis, screening, diagnosis and treatment of osteoporosis is vital for all practitioners.

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Table 1:

Secondary Causes of Osteoporosis [30–35]

Osteomalacia	**Vitamin D Deficiency**
Malabsorption (Celiac Disease, Gastric Bypass)	Hypogonadism/Premature Ovarian Insufficiency
Primary Hyperparathyroidism	Hyperprolactinemia
Hypophosphatasia	Hyperthyroidism
GH Deficiency	Acromegaly
Chronic Kidney Disease	Cushing's Syndrome
Osteogenesis Imperfecta	Inflammatory Bowel Disease
Idiopathic Hypercalciuria/Kidney Stones	Primary Biliary Cirrhosis
Multiple Myeloma/MGUS	Systemic Mastocytosis
Beta Thalassemia Major	Transplant (solid organ, stem cell)
Rheumatoid Arthritis	Eating/Exercise Disorders and low BMI
Ankylosing Spondylitis	Systemic Lupus Erythematosus
Diabetes Mellitus (impaired bone microarchitecture)	COPD, Cystic fibrosis
Multiple Sclerosis	Immobility/Spinal Cord Injury
HIV	Hemochromatosis/Chronic Liver Disease
Ehlers-Danlos Syndrome	Marfan Syndrome
Alcoholism	Renal Tubular Acidosis
Medications (glucocorticoids, excess thyroid hormone, anti-epileptic drugs, aromatase inhibitors, depot medroxyprogesterone, etc)	

Table 2:

Suggested Lab Evaluation for Secondary Causes of Osteoporosis [30–32, 36]

Complete Blood Count (CBC)
Comprehensive Metabolic Panel (CMP)
Serum 25-hydroxyvitamin D (25OHD)
Serum phosphorous
24-hour urine calcium, creatinine and sodium
Parathyroid Hormone (PTH) - particularly if abnormal serum calcium
Testosterone (in men)
TSH (if on thyroid hormone replacement)

Table 3:

NOF Guidelines Criteria for Performing Dedicated Vertebral Imaging [31]

Women and men ≥50 years old with a low trauma fracture, subjective (historical) height loss of ≥1.5 inches (4 cm), prospective height loss of ≥0.8 inches (2 cm), or glucocorticoid exposure.
Women 65-69 years old and men 70-79 years old with a T-score ≤ −1.5
Women ≥70 years old and men ≥80 years old with T-scores ≤ −1.0

Table 4:

Individuals in Whom Pharmacological Therapy Should Be Considered [30, 31, 37, 38]

Postmenopausal women and men > 50 years old meeting WHO BMD Criteria from DXA (T-score ≤-2.5 at the lumbar spine, femoral neck, total femur, or (in certain circumstances) 33% radius)
Fragility Fracture
Postmenopausal women and men > 50 years old with osteopenia at Increased Risk of Fracture as determined by fracture risk calculator, such as FRAX
Rapid, non-physiologic bone loss (e.g., glucocorticoids, aromatase inhibitors, etc)

Table 5:

Pharmacological Treatment Options for Osteoporosis

Medication	Dose/Frequency	Fracture Risk Reduction (in post-menopausal osteoporosis)	Comments
Bisphosphonates			
Alendronate [48–51]	70 mg PO weekly	35-65% Vertebral 23% Non-vertebral 45-55% Hip	• Can cause hypocalcemia and esophagitis.
Risedronate [52, 53]	35 mg PO weekly	41% Vertebral 39% Non-vertebral 30% Hip	• Can cause hypocalcemia and esophagitis.
Ibandronate [54]	150 mg PO monthly	62% Vertebral	• Can cause hypocalemia and esophagitis. • No evidence of hip fracture protection
Zoledronate [55]	5 mg IV annually	70% Vertebral 25% Non-vertebral 41% Hip	• Can cause hypocalcemia • ~32% have an acute phase reaction with their first infusion consisting of fever, myalgias, and flu-like symptoms lasting 24-72 hours [55]
Raloxifene [56]	60 mg PO daily	30% Vertebral	• No data for hip fracture prevention
Denosumab [57]	60 mg subcutaneously every 6 months	68% Vertebral 20% Non-vertebral 40% Hip	• Can cause hypocalcemia and musculoskeletal pain • Cannot be stopped/delayed due to increased risk of multiple rebound vertebral compression fractures [58]
Teriparatide [59]	20 mcg subcutaneously daily x 2 years	65% Vertebral 40% Non-vertebral	• Contraindicated if history of radiation • Must be followed by anti-resorptive therapy to avoid loss of BMD gains
Abaloparatide [60]	80 mcg subcutaneously daily x 2 years	86% Vertebral 43% Non-vertebral	• Contraindicated if history of radiation • Must be followed by anti-resorptive therapy to avoid loss of BMD gains • Not FDA-approved in men • Unlike teriparatide, does not need to be refrigerated
Romosozumab [47]	210 mg subcutaneously monthly x 12 months	73% Vertebral	• May increase risk of myocardial infarction, stroke and cardiovascular death • Not FDA-approved in men

* Calcitonin is no longer commonly used for osteoporosis