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Felicia Cosman, M.D., Associate Professor of Clinical Medicine at Columbia University and Clinical Director of The National Osteoporosis Foundation, served as faculty for that program.

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Osteoporosis: Epidemiology and Impact

- Affects 4-6 million postmenopausal Caucasian women
- 50% of Caucasian women will experience osteoporotic fractures
- Hip fractures have a 24% mortality risk during first year postfracture
- Only 10-15% with hip fractures return to full, independent activity

Osteoporosis is very common; it currently affects 4-6 million postmenopausal Caucasian women.¹ Approximately half of all Caucasian women will experience an osteoporotic fracture during their lifetimes. In the United States, there are approximately 1.5 million osteoporotic fractures every year.² Of these, 250,000 are hip fractures, which carry a 24% mortality risk within the first year.³ Approximately one in six Caucasian women will fracture her hip.⁴⁻⁷ Half of those who suffer hip fractures are unable to walk without assistance² and about 8% require long-term nursing care.⁸ Only 10-15% will return to full, independent activity.

Osteoporosis presents an enormous burden to the healthcare system. The cost of the disease and its associated fractures is estimated to be \$14 billion annually. Hip fractures incur the greatest expenditures. Initial hospital care costs an average of \$7,000 and the average cost for the first year postfracture is \$21,000. In 1995, hip-fracture treatment costs totalled \$8.68 billion.⁹ Vertebral fractures are also associated with an increase in mortality that is directly related to the number of fractures as documented on x-ray.

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1. Looker AC, Orwoll ES, Johnston CC Jr, et al. *J Bone Miner Res.* 1997;12(11):1769-1771.
 2. Riggs BL, Melton LJ III. *Bone.* 1995;17(Suppl 5):505S-511S.
 3. Ray NF, Chan JK, Thamer M, et al. *J Bone Miner Res.* 1997;12(1):24-35.
 4. Cooper C. *Am J Med.* 1997;103(2A):12S-17S.
 5. Lauritzen J, Lund B. *Acta Orthop Scand.* 1993;64(3):297-300.
 6. Cummings S, Black DM, Rubin SM. *Arch Intern Med.* 1989;149(11):2445-2448.
 7. Kanis JA, Delmas P, Burckhardt P, et al. *Osteoporosis Int.* 1997;7(4):390-406.
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 9. Johnell O. *Am J Med.* 1997;103(2A):20S-25S.
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Risk Factors

Peak bone mass affected by:

- Genetic factors
- Nutritional factors (e.g., calcium intake)
- Age of menarche and regularity of menstrual function
- Exposure to alcohol and tobacco
- Diseases contributing to bone loss:
inflammatory bowel disease, multiple myeloma,
lupus, rheumatoid arthritis
- Medications (e.g., glucocorticoids, excessive
amounts of thyroid hormone)

In females, the bone acquisition process is nearly complete by age 17; in males by age 20. Maximum BMD is achieved around age 28. Genetic factors are largely responsible for determining the level of peak bone mass. Nutritional factors (e.g., calcium intake), exercise patterns, age of menarche, regularity of menstrual function, and exposure to alcohol and tobacco also affect peak bone mass. At the time of menopause, all women lose bone. This bone loss is accelerated in the first five years after menopause but continues through the rest of life. Several factors can increase or decrease the rate of bone loss at this stage of life, including exercise, calcium and vitamin D intake, and smoking. A variety of diseases, such as inflammatory bowel disease, multiple myeloma, lupus, and rheumatoid arthritis, can contribute to bone loss. Certain medications, such as glucocorticoids and excessive amounts of thyroid hormone, can also increase bone loss.

Diagnosis

- Assess risk factors
- Bone mineral density (BMD) measurement (all women over 65, regardless of risk factors)
- Documentation of fractures
- Evaluation of possible secondary causes of bone loss

The diagnosis of osteoporosis requires the assessment of risk factors, measurement of bone mineral density, documentation of fractures, and an evaluation of potential secondary causes of bone loss. The National Osteoporosis Foundation recommends that all postmenopausal women age 65 or older have a bone mineral density test regardless of other risk factors or therapies being used at the time. The Foundation also recommends that postmenopausal women under the age of 65 who have one or more additional risk factors for osteoporosis, including secondary causes, should undergo a bone mineral density test. The most important of these risk factors include a history of fractures occurring with minimal trauma, a positive family history of osteoporotic fractures (especially a maternal history of hip fracture), current smoking, being very thin, and frequent falls.

Treatment: Risk Factor Reduction

- Eliminating smoking and alcohol abuse
- Optimizing nutritional status (calcium intake — 1200-1500 mg/day)
- Exercise regimen (weight-bearing, aerobic)

The first area to be considered in the management of osteoporosis is the reduction in risk factors. These may include eliminating smoking and alcohol abuse and optimizing nutritional status. Total daily calcium intake, from both diet and supplements, should be 1200-1500 mg. (The American diet typically provides 600 mg/day of calcium.) A daily intake of 400 IU of vitamin D (or up to 800 units in those over 65), will help maintain an optimal skeletal status. The management of osteoporosis should also include an exercise regimen. The exact prescription to be followed is not known, but it should include some weight-bearing, aerobic exercise program, such as running, calisthenics, dancing, stair climbing, or racquet sports. The goal is to strengthen the large muscle groups, with concentration on the back, shoulder, and hip musculature. In addition to helping maintain bone mass, exercise helps maintain muscle mass, which improves coordination and balance, thus reducing the risk of falling and fractures.

Treatment: Estrogen

- Documented benefits on bone mass in both early and late postmenopausal women
- WHI trial shows reduction in risk of hip fracture of 33% and in all fractures of 24%
- Risks exceed benefits with long-term use (25% increase in breast cancer risk)
- HRT can no longer be routinely recommended for long-term therapy

A large body of clinical trial data has shown that estrogen produces beneficial effects on bone mass in both early and late postmenopausal women and in women who have osteoporosis. A recent meta-analysis by Torgerson et al, which examined 22 studies, showed that the relative risk of nonvertebral fractures was reduced by 27% in estrogen-treated women compared with placebo-treated women.¹ The Heart and Estrogen/Progestin Replacement Study (HERS) is sometimes cited to strengthen the case against estrogen replacement as an effective treatment for osteoporosis.² This study, which used conjugated estrogens plus medroxyprogesterone, showed no beneficial effect of estrogen on hip or other fractures. By contrast, results from the aborted Women's Health Initiative (WHI) trial indicate that hormone replacement therapy (HRT) reduced the risk of hip fracture by 33% and all fractures by 24%, despite the fact that this group was not at particularly high risk for osteoporosis.³

Many patients refuse to consider estrogen therapy because of a fear of breast cancer. Results from the WHI trial confirm that HRT results in an increased risk of breast cancer of about 25%, even within the first five years of therapy.³ This translates into eight additional cases per 10,000 women per year. These results, which received extensive publicity in the lay as well as the professional press, suggest that HRT, particularly the Prempro™ formulation, can no longer be routinely recommended for long-term therapy.

1. Torgerson DJ, Bell-Syer SE. *JAMA*. 2001;285(22):2891-2897.

2. Grady D, Herrington D, Bittner V, et al. *JAMA*. 2002;288(1):49-57.

3. Lacey JV Jr, Mink PJ, Lubin JH, et al. *JAMA*. 2002;288(3):334-341.

Treatment: SERMs

- Produce some of estrogen's multisystemic effects
- May reduce risk of breast cancer
- Raloxifene is approved for osteoporosis; produces modest effects on bone density

The selective estradiol receptor modulators (SERMs) produce some of estrogen's multisystemic effects, but do not increase the risk of breast cancer. In fact, the SERMs studied to date, tamoxifen and raloxifene, appear to reduce the risk of breast cancer. Only raloxifene is currently approved for the prevention and treatment of osteoporosis. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, raloxifene was shown to produce modest effects on bone density and to produce reductions in bone turnover markers.¹ Raloxifene reduces the risk of vertebral fractures, although there are no data confirming that it reduces nonvertebral fractures. Other major effects of raloxifene to emerge from the MORE trial include significant reductions in the incidence of breast cancer and cardiovascular and cerebrovascular disease. Tamoxifen has been used as an adjuvant therapy for breast cancer for several decades; however, it is not suitable as a substitute for estrogen in the prevention or treatment of osteoporosis. Tamoxifen has strong estrogenic effects on the uterus, producing endometrial hyperplasia and possibly cancer, and anti-estrogenic effects on the brain.

1. Ettinger B, Black DM, Mitlak BH, et al. *JAMA*. 1999;282(7):637-645.

Treatment: Calcitonin

- Potent inhibitor of osteoclast function
- Produces rapid decrease in bone resorption
- Weaker effect on bone mass than other available agents
- PROOF study did not show reduction in vertebral fractures¹

Calcitonin is a 32-amino acid, single-chain peptide secretory product of neuro-endocrine C-cells located in the human thyroid gland. Calcitonin is a potent inhibitor of osteoclast function. There are two approved dosage forms, injectable (which is rarely used and is associated with nausea, vomiting, and flushing) and a nasal spray. After administration of calcitonin, there is a rapid decrease in bone resorption and hypocalcemia. However, good evidence of anti-fracture efficacy is difficult to find. Evidence from the PROOF study of nasal calcitonin is compromised by the fact that only 378 women completed the study out of 1255 enrolled.¹ In this study, a 400-unit dose of calcitonin nasal spray did not produce a significant reduction in vertebral fractures. Clearly, calcitonin produces a much weaker effect on bone mass than other agents for osteoporosis management.

1. Chesnut CH III, Silverman S, Andriano K, et al. *Am J Med.* 2000;109(4):267-276.

Treatment: Alendronate

- Most potent drug currently available for treatment of osteoporosis
- Inhibits osteoclast-mediated bone resorption
- FIT results:
 - new vertebral fractures reduced by 50%
 - hip fractures reduced by 56%¹
- Meta-analyses show consistent reductions in hip fractures of approximately 50%²

Alendronate is the most potent drug currently available for the treatment of osteoporosis. Like other bisphosphonates, it works primarily by inhibiting osteoclast-mediated bone resorption. The agent was studied in the Fracture Intervention Trial (FIT), a very large, randomized, controlled trial that included 6,459 participants and several years of observation.¹ All of the enrolled women had low hip bone mineral density scores (T-scores < -1.6). Women were randomized to receive either 5 mg/day (later increased to 10 mg/day) of alendronate or placebo. The women who received alendronate achieved substantial increases in bone mineral density (mean, 7%-9% at the spine and 5%-8% at the hip compared to placebo). Alendronate was also shown in this trial to reduce the risk of hip fracture by 56% by year four in women who had osteoporosis. The incidence of new vertebral fractures was reduced by 50%.¹ Meta-analyses of all of the clinical trials of alendronate showed consistent reductions in hip-fracture risk of approximately 50%, as well as significant reductions in the risk of vertebral and wrist fractures.²

In over 17,000 patients studied, alendronate has been found to be safe and generally well tolerated.

1. Cummings SR, Black DM, Thompson DE, et al. *JAMA*. 1998;280(24):2077-2082.

2. Karpf DB, Shapiro DR, Seeman E, et al. *JAMA*. 1997;277(14):1159-1164.

Treatment: Risedronate

- Produces moderate positive effects on hip and spine bone mass
- VERT studies show reduction in vertebral fractures of approximately 40%^{1,2}
- HIP study:
 - Hip fractures reduced by approximately 40% in women aged 70-79 who had severe osteoporosis
 - No reduction in hip fractures in women over 80 with risk factors but no proven osteoporosis³

Risedronate has been shown to produce moderate effects on bone mass in both the spine and hip and reduces the risk of fracture throughout the skeleton. The fracture data with this agent derive from three studies; two assessing vertebral fracture and all nonvertebral fractures and one looking primarily at hip fracture. In the two vertebral fracture (VERT) studies, risedronate reduced the risk of vertebral fractures by approximately 40% at three years.^{1,2} Benefits became apparent early, after 12 months, and were sustained for at least five years. Risedronate hip fracture data come from the Hip Intervention Program (HIP) study of over 9,000 women.³ This study included two patient groups; the first were women aged 70-79 who had severe osteoporosis (T-scores ≤ -4 or T-scores ≤ -3 with additional risk factors). In this group, there was a reduction in the incidence of hip fracture of approximately 40% by the third year (pooled data from patients receiving 2.5 mg/day and 5 mg/day). However, in the other group enrolled in the HIP study, women over 80 who had risk factors but no proven osteoporosis, there was no statistically significant reduction in hip fractures. The group tested may simply have been unusually healthy, which suggests that bone mineral density testing is an important predictor of the efficacy of osteoporosis therapy. In addition to the conflicting data from the HIP study, the VERT studies showed no effect on the occurrence of hip fractures. Although hip fracture was not a primary endpoint, the results are surprising and possible due to the high dropout rates seen in these studies.

1. Harris ST, Watts NB, Genant HK, et al. *JAMA*. 1999;282(14):1344-1352.

2. Reginster J, Minne HW, Sorensen OH, et al. *Osteoporosis Int*. 2000;11(1):83-91.

3. McClung MR, Guesens P, Miller PD, et al. *N Engl J Med*. 2001;344(5):333-340.

Treatment: Parathyroid Hormone (PTH)

- Principal regulator of calcium homeostasis
- Stimulates bone formation
- Used alone or in combination with antiresorptive agents
- Potent effect on fractures: reduction of 65-69% in vertebral fractures and 35-45% in nonvertebral fractures¹

Parathyroid hormone (PTH) is a principal regulator of calcium homeostasis. Therapeutically, PTH acts to stimulate bone formation; it increases bone mass and also seems to restore bone architecture by filling in cavities and cancellous bone caused by the bone loss process. PTH can cause large increases in bone mass both when given alone and when combined with antiresorptive agents. Clinical trials are now underway assessing the effectiveness of PTH in combination with bisphosphonates or raloxifene. PTH may receive FDA approval in late 2002 or 2003.

The largest study of PTH included 1,637 women with low BMD and an average of 2.3 fractures at baseline.¹ After a median treatment period of 18 months, PTH was shown to have a potent effect on fracture occurrence, with a reduction of 65% to 69% in the incidence of vertebral fractures and a reduction of 35% to 45% in all nonvertebral fractures. Back pain, nausea, and headache were the most common side effects; these occurred infrequently and were dose-dependent. Fewer than 5% had sustained increases in serum calcium above the normal range.

It is likely that antiresorptive agents will be required to maintain the bone mass and bone architecture benefits induced by PTH. It is also possible that the anti-fracture benefits of PTH and antiresorptive therapy will be additive.

1. Neer RM, Arnaud CD, Zanchetta JR, et al. *N Engl J Med.* 2001;344(19):1434-1441.

Case Study 1

1

- 52-year-old woman
- BMD score: -2.2
- Mother had early-onset osteoporosis
- Substantial menopausal symptoms

Case Study 1

A 52-year-old woman, approximately nine months from her last menstrual period complains of hot flashes, night sweats and irritability. She asks for a bone density test because her mother had very stooped posture from a very young age. The BMD score in the spine is determined to be -2.2 . This woman is clearly a very good candidate for estrogen or hormone replacement therapy.

She has no specific contraindications for hormone replacement therapy and has substantial menopausal symptoms. This is a major indication for the use of estrogens. Her bone density is in the osteopenic, or low bone mass range, and she requires therapy for prevention of bone loss because of this as well as her family history of presumed osteoporosis in her mother. The question will be how long estrogen should be used in this woman. We can no longer consider hormone replacement therapy as a treatment for the rest of a person's life. It is wise to continue to reevaluate the need for hormone replacement therapy and the evolving data concerning hormone replacement therapy on an annual basis.

Case Study 2

2

- 56-year-old woman
- Recent back pain
- Height loss of approximately 1"
- Mild vertebral wedging on x-ray
- BMD scores: -2.3 (spine); -1.5 (hip)
- Family history of breast cancer

Case Study 2

A 56-year-old woman recently developed back pain and acknowledged to her doctor that she had had approximately a one-inch height loss. Her x-ray did not show any clear abnormalities but there is a possibility that there is some mild or minimum wedging of one vertebra. Her doctor suggested a bone density test. The BMD score in the spine was -2.3 and in the hip was -1.5 . Her mother was recently diagnosed with breast cancer.

This 56-year-old woman is a classic case of a woman with early osteoporosis of the spine on x-ray. It is important that physicians review x-rays with radiologists, because sometimes mild wedging on x-ray may not be reported in a typical x-ray report. However, this may be an early sign of vertebral osteoporosis. Her bone density T-score is also nearly in the osteoporotic range of -2.5 or below and with the x-ray evidence as well as the low bone density score, she is certainly a good candidate for treatment of osteoporosis whether or not her back pain was really related to this wedging. Because her mother was recently diagnosed with breast cancer, she is probably not a good candidate for hormone replacement therapy. She is an excellent candidate for raloxifene, which not only reduces risk of vertebral fractures but may also reduce the risk of breast cancer in the future.

Case Study 3**3**

- 62-year-old woman
- Wrist fracture at age 54
- BMD score: -2.3 (hip); -2.0 (spine)
- No menopausal symptoms

Case Study 3

A 62-year-old woman receives a comprehensive medical interview from her internist. She tells the doctor that she had a wrist fracture at age 54 after a fall when she slipped on a patch of ice on her driveway. The physician orders a bone-density test which shows her T-score in the hip to be -2.3. The T-score in the spine is -2. However, there is an apparent artifact overlying at least one of the vertebrae. This is a classic case where the hip T-score should be used to determine the need for medical therapy in combination with the clinical history. This woman has a bone density nearly in the osteoporosis range and she also had an osteoporosis-related fracture of the wrist. The T-score in the spine should not be used to dissuade therapy, since it probably involves artifact and because the hip BMD is probably the preferential test in women of her age group or perhaps in all postmenopausal women. Therapy, in addition to general nutrition and exercise should be considered here and the treatment of choice is probably a bisphosphonate. This woman is not having any menopausal symptoms, so starting estrogens at this point in time after menopause would therefore not be the treatment of choice. And because she already had a wrist fracture and a low bone density in the hip, she is at risk for non-vertebral fractures. The only drugs that clearly reduce nonvertebral fractures are the bisphosphonates, so a good choice would be alendronate 70 mg once weekly; because this is the easiest and most practical regimen currently available for osteoporosis treatment.

Summary

- A variety of effective drugs available for the reduction of vertebral fractures
- Bisphosphonates also reduce the risk of nonvertebral fractures, especially hip fractures
- Diagnosis remains a challenge:
 - Only one in three women with vertebral fractures has been diagnosed¹
 - Optimal treatment requires diagnosis before first fracture

Summary

In summary, clinicians are fortunate today in having a variety of effective antiresorptive therapies that reduce the risk of vertebral fractures. The bisphosphonates also reduce the risk of nonvertebral fractures, including hip fractures. These drugs can dramatically reduce the disability, the quality of life changes, and the mortality associated with osteoporotic fractures. However, much remains to be done in the area of diagnosis. Only one in three women with vertebral fractures has been diagnosed.¹ Osteoporosis can be treated at any stage, but for optimal treatment, it is important that we identify women with osteoporosis prior to the occurrence of the first fracture.

1. Gold DT. *Bone*. 1996;18(Suppl 3):185S-189S.



15 PowerPoint slides on enclosed CD

