Chapter 14
Osteoporosis

Aaroop Haridas and Seth Mark Berney

History

The term osteoporosis originated in France, in 1833, when Jean Martin Lobstein, a French pathologist, used the term to describe the histologic appearance of aged human bone.

In the 1960s, with the availability of bone densitometry, the association between osteoporosis and certain fractures was confirmed.

Definitions

Osteopenia refers to systemic low bone density or bone mass (matrix) with normal mineralization, resulting in increased bone fragility and risk of fracture.

Osteoporosis represents the extreme of osteopenia with very low bone density/bone mass (matrix) with normal mineralization, resulting in significantly increased bone fragility and risk of fracture. In 1994, an expert panel of the World Health Organization (WHO) established the most widely used definition of osteoporosis as "a state in which the bone mineral density (BMD) in women falls more than 2.5

A. Haridas (✉)
Assistant Professor, Faculty Trainer in Musculoskeletal Ultrasound, Division of Rheumatology, University of Arkansas for Medical Sciences, Little Rock, AR, USA
e-mail: AHaridas@uams.edu

S. M. Berney
The Eleanor A. Lipsmeyer Professor in Rheumatology, Professor of Medicine, Chief Division of Rheumatology, Director Rheumatology Fellowship Program, Unversity of Arkansas for Medical Sciences, Little Rock, AR, USA
e-mail: SBerne@uams.edu

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standard deviations below the young adult mean" [1]. However, as the data only included measurements of postmenopausal women and men older than 50 years, these definitions are only used for those populations. For premenopausal females and males less than 50 years of age, the Z score is used.

Osteomalacia is the progressive loss of calcium and phosphorus from bones with normal bone matrix resulting in increased bone fragility and risk of fracture.

Fragility Fractures are those that occur spontaneously or after minimal trauma, defined as falling from a standing height or less. Osteoporotic patients are prone to all fractures.

FRAX (Fracture Risk Assessment) tool—The FRAX tool is a computer algorithm to evaluate the 10-year probability of fracture, based on individual patient characteristics that integrate the patients clinical risk factors with bone mineral density (BMD) at the femoral neck [2].

Incidence and Prevalence

Osteoporosis is the most common metabolic bone disease and affects more than 200 million people worldwide. According to statistics from the International Osteoporosis Foundation, 1 in 3 women over the age of 50 years and 1 in 5 men will experience osteoporotic fractures worldwide [1]. Additionally, osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 seconds. Every osteoporotic fracture predicts subsequent fractures.

Natural Course of Osteoporosis [3]

Postmenopausal women progressively lose bone which follows a linear pattern at the hip and a quadratic pattern at the spine, with loss rates decreasing in older age. The rate of bone loss increases for the first 3 years post-menopause and then slows down, but without treatment never stops. In contrast, premenopausal women also experience bone loss but at a much slower rate.

Morbidity and Mortality

In the United States alone, more than 1.5 million osteoporotic fractures occur annually, including 250,000 hip, 250,000 wrist, and 500,000 vertebral fractures. Twenty percent of those with a hip fracture die, 25% are confined to long-term facilities and

50% of patients are unable to ambulate independently and require long-term care. Osteoporotic fractures result in a decreased quality of life, increased disability-adjusted life span and big financial burden to health insurance systems.

Economic Burden

Osteoporosis-related fractures cost patients, their families and the healthcare system approximately $19 billion annually [4] with projected costs by 2040 of $50 billion annually in the United States.

Bone Physiology

Bone constantly undergoes remodeling, during which osteoclasts resorb bone and osteoblasts produce new bone. Numerous metabolic changes, systemic and local inflammatory diseases can modify osteoblast and osteoclast number and activity, changing bone turnover, and resulting in either a net increase or decrease in BMD.

RANKL/RANK/OPG Pathway

RANK Ligand (RANKL) (a protein produced by osteoblasts) binds to its receptor, RANK, on osteoclasts which stimulates osteoclast maturation, survival, and subsequent bone resorption.

Osteoprotegerin (OPG) (also a protein produced by osteoblasts) blocks the activity of RANKL. RANKL expression is increased by parathyroid hormone, cytokines (TNF-α, IL-1, IL-11) and glucocorticoids. RANKL expression is decreased by estrogen and cytokines (TGF-β, IL-4) [5].

Etiology of Osteoporosis

Osteoporosis results from lifestyle changes, medical conditions (including gonadal failure, i.e., menopause) or medications. Ninety-five percent of osteoporosis in women result from menopause complicated by other risk factors, listed below.

Endocrine abnormalities	Cushing's syndrome, hyperthyroidism, hypogonadism hyperparathyroidism, hypercalciuria, hyperprolactinemia, Panhypopituitarism, diabetes, androgen insensitivity
Hematological disorders	Multiple myeloma, leukemia, lymphoma, systemic mastocytosis, hemophilia, thalassemia, monoclonal gammopathies
Rheumatologic	Rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, and other systemic inflammatory diseases
Gastrointestinal disorders	Gastric bypass, gastrectomy, IBD, primary biliary cirrhosis, celiac disease, pancreatitis
Renal	Renal failure, renal tubular acidosis
Pulmonary	Chronic respiratory diseases
Neurologic diseases	Epilepsy, multiple sclerosis, parkinsonism, muscular dystrophy, stroke, spinal cord injury
Genetic disease	Glycogen storage diseases, hemochromatosis homocystinuria, porphyria, Menke syndrome, Riley-Day syndrome, cystic fibrosis, homocystinuria, hypophosphatemia, Gaucher's disease Osteogenesis imperfecta, Ehlers-Danlos syndrome, Marfan syndrome
High-risk medications	Long-term steroids (≥5 mg/day prednisone or equivalent for ≥3 months), phenytoin and carbamazepine [6], heparin, gonadotropin-releasing hormone agonists, lithium, aromatase inhibitors, aluminum (in antacids), cancer chemotherapeutic drugs, depomedroxyprogesterone [7], proton pump inhibitors, tamoxifen (premenopausal use) [8], thiazolidinediones, thyroid hormones (in excess)

Risk Factors for Osteoporosis

Genetics and lifestyle risk factors contribute to the development of osteoporosis. A maternal history of hip fracture is associated with a twofold increased risk of a hip fracture in the patient. A prior fracture is associated with an 86% increased risk of any fracture. A long hip axis length may contribute to increased fracture risk; conversely, a short hip axis length may protect. Other protective factors include weight bearing exercise, African American ethnicity, a balanced diet with adequate amounts of calcium and vitamin D.

Non-modifiable risk factors of low bone mass	Modifiable risk factors of low bone mass
Advancing age	Low calcium or vitamin D intake
Race (white/Asian)	Sedentary lifestyle
Female gender	Cigarette smoking
Early menopause and late menarche	Lack of sunlight exposure
Slender build (<127 pounds)	Estrogen deficiency
Family history of hip fragility fracture	Alcohol excess or caffeine excess
Dementia	Glucocorticoid therapy
	Fracture after the age of 50 years
	Neurologic disorder
	Inability to stand from a chair without using arms
	Self-evaluation of health as fair to poor

Osteoporosis in Men [9]

This has become a significant health concern. Fractures in men increase dramatically after age 70, typically beginning 5–10 years later in life than women. The incidence of hip fracture is one-third to one-half of that in women. Hip and spine fractures are more prevalent in men older than 70 years. Men are less likely than women to be treated with antiresorptive therapy after a hip fracture. This is likely multifactorial in etiology, but provider ignorance and clinical inertia appears contributory. Severe hypogonadism from androgen deprivation therapy for prostate cancer is common in elderly men, as is hypogonadism, alcohol abuse, smoking, gastrointestinal and hepatic disorders and malabsorption.

Clinical Features of Osteoporosis

Osteoporosis has no clinical manifestations until a patient experiences a fracture.

Loss of height (>1.5 inch), localized spinal pain (indicative of fracture), accentuated kyphosis (Dowager's hump), or vertebral compression fracture on a chest radiograph may be seen. Almost all non–spine-related fractures occur as a result of trauma and have the acute signs and symptoms of a fracture. However osteoporotic vertebral fractures frequently do not result from overt trauma, leading to a delayed diagnosis.

Evaluation of Osteopenia/Osteoporosis

A clinical evaluation for osteoporosis consists of a careful history and physical examination to identify features of osteoporosis, as well as conditions that contribute to its development, including a height assessment, followed by the measurement of the patient's bone mineral density and a lab evaluation for the contributory conditions.

Basic lab evaluation
Serum creatinine, albumin, calcium, phosphorous, alkaline phosphatase levels
Serum 25-hydroxy vitamin D level
Serum thyroid stimulating hormone
Serum testosterone levels in men
Celiac disease antibody testing (if white with symptoms or low 25-OH vitamin D level)
24-hour urinary calcium level
Additional testing if the basic evaluation does not elucidate the cause
Serum protein electrophoresis if over the age of 50 years with undiagnosed anemia
Serum parathyroid hormone level
Bone biopsy under calcified sections with double tetracycline label
Serum biochemical markers of bone turnover
Urinary free cortisol

Methods of Evaluating Bone Mineral Density

Radiographs

Osteopenia/Osteoporosis on radiographs in the absence of fracture is a very subjective observation, and this terminology is frequently misused. Conventional X-ray techniques are insensitive in the evaluation of bone density at any skeletal site because 30–40% bone must be lost before it is radiologically evident.

Single Photon Absorptiometry of the Radius or Heel

This involves determining the mineral content of bone by measuring the absorption of a monochromatic, low energy photon beam, produced by a radioactive source (iodine-125 or americium-241). However, disadvantages include the fact that the object of study might consist of only two materials with different absorption coefficients. Also, the radioactive source needs to be replaced after a certain period.

Quantitative CT Scan (QCT) of the Lumbar Spine

QCT is a true bone density measured in g/cm^3, and it can analyze the trabecular and cortical compartments of bone unlike DEXA. Unfortunately, the disadvantages include lower precision, a higher dose of ionizing radiation, lesser availability and complex scanner operation when compared to DEXA. Additionally, most large epidemiological osteoporosis studies with fracture endpoints have not used QCT measurements.

Calcaneal Ultrasound (Quantitative Ultrasound/QUS)

QUS employs high-frequency sound waves to determine bone density, and QUS correlates with the BMD measured by DEXA. QUS could discriminate subjects with and without a fracture history and predict risk for future fracture. Therefore, QUS is convenient and provides information on bone microarchitecture as well as BMD. However as numerous QUS devices have been developed by many manufactures, each with its own designed logarithm for the calculation and interpretation of QUS indices, inter-device comparison of the results of bone health assessment is not possible. Furthermore, the precision of QUS is reported to be poorer compared to DEXA.

Dual Energy X-Ray Absorptiometry (DEXA)

This is currently the gold standard for measuring bone mineral density and determining whether someone has normal/osteopenic or osteoporotic bone. Its advantages include a low radiation exposure of 1–5 micro Sieverts and short procedure time of less than 20 minutes. Also, it does not require a complex scanner operation and has lower cost compared with QCT.

The disadvantages of DEXA include its inability to capture three-dimensional bone microarchitecture; the bone mineral density values obtained with dual X-ray absorptiometry do not represent true volumetric bone mineral density, but a projected areal bone mineral density and DEXA cannot distinguish between increased bone mineral density values arising from thicker bones and those arising from increased tissue mineral density (such as from osteophytes). Hence DEXA may give falsely high BMD values in those with bone-forming pathologies such as osteoarthritis and spondyloarthropathies and in patients who have had orthopedic or neurologic surgery. DEXA scans can be distorted by aortic calcification, soft-tissue calcification and other artifacts in older individuals.

According to the guidelines of the Scientific Advisory Board of the National Osteoporosis Foundation, bone densitometry using DEXA is useful in determining which patients might benefit from bone protective therapy [10].

- T-score: the number of SD (standard deviations) the patient is below or above the mean value for young (30 years old) normal subjects (peak bone mass) but is used only for postmenopausal women and men >50 years of age. This is a good predictor of the fracture risk.
- Z-score: defines how the bone mineral density (BMD) compares to age matched controls and is used for premenopausal women and men <50 years old.
- Absolute BMD: This is expressed in g/cm^2. This is the value needed to calculate changes in BMD, and whether those changes are significant.

The World Health Organization Criteria for Osteoporosis [11]

For postmenopausal women and men >50 years of age

Diagnostic criteria	Classification
$T \geq -1$	Normal
$T = -1$ to -2.5	Osteopenia(low bone mass)
$T \geq -2.5$	Osteoporosis
Osteoporosis + fracture	Severe or established osteoporosis

For premenopausal women and men <50 years of age

A Z-score of < -2.0 is interpreted as “bone density which is below the expected range for age.”

A Z-score of > −2.0 is interpreted as "bone density which is within the expected range for age."

Because very small changes in a patient's bone mass may be significant, and the BMD is reported to the thousandth decimal place, the BMD is used to determine whether a patient's bone density has significantly changed when compared with a prior DEXA.

To assess response to therapy, the follow-up DXAs must be performed on the same machine as the prior scan or on a machine with which it was cross calibrated, to avoid or minimize intermachine variability. The Least Significant Change (standard error) is the amount that is considered a statistically significant difference, when compared with a prior timepoint. The National Osteoporosis Foundation recommends treatment for all people who have a lumbar spine, hip or femoral neck T-score of −2.5 or lower. For people who have a bone density between −1 and −2.5, the National Osteoporosis Foundation recommends performing a Fracture Risk Assessment (FRAX), which provides a 10-year risk of a hip fracture or a major osteoporotic fracture. At least two different locations must be tested: spine, right hip, left hip or nondominant mid shaft radius (especially if the patient has a cortical bone disorder such as hyperparathyroidism). Additionally, the spine measurement must contain at least two contiguous vertebrae. Because osteoporosis is a systemic disease, the lowest T score found determines the patient's single diagnosis.

Clinical Indications for Measuring a Patient's Bone Mineral Density

According to the International Society of Clinical Densitometry in 2004:

1. All postmenopausal women <65 years who have one or more additional risk factors for osteoporosis (besides menopause)
2. All women >65 years and men >70 years regardless of additional risk factors
3. Adults with bone fragility fractures
4. Adults with a condition associated with low bone mass or bone los
5. Anyone being considered for therapy for osteoporosis
6. Anyone being treated with bone anti-osteoporotic therapy to monitor treatment effect
7. Anyone not receiving therapy in whom evidence of bone loss would lead to treatment

Fracture Risk Assessment (FRAX) https://www.shef.ac.uk/FRAX/tool [2]

The clinical risk factors included in the FRAX program include:

1. Age
2. Sex
3. Weight
4. Height
5. Previous fragility fracture
6. Parental hip fracture
7. Current smoking
8. Current glucocorticoid use (≥5 mg prednisone for 3 months or more)
9. Rheumatoid arthritis
10. Secondary causes of osteoporosis, i.e., myeloproliferative disorders, chronic kidney disease, chronic liver disease, etc.
11. Alcohol intake of 3 or more units/day (a unit of alcohol is equivalent to a glass of beer [285 mL], an ounce [30 mL] of spirits, or a medium-sized glass of wine [120 mL])

These risk factors are added to the femoral neck BMD in the FRAX equation to calculate the 10-year fracture risk. *In the United States, either a 10-year risk of hip fracture of 3% or more or a major osteoporotic fracture of 20% or more is the threshold to recommend treatment.* The fracture risk threshold for treatment is individualized by country, so it is important to enter the country in which the patient resides into the formula.

Treatment of Low Bone Mineral Density, Osteopenia, and Osteoporosis

The decision to initiate a bone-active agent for those with low bone mass is based on the patient's risk stratification using the WHO FRAX tool, the lowest T-score value, and history of a fragility fracture.

The patients risk may be stratified as either:

- Low risk: FRAX 10-year risk for a major osteoporotic fracture of <10%
- Medium risk: FRAX 10-year risk of 10–20%
- High risk: FRAX 10-year risk >20%, or a T-score below −2.5 at any site, independently or along with a history of a previous fragility fracture

Non-pharmacologic Interventions to Prevent Low Bone Mass or Fractures

- Physical therapy—structured weight bearing exercise programs and gait training to improve coordination.
- Interventions to prevent falls and resulting fractures.

- Maintaining ideal body weight (there is no evidence that interventions aimed at gaining or losing weight in thin and obese persons, respectively, can reduce fracture risk).
- Discontinue tobacco and excessive alcohol use.
- Address modifiable risk factors including polypharmacy and environmental hazards.
- Hip protectors, walking aids, safety aids at home (home safety check).

Pharmacologic Interventions

Vitamin D and calcium supplementation guidelines according to the National Osteoporosis Foundation (NOF) [12]

	Daily calcium intake	Daily vitamin D intake
Women <50 years	1000 mg	400–800 IU
Women >50 years	1200 mg	800–1000 IU
Men 51–70 years	1000 mg	800–1000 IU
Men >71 years	1200 mg	800–1000 IU

In addition to calcium and vitamin D, pharmacological interventions are broadly divided into two categories, based on their net result as anti-resorptive and anabolic agents. Anabolic agents stimulate bone formation thereby increasing BMD-Teriparatide (Forteo). Strontium ranelate is not approved by the FDA. Anti-resorptive therapies (bisphosphonates, estrogen and selective estrogen receptor modulators, denosumab) reduce bone resorption thereby preserving bone mineral density (BMD).

Bisphosphonates

Alendronate, risedronate and ibandronate are oral formulations. Zoledronic acid, ibandronate and pamidronate are intravenous formulations. Although it was the first bisphosphonate used for osteoporosis, etidronate is not FDA approved for osteoporosis in the United States. Pamidronate is also not specifically approved for osteoporosis by the FDA. Oral bisphosphonates are poorly absorbed from GI tract and carry a risk of esophagitis. Weekly, monthly and yearly dosing improve patient compliance. Rare risks include atypical femur fractures and osteonecrosis of the jaw. Due to the potential of atypical femur fractures, many authorities recommend a two-year drug holiday after 5 years for oral bisphosphonates and after 3–5 years for zoledronic acid.

Contraindications to bisphosphonates include pregnancy, chronic kidney disease stage 4 or 5, low serum calcium (<8.5 mg/dl in the presence of a normal albumin), osteomalacia, vitamin D deficiency (until it is corrected), pre-existing esophageal conditions such as Barret's esophagus, and patients who cannot stay upright for an hour, after taking the oral medication. A 25(OH) vitamin D level > 40 ng/ml has been associated with a more favorable response to bisphosphonate therapy [13].

After ingesting an oral bisphosphonate, the patient should be instructed to consume a tall glass of plain water and maintain an upright posture for 30 minutes. The side effects of nausea, dyspepsia, abdominal pain and gastritis are not significantly different between alendronate, risedronate or ibandronate and placebo.

Side effects of bisphosphonates include esophagitis (oral bisphosphonates), musculoskeletal pain (both oral and IV forms), an acute phase reaction consisting of fever, myalgia, and arthralgia for IV bisphosphonates, hypocalcemia for IV bisphosphonates, esophageal cancer which could be secondary to nonadherence to prescribing directions and resulting esophagitis, rare osteonecrosis of the jaw, and sub trochanteric fractures (the association of which have been questioned).

Denosumab

A monoclonal antibody which binds to and prevents RANKL from binding to RANK. It inhibits osteoclast formation, function and survival. Can be used in patients with renal dysfunction but not in hypocalcemia. The dosage is 60 mg subcutaneous every 6 months. Side effects reported in clinical trials include infections of the skin, GI tract, urinary system, ear, endocarditis [14] musculoskeletal pain and rash.

Teriparatide

Stimulates net bone formation when given subcutaneous. Its side effects include nausea, dizziness, headaches, muscle cramps, and hypercalcemia. Teriparatide is approved by the US Food and Drug Administration (FDA) to treat men and women with osteoporosis for up to 2 years. It is administered 20 mcg subcutaneous daily. Based on the first 7 years of the Osteosarcoma Surveillance Study (a 15-year study), there does not appear to be a causal association between teriparatide treatment and osteosarcoma in humans [15].

Calcitonin

Calcitonin prevents bone resorption and is administered intranasally or subcutaneous. Calcitonin at doses of 200 IU/ day stabilizes and may produce a short-term increase in bone density at the lumbar spine. However, the effect on nonvertebral fractures was not significant. But calcitonin diminishes bone pain in osteoporotic vertebral fractures; thus, its niche appears to be decrease pain in acute osteoporotic fractures.

FDA-Approved Agents for Osteoporosis

A. *Anti-resorptive agents that lower the risk of spine, hip and non-vertebral fractures (first line agents)*

   1. Alendronate (Fosamax)
   2. Risedronate (Actonel)
   3. Zoledronic acid (one infusion may last for more than 6 years) (Reclast)
   4. Denosumab (Anti–RANKL antibody) (Prolia) no drug holiday

B. *Anti-resorptive agents that lower the risk of spine fractures but now show evidence effects on the risk for hip or non-vertebral fractures (second line agents)*

   1. Calcitonin (Miacalcin, Fortical)
   2. Ibandronate (Boniva)
   3. Raloxifene (Evista)

C. *Anabolic agents that lower the risk of spine and non-vertebral fractures*

   1. Teriparatide (PTH, Forteo)
   2. Abaloparatide (PTHrP, Tymlos)

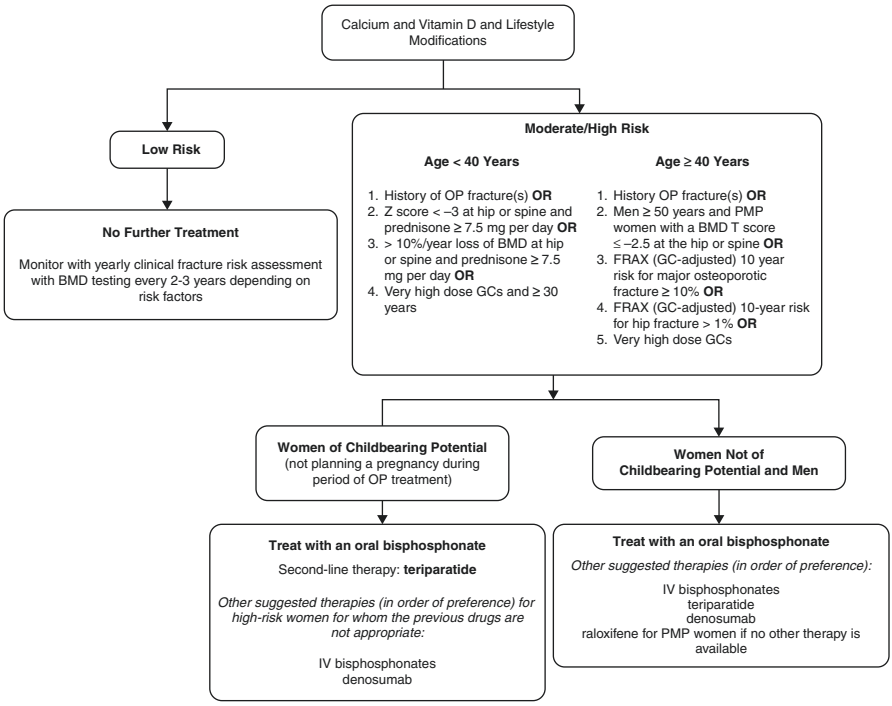
Guidelines for Glucocorticoid-Induced Osteoporosis (GIOP)

Etiology

Bone loss occurs within 6–12 months of the start of steroids, due to glucocorticoid-induced increased osteoclast activity, urinary Ca excretion and decreased osteoblast activity, GI calcium absorption, and estrogen and testosterone levels.

No dose of prednisone is safe for bone mineral density. In fact, prednisone doses as low as 2.5 mg/day orally or even intraarticular triamcinolone suppresses osteocalcin, a serum marker of bone formation, and increases the risk of fracture. The increased risk for fractures during GC treatment appears to be dose-dependent. If glucocorticoid (GC) treatment is >7.5 mg/day, the FRAX risk increases by 1.15 for major osteoporotic fracture and 1.2 for hip fracture.

American College of Rheumatology Guidelines for Glucocorticoid-Induced Osteoporosis Prevention and Treatment [16]



(Very high-dose glucocorticoid (GC) treatment was defined as treatment with prednisone >30 mg/day and a cumulative dose of 5 gm in the past year)

Guidelines for Premenopausal Women with Childbearing Potential Who Have Had a Previous Fragility Fracture

There are no tools to estimate the absolute fracture risk in children or adults <40 years of age.

The ACR Voting Panel designated men and women <40 years of age to be at moderate risk if they were expected to continue prednisone treatment at >7.5 mg/day for 6 months and had either 1) a hip or spine BMD Z score of < −3 or 2) a rapid decline in hip or spine BMD (equivalent to >10% in 1 year) during GC treatment [16].

Guidelines for Patients on Intermittent Pulses of Intravenous Glucocorticoids and Inhaled Steroids

Specific guidelines for prevention and treatment of GIOP in patients receiving intermittent pulse glucocorticoids (>1 gm) without daily therapy are lacking, though the

American College of Rheumatology recommendations include treatment with an oral or IV bisphosphonate or teriparatide or denosumab, in those who have received >5 gm of prednisone equivalent in the last 1 year [16].

Effectiveness of Pharmacological Therapy

Risk reductions of between 30% and 70% have been demonstrated for vertebral fractures, 15–20% for non-vertebral fractures and up to 40% for hip fracture [17].

Reassessment of Risk [18]

The optimal interval for repeating Dual-energy X-ray Absorptiometry (DXA) scans is unknown.

Because the changes in bone density over short intervals are often small, frequent testing (e.g. <2 years) is unnecessary in most patients. Recent evidence suggests that healthy women age 67 and older with normal bone mass may not need additional DXA testing for up to 10 years if their osteoporosis risk factors do not significantly change. In all adults and children who continue GC treatment, a risk reassessment should be performed every 12 months [16].

In clinical practice, any patient with a T-score below −1.5 and a loss of 4% or more of their BMD after 1 year on glucocorticoids should be treated with a bone preserving agent.

Patient Education

Education of patients to obtain resources to prevent falls and fractures is available at the National Osteoporosis Foundation website. https://www.nof.org/patients/

High-Yield Review Points

1. Osteopenia refers to systemic low bone mass with normal mineralization, resulting in increased bone fragility and risk of fracture.
2. The WHO defines osteoporosis as a state in which the bone mineral density in women that falls more than 2.5 standard deviations below the young adult mean.
3. Osteomalacia is the progressive loss of calcium and phosphorus from bones with normal bone matrix resulting in increased bone fragility and risk of fracture.
4. Fragility Fractures are those that occur spontaneously or after minimal trauma.

5. FRAX (Fracture Risk Assessment) tool is a computer algorithm to evaluate the 10-year probability of fracture, based on individual patient characteristics that integrate the patients clinical risk factors with bone mineral density at the femoral neck.
6. Bone constantly undergoes remodeling in a person's lifetime, during which osteoclasts resorb bone and osteoblasts produce new bone.
7. RANK Ligand, produced by osteoblasts, binds to RANK on osteoclasts which stimulates bone resorption. Osteoprotegerin produced by osteoblasts blocks the activity of RANKL.
8. A maternal history of hip fracture is associated with a two-fold increased risk of a hip fracture. A prior fracture is associated with an 86% increased risk of any fracture.
9. Dual Energy X-ray Absorptiometry (DEXA) is the gold standard for measuring bone mineral density.
10. According to the WHO, for postmenopausal women and men >50 years of age, a T score more than −1 is considered normal bone density, T score of −1 to −2 is considered osteopenia, and a T score less than −2.5 is osteoporosis.
11. For premenopausal women and men <50 years of age, the Z score is used. A Z-score of < −2.0 is interpreted as "bone density below the expected range for age," and a Z-score of > −2.0 is interpreted as "bone density within the expected range for age."
12. In the United States, either a 10-year risk of hip fracture of 3% or more or a major osteoporotic fracture of 20% or more is the threshold to recommend treatment.
13. Alendronate, risedronate, and ibandronate are oral bisphosphonates, and zoledronic acid, ibandronate, and pamidronate are intravenous formulations.
14. Denosumab is monoclonal antibody which binds to RANKL and prevents it from binding to RANK. It inhibits osteoclast formation and can be used in those with renal dysfunction.
15. Teriparatide given subcutaneous is anabolic and stimulates bone formation.
16. Calcitonin decreases pain in acute vertebral osteoporotic fractures.
17. Contraindications to bisphosphonates are pregnancy, chronic kidney disease stage 4 or 5, low serum calcium, osteomalacia, uncorrected vitamin D deficiency, Barrett's esophagus and patients who cannot stay upright for an hour, after taking the oral medication.
18. Bone loss occurs within 6 months of the start of steroids. There is no bone safe dose of prednisone.

Questions

1. A 68-year-old woman who takes alendronate 70 mg weekly for 2 years and calcium and vitamin D returns for a routine clinic appointment. In the past year, she experienced one vertebral compression fracture. DEXA reveals a T score of −3.0 in the hip and −3.2 in the spine, and a significant decrease in the BMD compared with the DEXA from 2 years ago. What is the next step in management?

   A. Add teriparatide
   B. Wear a hip protector
   C. Replace alendronate with risedronate
   D. Stop alendronate and start teriparatide
   E. Add Raloxifene to alendronate

   The correct answer is D.
   Teaching point—choice of osteoporotic therapy.
   Discussion
   This patient has osteoporosis and has received appropriate first line management with a bisphosphonate. However, she has experienced progressive bone loss and a fracture. As the bone loss is significant and progressive, this warrants treatment with a therapy with a different mechanism of action. Teriparatide is useful in those with severe osteoporosis who fail a bisphosphonate. There is no evidence that the addition of an anabolic agent to a bisphosphonate will decrease fracture risk.
   In randomized control trials, hip protectors have not been shown to reduce hip fractures.
   Raloxifene is a selective estrogen receptor modulator (SERM) that suppresses bone resorption and improves bone density. However, it is has not been shown to reduce fractures in combination with a bisphosphonate. Additional correct answers could have been to replace alendronate with IV ibandronate or zoledronic acid or subcutaneous denosumab. However, these options were not offered.
2. A 75-year-old woman developed back pain 4 weeks ago, which has progressively worsened and unresponsive to acetaminophen and ibuprofen. Her physical examination is unremarkable except for mid back midline vertebral tenderness on palpation with muscle spasm. A lateral spine radiograph reveals a non-displaced T 10 compression fracture.
   Which of the following may provide early relief of her bone pain?

   A. Cyclobenzaprine
   B. Alendronate
   C. Thoracolumbar orthoses (TLO) brace
   D. Calcitonin
   E. Vertebroplasty

   The correct answer is D.

Teaching point—management of acute compression fracture.
Discussion
This patient presents with an acute vertebral compression fracture. While many patients experience relief with acetaminophen or an NSAID, when pain persists, intranasal calcitonin could significantly reduce pain from vertebral compression fractures.
Muscle relaxants do not help pain from vertebral fractures, without an accompanying component of muscle spasm.
Additionally, while popular, no evidence exists supporting the use of back braces for acute pain relief. A bisphosphonate is useful for long-term treatment of osteoporosis but would not help for acute pain relief. Prospective trials have demonstrated no efficacy for vertebroplasty in acute pain relief.

3. A 65-year-old woman underwent a DEXA scan. Her lab testing including renal function, electrolytes, TSH, and vitamin D levels are normal. Results of the DEXA scan are:

	Bone density (g/cm^2)	Young adult (T score)	Age matched (Z score)
Lumbar spine L1-L4 (average)	0.924	−2.4	−0.7
Total proximal femur			
Left	0.638	−2.8	−1.8
Right	0.740	−2.1	−1.2
Mean	0.690	−2.7	−1.4

What is the next step in management?

A. Diagnose osteoporosis and discuss treatment
B. Diagnose osteopenia and discuss management
C. Calculate the FRAX score and decide whether to treat
D. Reassure the patient, that she has a normal bone density, because her Z scores are normal
E. Recommend OTC calcium and vitamin D, and advice follow up in 6 months.

The correct answer is A.
Teaching point—diagnosis of osteoporosis.
Discussion
The World Health Organization and the International Society for Clinical Densitometry define osteopenia as a T score −1.1 to −2.4 and osteoporosis as a T score less than −2.5.
Because she meets criteria for osteoporosis, she deserves treatment.
FRAX tool is only to guide management in patients with osteopenia and not been on any osteoporosis therapy. Z scores are useful for fracture risk estimation in premenopausal women, men younger than 50 years or in children.

4. A 75-year-old man with a history of fracture after falling from a standing position, diabetes, atrial fibrillation, GERD, and hypothyroidism presents for a follow-up visit. His medications include metformin, Xarelto, omeprazole and levothyroxine. What is the strongest risk factor for osteoporosis in this patient?

   A. Anticoagulation
   B. Omeprazole use
   C. Diabetes
   D. Prior fracture
   E. Hypothyroidism

   The correct answer is D.
   Teaching point—risk factor for fracture.
   Discussion
   History of a prior fragility fracture is the strongest risk factor and is predictive of a future osteoporotic fracture.
   While the use of a proton pump inhibitor, diabetes, hypothyroidism, anticoagulation and elderly age are all risk factors that predispose to osteoporosis, they do not predict subsequent fractures as strongly as a prior fracture.
5. A 60-year-old woman with current alcohol and tobacco abuse and a T4 compression fracture is evaluated in her primary care provider's office. A dual-energy X-ray absorptiometry (DEXA) scan showed a right hip T-score of −2.4 and vertebral T-score of −3.0. She has taken alendronate, calcium and vitamin D since then. On physical examination, she has thoracic kyphosis. Laboratory studies show normal calcium level and 25-hydroxy-vitamin D levels. A basic metabolic panel is normal. Repeat DEXA shows a stable bone mineral density. In addition to recommending alcohol cessation, what medication change would you make at this time?

   A. Add denosumab
   B. Stop alendronate
   C. Replace alendronate with teriparatide
   D. No change in current treatment.

   The correct answer is D.
   Teaching point—management of follow-up osteoporosis.
   Discussion
   After recommending complete tobacco and alcohol cessation, this patient should continue alendronate. She has documented osteoporosis and is at high risk for subsequent fractures due to multiple risk factors, including a prior fracture. Her bone mineral density (BMD) has stabilized on an oral bisphosphonate, which is the goal.
   A drug holiday is indicated for patients who have been on bisphosphonates for 3 to 5 years, have had no progression of the disease, and have minimal risk factors for additional fractures. This patient has multiple risk factors for fractures; hence, a drug holiday is not appropriate.

6. A 44-year-old woman with a history of Adult Onset Stills disease, tobacco abuse and status post total hysterectomy with bilateral salpingo-oopherectomy presents for follow-up evaluation. She has required prednisone 7.5 mg/day for the last 7 months to control worsening joint swelling in the hands and wrists. In addition to prednisone, she takes methotrexate 20 mg orally weekly, leflunomide 20 mg orally daily and sulfasalazine 1000 mg oral twice a day.

   On physical examination, she has active synovitis of multiple pips and mcp joints bilaterally. Her dual X-ray absorptiometry (DEXA) scan shows a T-score of −1.6. Her Fracture Risk Assessment Tool (FRAX) score shows a 10-year glucocorticoid-adjusted risk of hip fracture of 2%. In addition to smoking cessation and initiation of calcium and vitamin D, according to the 2017 guideline of the American College of Rheumatology, which of the following is the most appropriate action to prevent osteoporosis in this patient?

   A. Denosumab
   B. Teriparatide
   C. Alendronate
   D. Intravenous bisphosphonate therapy

   The correct answer is C.
   Teaching point—management of glucocorticoid-induced osteoporosis.
   Discussion
   The most appropriate treatment for this woman is initiation of an oral bisphosphonate.
   The American College of Rheumatology guidelines in 2017 are a helpful tool, to guide the prevention of glucocorticoid-induced osteopenia and osteoporosis.
   Initial GC-induced osteoporosis prevention involves lifestyle modifications, weight-bearing exercise, smoking cessation, and treatment with calcium (800–1000 mg/day) and vitamin D (600–800 IU/day). These preventive strategies should be used in patients who are under the age of 40 or have a low risk of fracture.
   In adults who are 40 years or older with a moderate or high risk of fracture, oral bisphosphonate therapy is recommended in addition to calcium and vitamin D and lifestyle modifications. According to the guidelines, this patient, who has a glucocorticoid adjusted Fracture Risk Assessment Tool (FRAX) score of 2% and has a moderate (>1% and < 3%) 10-year risk of hip fracture, should be treated with an oral bisphosphonate.
   The current guidelines place any patient taking prednisone ≥2.5 mg for ≥3 months at risk for osteoporosis. A clinical fracture risk assessment should be performed within 6 months of the initiation of long-term glucocorticoids. For adults aged more than 40 years, an initial assessment should include FRAX scoring for risk assessment. Bone mineral density screening should be obtained for adults younger than 40 years of age who have additional risk factors within 6 months of therapy initiation. Clinical risk fracture reassessment should then be performed annually in patients continuing steroid therapy. Intravenous

bisphosphonates are not indicated unless patients cannot tolerate oral bisphosphonates or are non-compliant.

7. A 50-year-old postmenopausal woman with a history of anorexia nervosa is evaluated for a new-patient visit. Her current BMI is 16. She has otherwise been healthy and currently feels well. She never smoked. Her family history is significant for a fragility fracture in her father. Her medications are over-the-counter calcium and vitamin D supplements.

   Her physical examination is normal. Results of laboratory studies reveal a serum calcium level of 9.0 mg/dL and 25-hydroxyvitamin D level of 50 ng/mL; TSH is 2.0. A dual-energy X-ray absorptiometry (DEXA) scan shows T-scores of −1.6 in the femoral neck and −1.6 in the lumbar spine. Her 10-year fracture risk using the Fracture Risk Assessment Tool (FRAX) is 5% for major osteoporotic fracture and 0.9% for hip fracture.

   Which of the following is the most appropriate management of this patient?

   A. Begin a SERM.
   B. Repeat DEXA scan in 2 years
   C. Replace calcium with cholecalciferol
   D. Start bisphosphonate therapy

   The correct answer is B.

   Teaching point—management of low bone mass in postmenopausal woman.

   Discussion

   Treatment for low bone mass in postmenopausal women involves lifestyle modification (weight-bearing exercises and avoidance of tobacco or excessive alcohol), vitamin D and calcium supplementation.

   As her bone density by DEXA is between −1 and −2.5, the need for pharmacologic therapy is based on the FRAX score—a 10-year estimated fracture risk (≥20% for a major osteoporotic fracture or ≥ 3% for hip fracture).

   A repeat dual-energy X-ray absorptiometry (DEXA) scan should be performed in 2 years in this patient with low bone mass and relatively low 10-year fracture risk.

   As she has a low BMI, she is at increased risk for osteoporosis. Additionally, her calcium and vitamin D levels are appropriate. Continuing lifestyle activities (such as maximizing weight-bearing exercise and avoidance of tobacco or excessive alcohol) is appropriate management of this patient.

   SERM (selective estrogen receptor modulator) like raloxifene are associated with an increased risk of thromboembolism and vasomotor symptoms. There is limited data supporting use of raloxifene for treating patients with low bone mass.

   Bisphosphonates are considered first-line therapy for osteoporosis, although they are not used routinely in women with low bone mass, unless the FRAX score suggests an increased risk.

8. A 36-year-old man presented to the physician's office with a 6-month history of lower back pain. There was no history of trauma or fall. He is an astronaut and

takes no medications or supplements, does not smoke or consume alcohol, or use recreational drugs.

His last visit in space about 1 year ago, for a duration of 3 months. He has never been on corticosteroids and has no history of prior fractures. He has tried a course of physical therapy for 6 weeks for his back, with worsening of back pain. Review of systems and physical examination are unremarkable, except for low back pain and tenderness on palpation at L4. On further testing, serum levels for luteinizing hormone (LH), follicle-stimulating hormone (FSH), TSH, free T4 and testosterone are normal. Complete blood count and a complete metabolic panel are normal.

Which of the following is the most appropriate next step for this patient?

A. Scheduled acetaminophen
B. Referral to pain management
C. Obtain a lumbar radiograph
D. Start bisphosphonate therapy

The correct answer is C.

Teaching point—obtain appropriate imaging in a patient with risk factors for bone loss and focal signs. Space travel is a risk factor for bone loss. It is unclear how to prevent this from occurring.

Discussion

When the effects of gravity on the longitudinal skeleton are removed, as with space travel or inactivity, bone resorption is greater than bone formation. This was demonstrated in patients who were on continuous bed rest. It was found that their urinary calcium increases rapidly and by the sixth week of bed rest, plateaus for several weeks, and then decreases but remains above the ambulatory baseline thereafter. This occurred even though the patients received vitamin D supplementation. Bone loss continues at this rate for at least 36 weeks. Attempts to prevent disuse osteoporosis with both mechanical and biochemical means, including exercise, skeletal compression, increased hydrostatic pressure to the lower body, supplemental calcium and phosphorus, calcitonin, or bisphosphonate use were not successful.

9. 76-year-old white male with a history of malleolus fracture during a skiing accident at age 60 years, left hip fracture at age 75, and hypothyroidism treated with 100 mcg of levothyroxine is seen at his primary care physician office for an evaluation. BMD by DEXA confirms osteoporosis, and he is started on therapy.

Which of the risk factors or mechanisms are thought to play an important role in the development of osteoporosis, by an estrogen independent mechanism?

A. Increased IFN-γ production
B. TGF-β down regulation
C. Age
D. Decreased IL 7 production

The correct answer is C.

Teaching point—recognize the importance of aging by itself, as a risk factor for the development of osteoporosis, which may operate through estrogen dependent and estrogen independent mechanisms.

Discussion

It is known that the underlying mechanisms of osteoporosis in older adults are different than those associated with estrogen deprivation. Markedly increased bone resorption leads to the initial fall in bone mineral density. With increasing age, there is also a significant reduction in bone formation. The exact mechanism of aging and its effect on the bone are not completely clear, but it plays an important role in the pathophysiology of age-related osteoporotic fractures.

A DEXA scan is useful to measure bone density but may not be able to measure age-related structural bone decline.

The loss of bone may be secondary to age-related changes in other organs and tissues, such as the ovary (estrogen deficiency), the adrenal gland (glucocorticoid excess or hyper-responsiveness), the kidney [loss of nephrons, reduced synthesis of calcitriol, calcium malabsorption, and secondary hyperparathyroidism], and muscle (sarcopenia, inactivity, reduced mechanical loading). However, additional age-related mechanisms intrinsic to the bone, like excessive accumulation of reactive oxygen species (ROS), contribute to age-related changes in many tissues including the bone.

Increased oxidative stress is strongly implicated in the biology of aging and the pathogenesis of age-related diseases. Recent evidence indicates that oxidative stress is a fundamental mechanism of the age-dependent decline of bone mass and strength and that loss of estrogens exaggerates the effects of aging on bone by decreasing defense against oxidative stress. The balance between the generation of reactive oxygen species versus defense against them is critical for bone homeostasis throughout life.

Estrogen deficiency up regulates IFN-γ production through TGF-β down regulation. Estrogen has a direct stimulatory effect on the production of this factor. TGF-β is a powerful inhibitor of T cell activation. Another mechanism by which estrogen regulates IFN-γ and TNF production is by repressing the production of IL-7, which is a potent inducer of bone destruction.

10. 32-year-old African American male referred to the bone clinic with recent onset of left knee pain for 7 days. He has a history of lactase deficiency and hence avoids all dairy products, SLE and biopsy proven lupus nephritis since the age of 20 years, has been on varying doses of prednisone (5–60 mg oral daily, for the last 10 years), post treatment with IV cyclophosphamide for lupus nephritis, and osteonecrosis of bilateral femoral heads. BMD by DEXA revealed.

Radial diaphysis T score	−2.0
Distal radius T score	−3.4
L3 lateral T score	−2.7
Lumbar L1–L4 T score	−3.5

He has no history of fractures, metal of both femoral heads, preempts interpretation of the hip BMD

Which of the following medications are not known to worsen bone loss?

A. Prednisone
B. Hydroxychloroquine
C. Cyclophosphomide
D. Both B and C

The correct answer is B.

Teaching point—hydroxychloroquine appears to protect against low BMD in patients with SLE, who are treated with corticosteroids.

Discussion.

In a study evaluating risk factors for low bone mineral density in patients with systemic lupus erythematosus (SLE), the following factors were found to be significantly related to lower BMD—Caucasian race, increased number of pregnancies, postmenopausal status, higher SLE damage index, and higher cumulative corticosteroid dose. An unexpected finding was that taking Hydroxychloroquine was the only factor associated with higher BMD of the hip and spine. Hydroxychloroquine has been shown to suppress bone resorption in vitro possibly by inducing osteoclastic apoptosis and thus decreased bone resorption. However more data and studies are needed in this regard.

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