

METABOLIC BONE DISEASE AND OSTEOPOROSIS

Revised by Nancy Lane, MD and Elena Flagg, MD (2002)

Reviews

1) Favus MJ. Primer on the metabolic bone diseases and disorders of mineral metabolism. Fourth Edition. Lippincott Williams and Wilkins, Philadelphia, PA, 1999.

2) Lane NE. An update on glucocorticoid-induced osteoporosis. *Rheum Dis Clin North Am* 2001 Feb;27(1):235-53.

Topic review.

3) Wolf RL, Zmuda JM, Stone KL, Cauley JA. Update on the epidemiology of osteoporosis. *Curr Rheumatol Rep* 2000 Feb;2(1):74-86.

Update on epidemiology, recent advances and trends in the field.

BMD and fractures

4) Levis S, Altman RD. Bone densitometry: clinical considerations. *Arthritis Rheum* 1998;41:577-87.

Review of clinical relevance of bone densitometry

5) Cummings SR, Palermo L, Browner W, et al. Monitoring osteoporosis therapy with bone densitometry: misleading changes and regression to the mean. Fracture Intervention Trial Research Group. *JAMA*. 2000 Mar 8;283(10):1318-21.

Using the principle of "regression to the mean" the study showed that women who lose BMD during the first year of treatment with alendronate or raloxifene will gain BMD if the same treatment is continued for a second year.

6) Gregg, et al. Physical activity and osteoporotic fracture risk in older women. *Ann Intern Med* 1998; 129: 81-88.

Physical activity decreases the rate of hip fracture but not vertebral fractures in the elderly.

7) Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, Licata A, Benhamou L, Geusens P, Flowers K, Stracke H, Seeman E. Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001 Jan 17;285(3):320-3

Elderly women with a vertebral fracture are at substantial risk for an additional fracture within the next year.

Estrogen

Fractures:

8) Cauley J, Seeley DG, Ensrud K, et al. Estrogen replacement therapy and fractures in older women. (Study of Osteoporotic Fractures Research Group). *Ann Internal Med* **1995**; 122:9-16.

Current users of estrogen (started within 5yrs of menopause) had decreased risk of hip fractures (RR .29) compared to those women who had never taken estrogen. Most effective in women >75 yrs; little protective effect from long term (>10yrs) past use.

9) Stone K, Bauer CD, et al. Hormonal predictors of bone loss in the elderly.(SOF study) *J Bone Min Res* **1998**; 13:1167-74.

Postmenopausal women with higher endogenous estrogen have higher bone mineral density and lower vertebral fractures.

10) Grodstein F, Stampfer MJ, et al. Postmenopausal hormone therapy and mortality. *N Engl J Med*, **1997**; 336(25): 1769-1775.

11) Rosen CJ, Kessenich CR. The pathophysiology and treatment of postmenopausal osteoporosis; an evidence-based approach to estrogen replacement therapy. *Endocrinol Metab Clin North Am* **1997**;26:295-311.

Elaborates on the effects of estrogen on bone and the data supporting its use in the postmenopausal period.

12) Riggs BL, Khosla S, Melton LJ. A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. *J Bone Miner Res* **1998**;13:763-73.

Reviews the effects of estrogen on bone.

13) Cauley JA, Zmuda JM, Ensrud KE, Bauer DC, Ettinger B. Timing of estrogen replacement therapy for optimal osteoporosis prevention.(SOF). *J Clin Endocrin Metab* **2001** Dec;86(12):5700-5.

Early initiation and long-term continuation of estrogen is associated with a reduction in the risk of nonspine fractures, and initiation at or after age 60 yr with long-term continuation may also be associated with a reduced fracture risk.

Mortality, thrombosis, CVD, cancer risk

14) Grady D, Sawaya G, et al. Postmenopausal therapy increases risk of deep venous thrombosis and pulmonary embolism. *Am J Med*, **1998**; 105: 41-43.

Estrogen replacement therapy increases risk of DVT by 2-4X (risk in gen pop of women >50 is 0.16%/patient/year).

15) Schairer C, Lubin J, Troisi R, et al. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* **2000**; 283: 485-491.

16) Simon JA, Hsia J, Cauley JA, Richards C, Harris F, Fong J, Barrett-Connor E, Hulley SB. Postmenopausal hormone therapy and risk of stroke: The Heart and Estrogen-progestin Replacement Study (HERS). *Circulation* **2001** Feb 6;103(5):638-42.

Hormone therapy was not significantly associated with risk of nonfatal stroke (relative hazard [RH] 1.18; 95% CI 0.83 to 1.66), fatal stroke (RH 1.61; 95% CI 0.73 to 3.55), or transient ischemic attack (RH 0.90; 95% CI 0.57 to 1.42).

17) Grodstein F, Manson JE, Stampfer MJ. Postmenopausal hormone use and secondary prevention of coronary events in the nurses' health study. A prospective, observational study. *Ann Intern Med* **2001** Jul 3;135(1):1-8.

Raloxifene

18) Delmas P, Bjarnason N, Mitlack B, Ravoux AC, Shah AS, Huster WJ, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *NEJM* **1997**;337:1641-7.

A randomized trial of 601 postmenopausal women comparing raloxifene to placebo, showing raloxifene increases bone mineral density of the lumbar spine, total hip and femoral neck

19) Lufkin EG, Whitaker MD, Nickelsen T, et al. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. *J Bone Miner Res* 1998 Nov;13(11):1747-54.

20) Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. *JAMA* **1999** Jun 16;281(23):2189-97.

21) Lippman ME, Krueger KA, Eckert S, Sashegyi A, Walls EL, Jamal S, Cauley JA, Cummings SR. Indicators of lifetime estrogen exposure: effect on breast cancer incidence and interaction with raloxifene therapy in the multiple outcomes of raloxifene evaluation study participants. *J Clin Oncol* **2001** Jun 15;19(12):3111-6.

The MORE trial confirms that increased lifetime estrogen exposure increases breast cancer risk. Raloxifene therapy reduces breast cancer risk in postmenopausal osteoporotic women regardless of lifetime estrogen exposure, but the reduction is greater in those with higher lifetime exposure to estrogen.

Alendronate

22) Saag KG. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. *N Eng J* 339:292-299, **1998**.

23) Hochberg MC, Ross PD, Black D, Cummings SR, Genant HK, Nevitt MC, et al. Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. Fracture Intervention Trial Research Group. *Arthritis Rheum* **1999**;42:1246-54.

Study of 2,984 women with osteoporosis demonstrates benefit of alendronate. Points out the benefit of increasing bone mineral density on fracture risk.

24) Hosking D, Chilvers CED, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. *NEJM* **1998**; 338:485-492.

5mg of alendronate increased LS BMD 3 % and hip BMD 1.3% in two yrs in postmenopausal women < 60 yrs; estrogen increased LS BMD 4% and hip BMD 1.8%.

25) Schnitzer T, Bone HG, Crepaldi G, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. *Aging (Milano)* 2000 Feb;12(1):1-12
Weekly dosing as effective as biweekly and daily dosing on BMD.

26) Bone HG, Greenspan SL, McKeever C, et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. *J Clin Endocrinol Metab* 2000 Feb;85(2):720-6.

At 2yrs, lumbar spine BMD increased 6% with alendronate, 6% with estrogen, 8.3% with alendronate plus estrogen and loss of 0.6% in placebo group. Femoral neck increased 4.0%, 3.4%, 4.7%, and +0.3% for the alendronate, estrogen, alendronate plus estrogen, and placebo groups, respectively.

Residronate

27) Harris ST, Watts NB, Genant HK. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA* 1999 Oct 13;282(14):1344-52.

28) Fogelman I, Ribot C, Smith R, Ethgen D, Sod E, Reginster JY. Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. BMD-MN Study Group. J Clin Endocrinol Metab 2000 May;85(5):1895-900.

29) McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001 Feb 1;344(5):333-40.

Calcium/Vit D

30) Buckley LM, Leib ES, Cartularo KS, et al. Calcium and vitamin D3 supplement prevents bone loss in the spine secondary to low-dose corticosteroids in patients with rheumatoid arthritis. Ann Intern Med 1996;125:961-968.

Calcium and vitamin D supplementation prevented bone loss due to long term low dose corticosteroid treatment.

31) Reid IR. The roles of calcium and vitamin D in the prevention of osteoporosis. Endocrinol Metab Clin North Am 1998;27:389-98.

Reviews the effects of calcium and vitamin D in osteoporosis.

PTH

32) Lane NE, Sanchez S, Modin GW, et al. Parathyroid treatment can reverse corticosteroid-induced osteoporosis. J Clin Invest 1998; 102:1627-1633.

PTH increases LS BMD by 11% in women already receiving HRT.

33) Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001 May 10;344(19):1434-41.

Parathyroid hormone (1-34) decreases the risk of vertebral and nonvertebral fractures, increases vertebral, femoral, and total-body bone mineral density in postmenopausal women with osteoporosis.

Corticosteroid Osteoporosis

34) Wallach S, Cohen S, Reid DM, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. *Calcif Tissue Int* 2000 Oct;67(4):277-85

35) Buckley L, Greewald M, Hochberg M, Lane N, Lindsey S, Paget S, Saag K, Simon L. Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis -2001 Update. *Arthritis Rheum.* July 2001;44 (7); pg. 1496-1503.

Osteoporosis in men

36) Orwoll ES, Bevan L, Phipps KR. Determinants of bone mineral density in older men. *Osteoporos Int* 2000;11(10):815-21.

Identification of potential risk factors for osteopenia in males.

37) Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, Adami S, Weber K, Lorenc R, Pietschmann P, Vandormael K, Lombardi A. Alendronate for the treatment of osteoporosis in men. *N Engl J Med* 2000 Aug 31;343(9):604-10.

Alendronate significantly increases spine, hip, and total-body bone mineral density and helps prevent vertebral fractures and decreases in height in men with osteoporosis.

Misc.

38) Miller PD, Baran DT, Bilezikian JP, Greenspan SL, Lindsay R, Riggs BL, Watts NB. Practical clinical application of biochemical markers of bone turnover. *J Clin Densitometry* 1999;2:323-41.

Review of status of bone markers for osteoporosis and their indications.

39) Kong Y-Y, Yoshida H, Saros I, et al. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. *Nature* 397: 315-323,1999.

40) Ferrari SL, et al. Allelic variations in Il-6 determine degree of bone resorption in PMP women. *J Bone Min Res* 2000; 15: S162.