Osteoporosis

Writing sample

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Overview

Osteoporosis is a bone disorder that is expected to impact healthcare worldwide as the population ages. Osteoporosis leads to fractures with concomitant effects on morbidity, mortality, level of function, mobility, and financial obligations for those people with the disorder. This article discusses the epidemiology of osteoporosis, diagnosis and risk factors, pathophysiology, and current treatment options.

Learning Objectives

Upon completion of this course, you should be able to:

- Understand the socioeconomic impact of osteoporosis
- Recognize patients at risk for developing osteoporosis
- Understand the available diagnostic modalities
- Choose therapeutic options for treatment of patients with osteoporosis
- Implement screening programs in your practice for patients at risk for osteoporosis

Target Audience

This CME activity is designed to meet the learning needs of primary care physicians, as well as other healthcare providers who are involved in the care of patients with osteoporosis.

EPIDEMIOLOGY OF OSTEOPOROSIS

AR is a 42-year-old Caucasian, right-hand dominant, female who presents to the clinic having tripped at work and fallen on her outstretched right hand. She complains of pain and swelling in the right wrist. X-rays reveal a Colles fracture of the distal radius as well as evidence of osteopenia. The fracture is reduced and casted, and she is advised to take vitamin D and calcium as well as to follow up with her primary care provider as she may have osteoporosis. Subsequent workup reveals that she does have osteoporosis. Her dual x-ray absorptiometry (DEXA) shows a bone mineral density (BMD) of 3.0 standard deviations below normal. She is started on therapy for the osteoporosis. The cast is removed after 8 weeks and after an additional 12 weeks of physical therapy she is left with ~5% loss of range of motion in the wrist. AR may regain another 1-2% of range of motion in the wrist with time.

AR illustrates the epidemiology associated with osteoporosis, a bone disorder that may be present and 'silent' until a fracture is sustained. This disease is characterized by decreased bone strength resulting in a greater susceptibility to fractures of the wrist, hip, and spine. Bone strength is a combination of bone density and bone quality. Bone density is determined by peak bone mass and amount of bone loss and is expressed in grams per area or volume. Bone quality is a combination of underlying trabecular architecture, the rate of bone turnover, the amount of damage accumulated over time (e.g. microfractures), and mineralization. Loss of bone strength is due to a combination of these factors. [1-2]

Current estimates suggest there are 10 million Americans with osteoporosis and another 34 million with low bone mass placing these individuals at risk for fracture. Of this 10 million, 8 million are women and 2 million are men.

Fifty percent of women and 25% of men over the age of 50 will have one osteoporosis related fracture during their lifetime. Women of all ethnic groups over age 50 are at risk. [3]

Table 1. Risk of Osteoporosis by Ethnic Group

Ethnic Group	Risk of Osteoporosis	Risk for Low Bone Mass
Non-Hispanic African-American	5%	35%
Hispanic	10%	49%
Non-Hispanic White	20%	50%
Asian	20%	52%

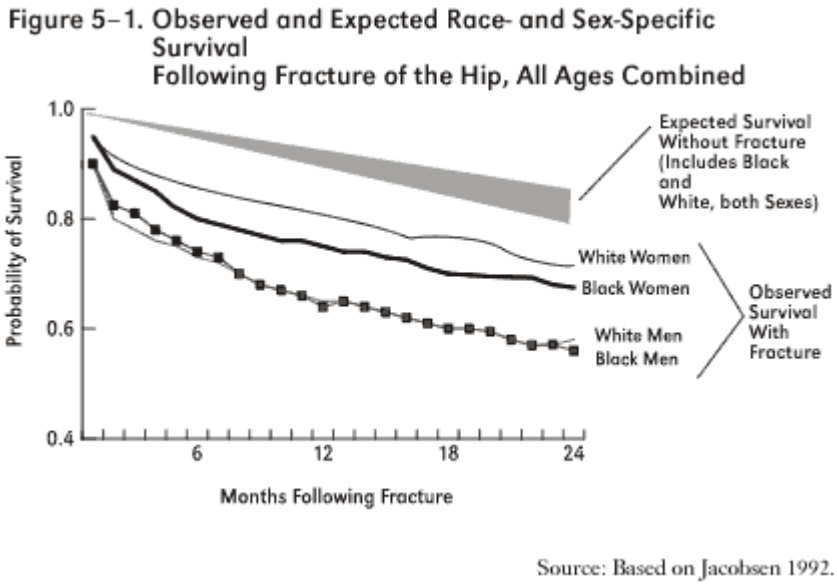
Source: Based on statistics of the National Osteoporosis Foundation. Available at: http://www.nof.org/osteoporosis/diseasefacts.htm. Accessed April 15, 2005.

Osteoporosis leads to more than 1.5 million fractures per year: over 300,000 hip (18% female, 6% male), approximately 700,000 vertebral (18% female, 6% male), 250,000 distal radius fractures (16% female, 3% male), and 300,000 fractures of other sites. The incidence of hip fractures for females increases from 300 per 100,000 person years at age 65 to 3000 per 100,000 person years by age 85. For males, the rise is from 150 at age 65 to 2,000 per 100,000 person years by age 85. [3-5]

These fractures lead to more than 800,000 emergency room visits and 2.6 million physician office visits. Hip fractures are responsible for 140,000 nursing home placements. Approximately 20% of patients sustaining a hip fracture will

die within one year of the fracture with the oldest patients most at risk. By age 80, hip fractures result in permanent disability. [2, 6-7]

Graph 1



Source: The burden of bone disease. In: *Bone health and osteoporosis: a report of the Surgeon General*. Rockville, Md.: U.S. Dept. of Health and Human Services, Public Health Service, Office of the Surgeon General; Washington, D.C. 2004: 88-107

Estimated costs of osteoporosis and fracture care are between $12-18 billion dollars US annually. The costs will only increase. Progressive aging of the population is occurring in North America, Western Europe, and Japan. The number of individuals in the US older than 65 will rise from 32 to 69 million by the year 2050. Worldwide the number of hip fractures is projected to be 6.3 million by 2050. North America and Europe account for one-half of all hip fractures at present, but by 2050, the majority of hip fractures will be in Latin America and Asia. One estimate projects costs related to hip fractures worldwide to rise to $45.6 billion US by 2025. [2, 5-8]

While the mortality rate directly due to osteoporosis is low, the morbidity for individuals can be high, including loss of function, loss of height, change in body image, decreased mobility, increased dependence on family, and increased financial burden. Wrist fractures over the short term can have persistent pain, carpal tunnel syndrome, bone deformities, and arthritis. [6-7]

AR has deformity of and loss of function at the wrist, which may ultimately affect her job performance and her earning power.

Improved bone health is key. Whole bone strength/bone health refers to bones that have enough strength to resist breaking at peak loads. [9]

Therefore, early diagnosis, treatment, and prevention are essential to improving bone health and reducing the number of fractures, the associated morbidity, and the consumption of health care dollars. Had AR been diagnosed earlier, her wrist fracture may have been prevented. A high index of suspicion, especially for individuals at risk, and a low level of referral for testing on the part of primary care providers are required.

Diagnosis of Osteoporosis

Osteoporosis may be primary (postmenopausal or involutional) or secondary. Secondary causes include chronic illness, intestinal diseases that decrease calcium absorption, hyperparathyroidism, steroid use, and lifestyle factors. In men, secondary osteoporosis is more common. A comprehensive history including family history and lifestyle factors (smoking, alcohol use, and

level of physical activity) should be reviewed along with a complete physical exam, and routine blood chemistries including thyroid stimulating hormone (TSH) and parathyroid hormone (PTH). [1, 4]

Risk factors include:

- Advanced age
- Female sex
- Caucasian or Asian origin
- Thin build
- Premature menopause
- Family history of osteoporosis
- Low dietary intake of calcium
- Smoking
- Heavy alcohol use
- Endocrine related (loss of sex hormones, hyperthyroidism, and hyperparathyroidism)
- Corticosteroid use.

Osteoporosis is currently defined by the World Health Organization (WHO) as a BMD $\geq$ 2.5 standard deviations (SD) below the peak bone mass with the definition for severe osteoporosis including evidence of fracture. DEXA scans precisely measure BMD with less radiation than that of a chest x-ray. [1, 6-7, 10]

Clinicians receive a report in which the BMD is converted to statistical T and Z scores. T score is a statistical comparison of the patient's bone mass to a young healthy control group. Z score is the patient's deviation from an age, sex, and race-matched group. Sites measured include the proximal femur and lumbar spine. Each SD below peak bone mass represents a 10 to 12% loss of bone mineral content and 2 to 2.5-fold increase in fracture risk at the measured site.[1, 4]

Along with DEXA scan results, fracture risk includes bone strength, the type and location of the bone, general musculoskeletal function, and the risk of falling. Individuals at increased risk for falling include those with visual loss,

decreased mobility, cognitive impairment, sedative drug use, and those who are nursing home residents.

DEXA scans are recommended to screen patients older than 65, follow those with prior osteoporotic fractures, for individuals with fractures from mild to moderate trauma, to confirm decreased bone mass noted on routine x-rays, and for patients on steroids. At risk individuals should be screened earlier.[1, 4]

AR was of thin build, Caucasian, female, had a family history of osteoporosis, and testing revealed she was in early menopause. Her DEXA scan indicated that she had a 25 to 30% loss of bone mineral content and an increased risk for fracture. She would have benefited from early screening.

PATHOPHYSIOLOGY OF OSTEOPOROSIS

Regulation of bone mass and bone strength is based on a balance between bone formation (osteoblasts) and bone resorption (osteoclasts). Changes in the number of osteoclasts and osteoblasts are related to problems with aging, hormone deficiency, or glucocorticoid excess. [11-12]

To understand bone loss, a brief review of normal bone development and remodeling is warranted.

NORMAL BONE STRUCTURE AND FUNCTION

The adult human skeleton is a dynamic organ comprised of 206 bones that are constantly changing and remodeling. Every ten years the entire skeleton regenerates. [11]

Bone has the appearance of stiff inflexibility, but it is a permeable structure comprised of cells, blood vessels, and crystalline calcium compounds that serves four purposes:

- To contain minerals for use by cells
- To generate blood cells for the immune and circulatory systems
- To protect specialized organs such as the brain, heart, and lungs
- To provide scaffolding for muscles and joints [13]

As scaffolding, bone has some flexibility to resist impact loading and allow absorption of energy without structural failure (fracture). [14]

At birth, the skeleton is mostly cartilage particularly at the ends of the long bones. Growth and ossification of cartilage increases height throughout child and early adulthood.

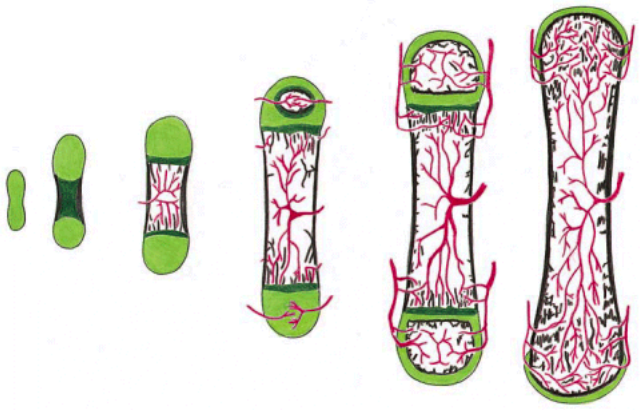


Fig 1. The development of a long bone. Long bones, such as the femur or the humerus, develop from a miniature cartilage model. Uncalcified cartilage is shown in *light green*, calcified cartilage in *dark green*, bone in *black*, and blood vessels in *red*. The cartilage is not converted to bone but is gradually replaced by it through the action of osteoclasts and osteoblasts, which invade the cartilage in association with blood vessels.

Source: Alberts B, Johnson A, Lewis J, Raff M, Roberts K, and Walter P. Fibroblasts and their transformations: the connective tissue cell family. In: Alberts B, et. al. eds. *Molecular biology of the cell*, 4th ed. New York, NY: Garland Science: 2002. National Center for Biotechnology Information Web site. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=books&doptcmdl=GenBookHL&term=osteoblasts+AND+mboc4%5Bbook%5D+AND+374829%5Buid%5D&rid=mboc4.figgrp.4196. Accessed March 13, 2005.

By approximately age 20, peak bone mass is reached and from that time until around age 45 (in women) bone mass is stable, and there is perfect balance between bone loss and bone formation. Bone mass declines after age 45. [13, 15]

Once adulthood is reached the balance between bone loss and formation is the result of a process called remodeling. Remodeling occurs in cycles and is under the control of various signals both chemical and mechanical. Chemical signals include hormones and serum mineral levels. For example, pregnancy and lactation can increase the demand for calcium leading to increased levels of remodeling. Mechanical signals such as load bearing stresses serve to repair damaged areas of bone. [11, 13]

BONE REMODELING IN OSTEOPOROSIS

As noted earlier, osteoporosis is a decrease in bone strength—both a decrease in bone density and bone quality. The tightly controlled balance between bone loss and bone deposition is compromised. At menopause and with aging, the rate of bone remodeling increases, doubling after menopause, then tripling 13 years later and, with osteoporosis, remains high. More resorption occurs resulting in a loss of trabecular connectivity, deterioration of the skeletal architecture, and a loss of bone strength. [2]

TREATMENT OF OSTEOPOROSIS

Treatment for osteoporosis can be divided into nutritional therapy, anti-resorptive therapy, and bone rebuilding agents, each targeting a specific aspect of bone remodeling. Current therapy focuses primarily on improving bone strength by improving bone mass, but not necessarily improving bone quality.

NUTRITIONAL THERAPY

Since bone is 50% mineral, increasing and maintaining bone requires adequate intake of calcium and vitamin D to offset losses through urine and skin.

Vitamin D is produced by ultraviolet radiation when cholecalciferol is converted to calcitrol in the kidney. Calcitrol binds to an intestinal mucosal receptor inducing transport of calcium across the intestinal muscosa. Vitamin D and calcium modulate the increased levels of PTH and bone resorption related to aging. Vitamin D decreases vertebral fractures and may decrease fractures at other sites. [1, 16-17]

Nutritional therapy includes calcium and vitamin D intake preferably from dietary sources such as milk products and calcium fortified foods. Food provides additional nutrients such as protein, potassium, magnesium, and phosphorus important to bone health. Supplements should be added if the individual is unable to consume enough calcium. Recommended dietary intake for calcium is noted in the table below. Recommended vitamin D intake is 400 to 800 IU/day, but true intake may be 3000 to 5000 IU/day when all sources including sunlight are included. Older individuals are more likely to have decreased sun exposure. Intake should be 1000 IU/day for those with osteoporosis. [16]

Table 2. Dietary Reference Intake (DRI) for Calcium*

Population	Age (yr)	DRI (mg)
Children	1-3 4-8	500 800
Males and Females	9-18 19-50 >50	1,300 1,000 1,200
Pregnant/Lactating women	≤ 18 ≥ 19	1,300 1,000

*Recommended Daily Allowances (RDA) are being replaced with DRI. Inzucchi S. Endocrinology: diseases of calcium metabolism and metabolic bone disease [serial online]. 2003; 1-14 ACP Medicine Website. Available at: http://www.acpmedicine.com/abstracts/sam/med0306.htm. Accessed March 27, 2005

AR was advised to begin calcium and vitamin D therapy at the initial diagnosis of her fracture, and nutritional therapy was continued after she was seen by an endocrinologist.

ANTI-RESORPTIVE THERAPY

Anti-resorptive therapies include estrogen, selective estrogen receptor modulators (SERMs), bisphosphonates, and calcitonin.

Estrogen Replacement Therapy

Estrogen or hormone replacement therapy (HRT) prevents postmenopausal bone loss by directly replacing estrogen. Estrogens slow bone turnover, leading to an increase in BMD of 2-7% with a decline in fracture risk of 40-60% at the hip and spine. [4]

However, long term use of HRT is associated with side effects that may be unacceptable including uterine bleeding, breast tenderness, and an increased risk of breast and ovarian cancer. Long term studies show that women taking estrogen and progesterone had a reduced fracture risk, but a 26% increased risk for breast cancer, 29% for myocardial infarction, 41% for stroke, and double the risk for other thromboembolic events. Studies examining estrogen in osteoporosis continue. [18]

Selective Estrogen Modulators (SERMs)

SERMs were developed when women taking tamoxifen for breast cancer were found to have less osteoporosis, similar to the effects of estrogens. Raloxifene, a non-steroidal benzothiofene, is the SERM most investigated. It has less potent effects on bone density when compared to HRT. [18]

Raloxifene acts as an estrogen agonist. It decreases urinary markers for bone turnover, increases BMD, and decreases the risk for vertebral fractures, but not the risk for hip fractures. [4, 18-19]

Bisphosphonates

Bisphosphonates are analogs of pyrophosphonate and bind to hydroxyapatite at active remodeling sites and reduce bone resorption. As a result, bone remodeling is slowed and turnover reduced. Bisphosphonates increase cortical wall thickness and may reduce death of osteoblasts and osteocytes. These compounds do not improve skeletal architecture but do reduce the remodeling space. Bisphosphonates produce a 6-10% increase in BMD and a 30-60% decrease in fracture risk for vertebral and other sites over 2-3 years. [1, 4, 11, 19-21]

Side effects for these drugs include esophageal irritation and ulceration with rare GI bleeding, and hypocalcemia. [4, 20]

AR was begun on a bisphosphonate and in the future would have follow-up DEXA scan at scheduled intervals.

Calcitonin

Calcitonin is a 32-amino acid polypeptide hormone produced by parafollicular cells in the thyroid. It lowers serum calcium concentrations and inhibits osteoclasts by binding to osteoclast receptors. Calcitonin increases BMD in vertebrae but has not been shown to prevent bone resorption in early

menopause. It reduces the risk for vertebral fracture in similar fashion to SERMs; however, it has not been shown to reduce the risk of hip fracture. [22]

This drug is available as a nasal spray and the standard dose is 200 IU. Calcitonin reduces urine and serum markers of bone turnover. Patients may develop antibodies to calcitonin and resistance to the drug. [22]

BONE BUILDING AGENTS

Anabolic agents can improve skeletal architecture in severe osteoporosis.

Parathyroid hormone

PTH is an 84-amino acid peptide secreted by the parathyroid gland in response to calcium levels. Its analog, teriparatide, is a recombinant human PTH.[1, 34] These compounds act to directly increase renal absorption of calcium and indirectly to enhance intestinal absorption. Low intermittent doses of PTH promote bone formation and increase BMD. PTH increases the amount of bone laid down by increasing the lifespan of osteoblasts and reducing osteoblast cell death. PTH may uncouple bone formation from bone resorption by directly stimulating bone formation without prior resorption having taken place. [21]

Phase III trials of teriparatide showed a significant reduction in both vertebral and non-vertebral fractures over 19 months. BMD as measured by DEXA scan was increased in the spine, in the femur, and improved in postmenopausal women taking glucocorticoids. However, teriparatide is three times the cost of bisphosphonates.

Intact PTH is undergoing Phase III trials but Phase II trials over 12 months showed a gain in BMD of 7.8% at the lumbar spine and 0.5% at the femoral

neck. Risk of new vertebral fractures and nonvertebral fractures was reduced 65% and 54% respectively. [19, 21]

Side effects included ~8% headaches and nausea similar to placebo. Nine percent of patients reported dizziness and 3% leg cramps within a few hours of injection. Three percent of patients had an increase in serum uric acid with both teriparatide and intact-PTH and several developed gout. PTH increases serum calcium, and 11% of patients on a teriparatide dose of 20 μg/day had elevated calcium levels.

All major trials for both teriparatide and intact-PTH were stopped due to findings of induced osteosarcoma in rats at all dose levels. In humans, there are reports of a dose-related incidence of osteosarcoma, but a cause and effect relationship is unproven. At present, teriparatide can be given for no more than 2 years in the US.

Patients who are at risk for osteosarcoma, have had prior skeletal irradiation, unexplained increases in bone specific alkaline phosphatase, history of cancer in the last 5 years, a history of kidney stones or gout or other metabolic bone disease should not receive PTH. Nutritional vitamin D status should be assessed prior to starting treatment by measuring serum 25-OH vitamin D levels.[21]

Additional bone rebuilding agents are currently being investigated.

In the future, AR's story might differ. AR has an annual physical with her primary care physician. He reviews her history for bone health and

whole bone strength and determines she is at risk for osteoporosis. He orders appropriate blood work and a DEXA scan, which reveals she does have osteoporosis. She is instructed to take vitamin D and calcium and a new medication. Monitoring shows evidence of improved whole bone strength. When she trips and falls in the cafeteria and is evaluated at the clinic, x-rays are negative for a fracture. She has sustained a minor contusion and strain that resolves with ice and over the counter pain relievers.

Call outs

Page 3: “Bone strength combines bone density and bone quality. Bone density is peak bone mass to bone loss. Bone quality is a combination of architecture, bone turnover, mineralization, and damage over time.”

Page 4: “Osteoporosis leads to more than 1.5 million fractures per year; more than 800,000 emergency room visits; 140,000 nursing home placements due to hip fractures; and 20% of patients with hip fractures die within one year.”

Page 8: "Bone mass and bone strength is a balance between bone formation (osteoblasts) and bone resorption (osteoclasts). Changes in these cells are related to aging, hormone deficiency, or glucocorticoid excess.”

Page 10: “Treatment for osteoporosis consists of nutritional therapy with anti-resorptive therapy or bone rebuilding agents. Current therapy improves bone strength by improving bone mass. Providers will need to weigh risks vs. benefits in selecting treatment options.”

CME Questions

1. Osteoporosis is a bone disorder characterized by decreased bone strength resulting in a greater susceptibility to fractures of the:
   A. spine, ankle, and wrist
   B. ankle, wrist, and hip
   C. wrist, hip, and spine
   D. hip, spine, and hand

2. Annual estimated costs of osteoporosis and fracture care in the US are between:
   A. $10-$12 billion dollars
   B. $12-$18 billion dollars
   C. $10-$20 billion dollars
   D. $20-$30 billion dollars

3. Osteoporosis is diagnosed when the peak bone mineral density by DEXA scan is how far away from normal:
A. $\geq$ 0.5 SD
B. $\geq$ 1.0 SD
C. $\geq$ 2.0 SD
D. $\geq$ 2.5 SD

4. Females over the age of 50 should have a recommended daily reference intake of calcium of:
A. 1000 mg
B. 1200 mg
C. 1500 mg
D. 2000 mg

5. Bisphosphonates:
A. Reduce bone resorption with no change in skeletal architecture
B. Reduce bone resorption and improve skeletal architecture
C. Increase bone resorption with no change skeletal architecture
D. Increase bone resorption and improve skeletal architecture

Answer Key

1. C
2. A
3. D
4. B
5. B

Abbreviations

TSH	Thyroid stimulating hormone
PTH	Parathyroid hormone
BMD	Bone mineral density
DEXA scan	Dual x-ray absorptiometry scan
SERMs	Selective estrogen receptor modulators
HRT	Hormone replacement therapy
DRI	Daily reference intake
RDA	Recommended daily allowance

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