Osteoporosis in 2011: What's New and Clinically Relevant

Susan E. Brown, Ph.D.
Center for Better Bones
East Syracuse, NY
www. betterbones.com

Product development and educational materials consultant to Concordia Partners, LLC

Osteoporosis Basics

In the U.S. in 2005, of the nearly 2 million osteoporotic fractures:

- 27% were vertebral fractures
- 19% were wrist fractures
- 14% were hip fractures
- 7% were pelvic fractures
- 33% were “other fractures”

-Burge, R. et al. 2007. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025, *Journal of Bone and Mineral Research,* 22(3):465-475.

Osteoporosis Costs

- About $17 billion a year spent on treatment.

- Hip fractures account for 72% of total costs (and are 14% of all fractures).

-Burge, R. et al. 2007. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025, *Journal of Bone and Mineral Research,* 22(3):465-475.

Rethinking the Definition of Osteoporosis

In 1994, a WHO expert panel defined osteoporosis by Bone Mineral Density (BMD)

-World Health Organization (WHO). 1994. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Technical Report Series 843. WHO, Geneva.

Diagnostic Classification

Classification	T-score
Normal	-1 or greater
Osteopenia	Between -1 and -2.5
Osteoporosis	-2.5 or less
Severe/Established Osteoporosis	-2.5 or less and fragility fracture

Is the Earlier,1993 Definition of Osteoporosis More Valid?

In 1993, a U.S. Consensus Development Conference defined osteoporosis as:

"**A systemic skeletal disease characterized by low bone mass and architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fractures**"

-Diagnosis, prophylaxis, and treatment of osteoporosis. 1993. *American Journal of Medicine,* 94(6):646-650.

Limitations of Defining Osteoporosis by Bone Density

Overall,
Bone Mineral Density
Does Not Predict Fracture

Same BMD, Different Fracture Risk

The same bone mass in northern Europe is associated with substantially greater fracture risk than that in southern Europe.

-Heaney, R.P. 2000. *Osteoporosis International,* 11(Suppl 2):S43-S46.

BMD Takes on More Importance with Advancing Age

- In a 50 year old woman a -2.5 T-score is associated with a 1.7% risk of fracture.
- In a 75 year old women this same -2.5 BMD is associated with an 11.1% risk of fracture.

-Kanis, J.A. et al. 2005. Assessment of fracture risk. *Osteoporosis International* , 16(6):581-589.

Bone Mineral Density Limitations

- The US Study of Osteoporotic Fractures (SOF) looked at 8,065 women 65 and older.
- They reported that only 10 to 44% of osteoporotic fractures occurred in those women with an "osteoporotic bone density."

-Stone, K.L. et al. 2003. BMD at multiple sites and risk of fracture of multiple types: Long-term results from the study of osteoporotic fractures. *Journal of Bone and Mineral Research,* 18(11):1947-1954.

Bone Mineral Density Limitations

According to the National Osteoporosis Risk Assessment (NORA):

- more than two-thirds of hip fractures occur during the first year of follow-up in women (with an average age of 65 years) who were not deemed to be osteoporotic (they had osteopenia or normal BMD).

-Siris, E.S. et al. 2001. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. *JAMA*, 286(22):2815-2822.

European Data on BMD and Fracture Risk

- The SOTI and TROPOS trials found that **only 18% of all fractures occurred in women with an "osteoporotic" bone density.**

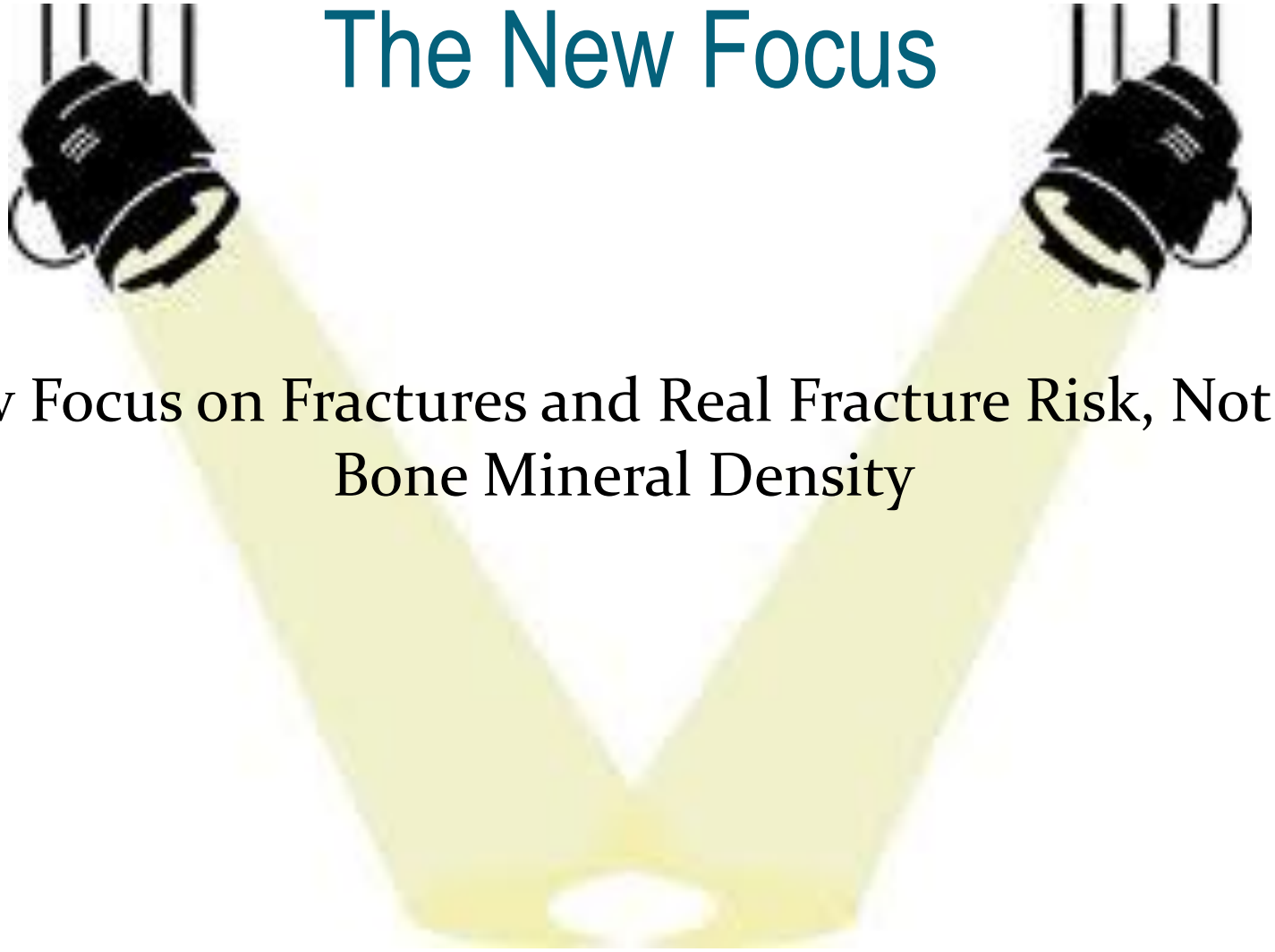
-Seeman, E., et al. 2008. Strontium ranelate reduces the risk of vertebral fractures in patients with osteopenia. *Journal of Bone and Mineral Research,* 23(3):433-438.

Bone Mineral Density Limitations

- As osteoporosis expert Robert Heaney has noted, "…low bone mass probably accounts for less than half of all osteoporotic fractures."
- And, he adds, the history of fracture after age 40 and maternal history of hip fracture are stronger fracture predictors than BMD and are independent of BMD.

Heaney, R.P. 2000. *Osteoporosis International* , 11(Suppl 2):S43-S46.

The New Focus

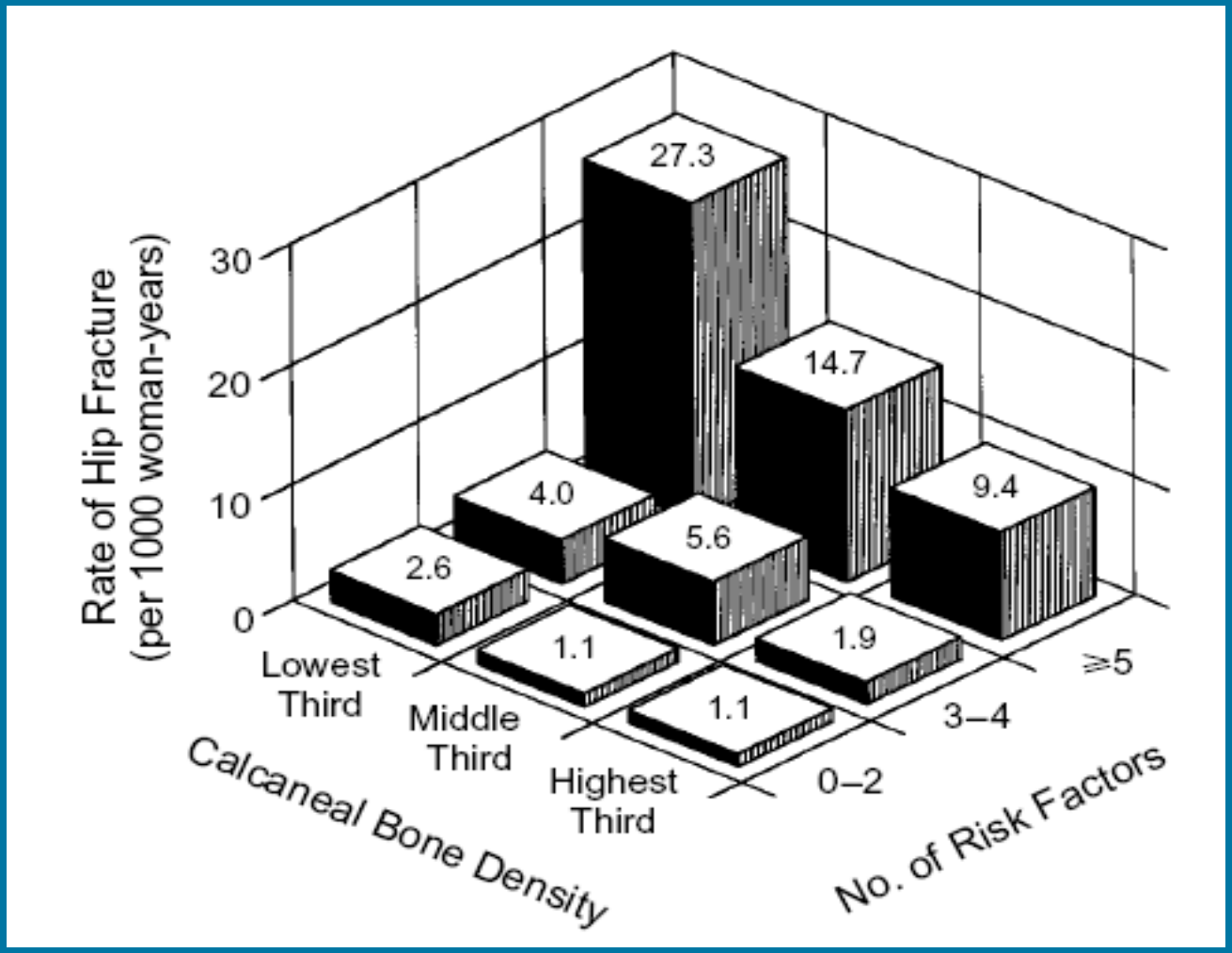


New Focus on Fractures and Real Fracture Risk, Not on Bone Mineral Density

The Importance of Multiple Risk Factors

Hip fracture risk was **17 times greater** among the **15 percent of the women** who had **five or more risk factors** (exclusive of bone density) than the 47 percent of the women with **two or fewer risk factors.**

-Cummings, S. R. et al. 1995. Risk factors for hip fracture in white women. *New England Journal of Medicine*, 332(12):767-73.



Annual Risk of Hip Fracture According to the Number of Risk Factors and the Age-Specific Calcaneal Bone Density

-Cummings, S. R. et al. 1995. Risk factors for hip fracture in white women. *New England Journal of Medicine*, 332(12):767-73.

The Total Load Model

FRAX® WHO Fracture Risk Assessment Tool

Home | Calculation Tool | Paper Charts | FAQ

Welcome to FRAX®

The FRAX® tool has been developed by WHO to evaluate fracture risk of patients. It is based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density (BMD) at the femoral neck.

Dr. John A Kanis
Professor Emeritus,
University of
Sheffield

The FRAX® models have been developed from studying population-based cohorts from Europe, North America, Asia and Australia. In their most sophisticated form, the FRAX® tool is computer-driven and is available on this site. Several simplified paper versions, based on the number of risk factors are also available, and can be downloaded for office use.

The FRAX® algorithms give the 10-year probability of fracture. The output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).

FRAX Risk Factors

- Age
- Sex
- Previous fracture
- Parent fractured hip
- Current smoking
- Glucocorticoids
- Rheumatoid arthritis
- Secondary osteoporosis
- Alcohol more than 3 units a day
- Femoral neck BMD
- Body or mass

FRAX Is Just a Beginning

Does not account for:

- Vitamin D levels and other nutritional factors
- Lifestyle factors
- Exercise factors
- Variety of other medical conditions, and secondary causes of osteoporosis
- Varity of medications that increase fracture risk
- Bone turnover markers

FRACTURE RISK & BONE HEALTH PROFILE

Here's a simple but reliable way to assess the health of your bones and your potential risk of fracture.

You'll also learn more about the lifestyle factors that contribute to the health of your bones, and to help you better understand your options for personal wellness.

First, are you at risk for a fracture?
Answer the following questions designed to assess your risk:

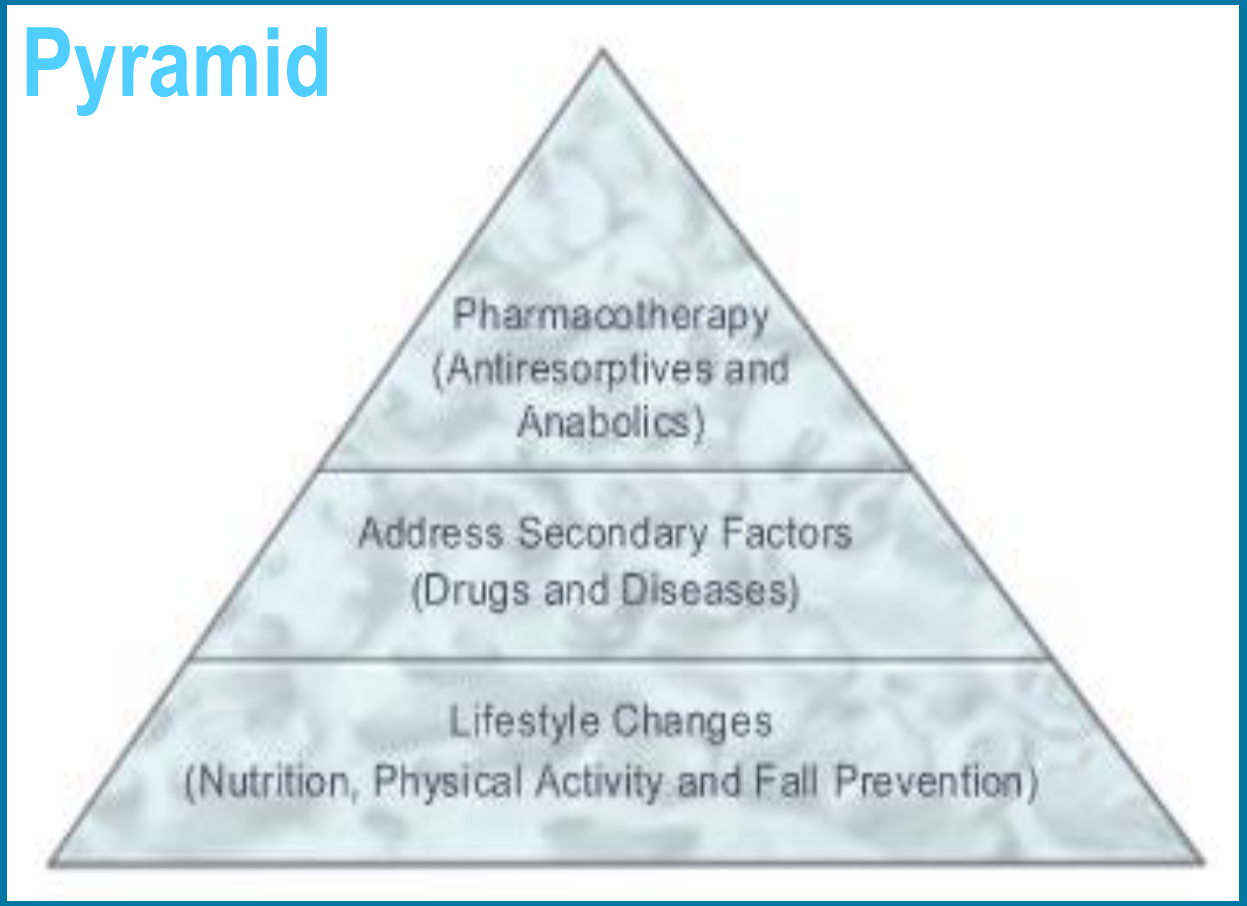
1	What is your gender?		○ Male	○ Female
2	Do you weigh less than 120 pounds?		○ Yes	○ No
3	Do you have weak muscles?		○ Yes	○ No
4	Do you worry or feel anxious a lot?		○ Yes	○ No
5	In the past year, have you been unhappy more often than happy?		○ Yes	○ No
6	Do you use anti-depressants?		○ Yes	○ No
7	Do you often use acid-blocking medications called proton pump inhibitors like Prilosec™ or Prevacid™?		○ Yes	○ No
8	Do you regularly use, or have you used over long periods of time, products containing steroids like Prednisone or steroidal inhalers?		○ Yes	○ No
9	Do you spend an average of 15 minutes per day outside in the sunlight with your arms exposed and without wearing sunscreen?		○ Yes	○ No
10	Do you consume at least 5 half cup servings of fruits and vegetables each day?		○ Yes	○ No
11	Do you drink more than two servings of alcohol each day?		○ Yes	○ No
12	Do you drink more than one serving of soda each day?		○ Yes	○ No
13	Do you drink more than two servings of coffee or other caffeinated beverages each day?		○ Yes	○ No
14	Are you perimenopausal or menopausal (men, please answer No to this question)?		○ Yes	○ No
15	If you answered Yes to question 14, how would you rate your menopause symptoms (e.g., hot flashes, night sweats, vaginal dryness, weight gain, insomnia, etc)?	○ Mild	○ Moderate	○ Severe

16	Are you a current smoker?	○ Yes	○ No
17	Have you experienced a bone fracture as an adult?	○ Yes	○ No
18	Has either of your parents fractured a hip?	○ Yes	○ No
19	Have you been told you have "osteopenia" or "osteoporosis" as the result of a bone density test?	○ Yes	○ No
20	Do you have on-going bone loss as documented by two or more consecutive bone density tests?	○ Yes	○ No
21	Have you lost and regained more than 15 pounds at least three times in your life?	○ Yes	○ No
22	Do you exercise less than 30 minutes per day, three days per week?	○ Yes	○ No
23	Have you lost half or more of your natural teeth?	○ Yes	○ No
24	Have you had three or more major surgeries in your life?	○ Yes	○ No
25	Do you have difficulty healing from injuries?	○ Yes	○ No
26	Do you suffer from joint pain and swelling?	○ Yes	○ No
27	Do you have difficulty falling asleep or staying asleep?	○ Yes	○ No

New Awareness Linked to New Practice Guidelines

- U.S. Surgeon General 2002 Osteoporosis Treatment Guidelines
- Osteoporosis Canada's 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada

U.S. Surgeon General's Osteoporosis Treatment Pyramid

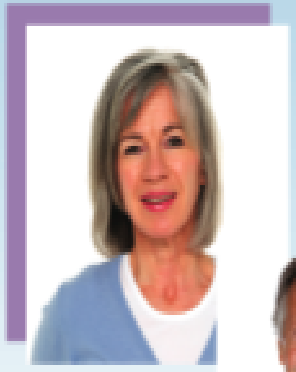


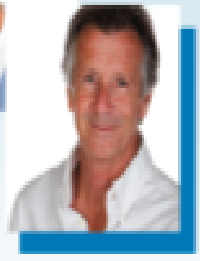
Source: U.S. Department of Health and Human Services. 2004. Bone health and osteoporosis: A report of the Surgeon General. U.S. Department of Health and Human Services, Office of the Surgeon General, Rockville, MD.

Osteoporosis Canada's 2010 Osteoporosis Clinical Guidelines

- Recommendations for Clinical Assessment:
  - History and physical exam
  - Recommendations for Biochemical Tests for Patients Being Assessed for Osteoporosis
  - Indications for BMD testing
    - Sorting out patients at high risk of fracture
  - Assessment of Basal 10 year Fracture Risk; 2010 CAROC System

(http://www.osteoporosis.ca/multimedia/guidelines.html)





Osteoporosis Canada

Ostéoporose Canada

Quick Reference Guide

2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada

This guide has been developed to provide healthcare professionals with a quick-reference summary of the most important recommendations from the **2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada**. For more detailed information, consult the full guideline document at www.osteoporosis.ca.

Recommendations for Clinical Assessment

Assessment	Recommended Elements of Clinical Assessment
History	☐ Identify risk factors for low BMD, fractures and falls: ☐ Prior fragility fractures ☐ Parental hip fracture ☐ Glucocorticoid use ☐ Current smoking ☐ High alcohol intake (≥3 units per day) ☐ Rheumatoid arthritis ☐ Inquire about falls in the previous 12 months ☐ Inquire about gait and balance
Physical Examination	☐ Measure weight (weight loss of >10% since age 25 is significant)
	☐ Measure height annually (prospective loss > 2cm) (historical height loss > 6 cm) ☐ Measure rib to pelvis distance ≤ 2 fingers' breadth ☐ Measure occiput-to-wall distance (for kyphosis) > 5cm] Screening for vertebral fractures
	☐ Assess fall risk by using Get-Up-and-Go Test (ability to get out of chair without using arms, walk several steps and return)

Recommended Biochemical Tests for Patients Being Assessed for Osteoporosis

- ☐ Calcium, corrected for albumin
- ☐ Complete blood count
- ☐ Creatinine
- ☐ Alkaline phosphatase
- ☐ Thyroid stimulating hormone (TSH)
- ☐ Serum protein electrophoresis for patients with vertebral fractures
- ☐ 25-hydroxy vitamin D (25-OH-D)*

**Should be measured after 3-4 months of adequate supplementation and should not be repeated if an optimal level ≥75 nmol/L is achieved.*

Indications for BMD Testing

Older Adults (age ≥ 50 years)

- All women and men age ≥ 65 years
- Menopausal women, and men aged 50-64 years with clinical risk factors for fracture:
  - Fragility fracture after age 40
  - Prolonged glucocorticoid use†
  - Other high-risk medication use*
  - Parental hip fracture
  - Vertebral fracture or osteopenia identified on X-ray
  - Current smoking
  - High alcohol intake
  - Low body weight (< 60 kg) or major weight loss (>10% of weight at age 25 years)
  - Rheumatoid arthritis
  - Other disorders strongly associated with osteoporosis such as primary hyperparathyroidism, type 1 diabetes, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (< 45 years), Cushing's disease, chronic malnutrition or malabsorption, chronic liver disease, COPD and chronic inflammatory conditions (e.g., inflammatory bowel disease)

Younger Adults (age < 50 years)

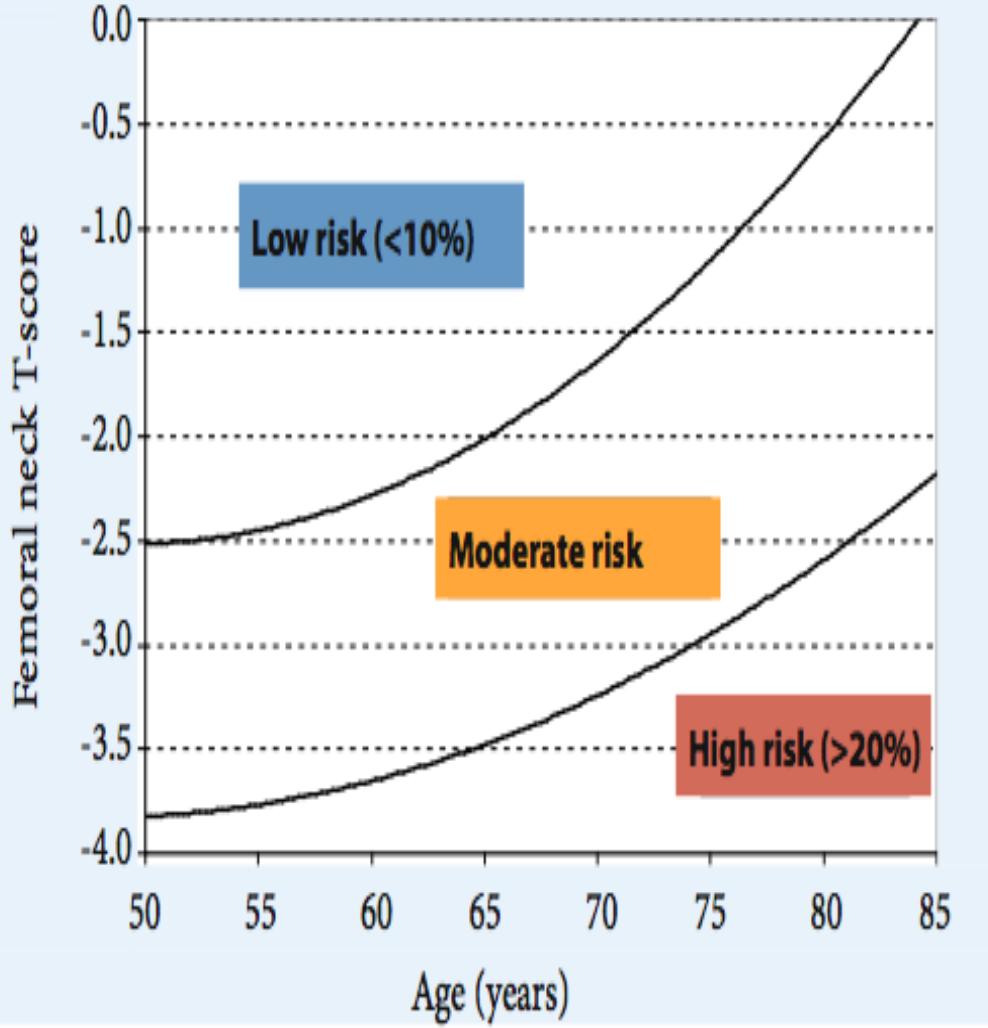
- Fragility fracture
- Prolonged use of glucocorticoids*
- Use of other high-risk medications†
- Hypogonadism or premature menopause
- Malabsorption syndrome
- Primary hyperparathyroidism
- Other disorders strongly associated with rapid bone loss and/or fracture

*†≥3 months in the prior year at a prednisone equivalent dose ≥7.5 mg daily; *e.g., aromatase inhibitors, androgen deprivation therapy.*

Assessment of basal 10-year fracture risk: 2010 CAROC* system

*Canadian Association of Radiologists and Osteoporosis Canada

Women

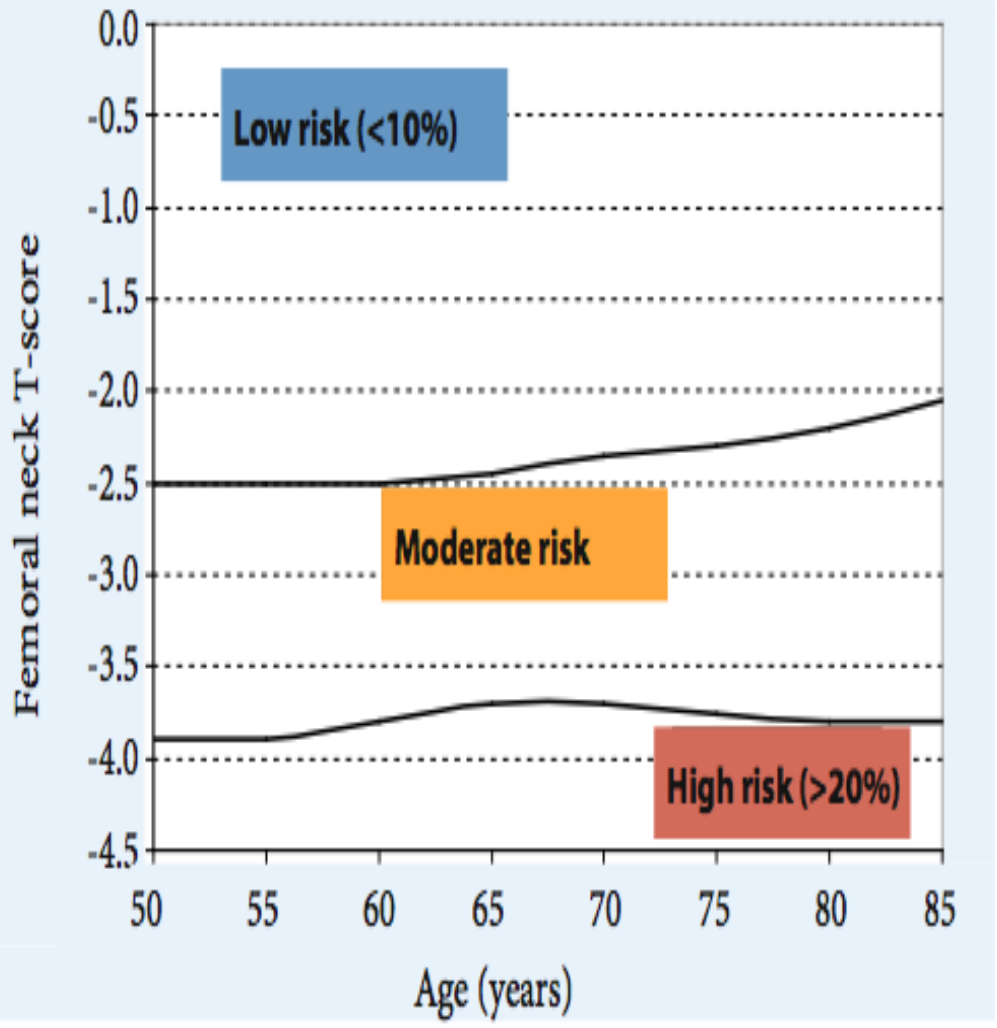


Age	Low risk	Moderate risk	High risk
50	above -2.5	-2.5 to -3.8	below -3.8
55	above -2.5	-2.5 to -3.8	below -3.8
60	above -2.3	-2.3 to -3.7	below -3.7
65	above -1.9	-1.9 to -3.5	below -3.5
70	above -1.7	-1.7 to -3.2	below -3.2
75	above -1.2	-1.2 to -2.9	below -2.9
80	above -0.5	-0.5 to -2.6	below -2.6
85	above +0.1	+0.1 to -2.2	below -2.2

Assessment of basal 10-year fracture risk: 2010 CAROC* system

*Canadian Association of Radiologists and Osteoporosis Canada

Men



Age	Low risk	Moderate risk	High risk
50	above -2.5	-2.5 to -3.9	below -3.9
55	above -2.5	-2.5 to -3.9	below -3.9
60	above -2.5	-2.5 to -3.7	below -3.7
65	above -2.4	-2.4 to -3.7	below -3.7
70	above -2.3	-2.3 to -3.7	below -3.7
75	above -2.3	-2.3 to -3.8	below -3.8
80	above -2.1	-2.1 to -3.8	below -3.8
85	above -2.0	-2.0 to -3.8	below -3.8

Tests for Secondary Causes of Osteoporosis Recommended by Osteoporosis Canada

- 25 (OH)D
- Calcium (corrected for albumin)
- Serum electrophoresis for those with vertebral fractures
- CBC
- Creatinine
- TSH
- Alk. Phosphatase

Additional Helpful Tests

- Ionized calcium and/or iPTH
- 24 hr. urine calcium
- C Reactive Protein
- Ovarian Hormones in premenopausal women
- Sex hormones in men
- Cortisol and DHEA
- Celiac's Disease Screening
- Questions about history of falling

The Better Bones Blog

By Dr. Susan E. Brown, PhD

Our neighbors to the north take the lead!

Recent changes to Osteoporosis Canada's 2010 Clinical Practice Guidelines mean that deciding who needs a bone medication will now depend on a multi-factorial fracture risk assessment, rather than on simple bone density testing. Canadian doctors will be looking at previous fractures, family history, alcohol use, smoking, and other factors including a physical exam to assess who needs bone medication. And doesn't this make good sense? It is well documented that **having multiple risk factors is a much more powerful predictor of fracture than low bone density**.

What this means is that fewer women in Canada are being classified as being at "high risk" of fracture and more are classified as being at "low" or "moderate" risk, as reported recently in the Annals of Internal Medicine. This is important because those at "high risk" of fracture are the most appropriate candidates for bone drugs. For lower risk patients, alternatives like exercise, fall prevention, and calcium and vitamin D supplementation are suggested. **The end result is that fewer Canadian women will be told to take osteoporosis medications.**

The move away from using bone drugs for low and moderate risk individuals is a progressive policy step I applaud. Over the years, I have noticed that Canadian osteoporosis agencies have taken a commendable science-based, public-interest approach to the burden of needless fragility fractures. Now, once again, our neighbors to the north take the lead — this time in the implementation of a more rational way to decide who should be given drugs for their bones.

Medical History That Increases Fracture Risk

Congenital porphyria	Hyperparathyroidism
Female athlete triad (disordered eating, amenorrhea, and osteoporosis)	Idiopathic scoliosis
Inadequate diet	Rheumatoid arthritis
Inflammatory bowel disease	Several liver disease, especially primary biliary cirrhosis
Insulin-dependent diabetes mellitus	Spinal cord transection
Lymphoma and leukemia	Celiac's disease
Malabsorption syndromes (ex., lactose intolerance)	Stroke (cerebrovascular accident)
Mastocytosis	Thalassemia
Multiple myeloma	Thyrotoxicosis
Multiple sclerosis	Tumor secretion of parathyroid hormone-related peptide
Pernicious anemia	Weight loss

New Link Found Between Osteoporosis And Celiac Disease

ScienceDaily (Oct. 8, 2009) — People with celiac disease may develop osteoporosis because their immune system attacks their bone tissue, a new study has shown.

See Also:

Health & Medicine

- Osteoporosis
- Women's Health
- Chronic Illness
- Bone and Spine
- Leukemia
- Diseases and Conditions

It is the first time an autoimmune response – a condition whereby the body can attack itself – has been shown to cause damage to bones directly.

Researchers from the University of Edinburgh studied a protein called osteoprotegerin (OPG) in people with celiac disease – a digestive condition that affects 1 in 100 people.

Medications That Increase Fracture or Osteoporosis Risk

Aluminum (ex., aluminum-containing antacids)	Immunosuppressants
Glucocorticosteroids and adrenocorticotropin	Tamoxifen (premenopausal use)
Gonadotropin-releasing hormone agonists	Thyroxine (at supraphysiologic doses)
Heparin (long-term use)	Total parenteral nutrition
Nexium, Dexilant, Prilosec, Zegerid, Prevacid, Protinix, Aciphex, and Vimovo	Proton Pump Inhibitors
Carbamazepine, Clonazepam, Gabapentin, Phenobarbital, and Phenytoin	Antiepileptic Drugs
Thiazolidinediones (rosiglitazone & pioglitazone), Avandia, Actos, and loop diuretics (lasix or bumex)	Diabetes Drugs

Anti-Depressants Double Fracture Risk

- Canadian 5-year CaMos study done in 50-year plus subjects.
- Selective serotonin reuptake inhibitor (SSRI) **use for at least five years was associated with twice the risk of wrist, ankle, hip and other fractures**.
- Bone density 4% lower in hip and 2.4% lower in spine.

-Richards, J.B. et al. 2007. Effect of selective serotonin reuptake inhibitors on the risk of fracture. *Archives of Internal Medicine*, 167(2):188-194.

Acid Blockers Increase Fracture Risk

British study of 13,556 individuals 50 and older:

- Those using PPIs (proton pump inhibitors) in high doses for **more than a year** were **2.6 times more likely to fracture a hip than non-users.**
- Modest doses of PPIs used regularly for 1-4 yrs increase risk 1.2 to 1.6 times.

-Yang, Y.X. et al. 2006. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA,* 296(24):2947-2953.

Steroids

It is estimated that 4 million cases of osteoporosis in the United States, or 20% of the total number, are attributable to corticosteroid use.

-American College of Rheumatology Task Force on Osteoporosis Guidelines. 1996. Recommendations for prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis and Rheumatism*, 39(11):1791-1801.

Endogenous Cortisol

- The body's own production of cortisol can contribute to osteoporosis.
- Cushing's Disease increases risk for osteoporosis and bone fractures.
- Even in "normal, healthy people" (34 "healthy" men ages 61 to 72 years), bone density was inversely correlated with cortisol levels.

-Dennison, E. et al. 1999. Profiles of endogenous circulating cortisol and bone mineral density in healthy elderly men. *Journal of Clinical Endocrinology and Metabolism,* 84(9):3058-3063.

Bone Specialist

- An attitude of worry, even just worrying about eating and the possibility of weight gain, increases cortisol and decreases bone mass.
- Worried thoughts lead to bone weakening.

-2010 interview with Jerilynn C. Prior, MD, www.betterbones.com

Ancient Insights on Stress

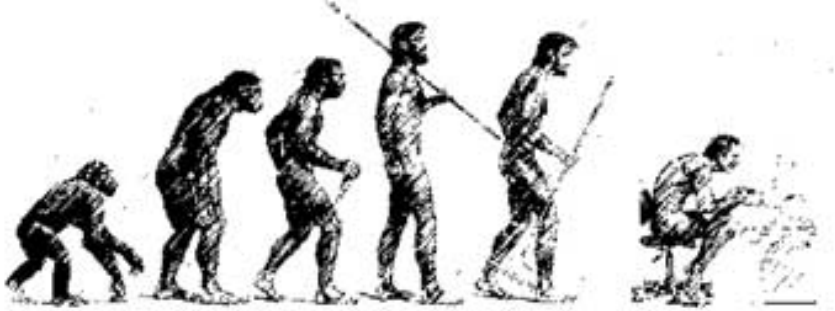
- A cheerful look brings joy to the heart, and good news gives health to the bones. (Proverbs 15:30)

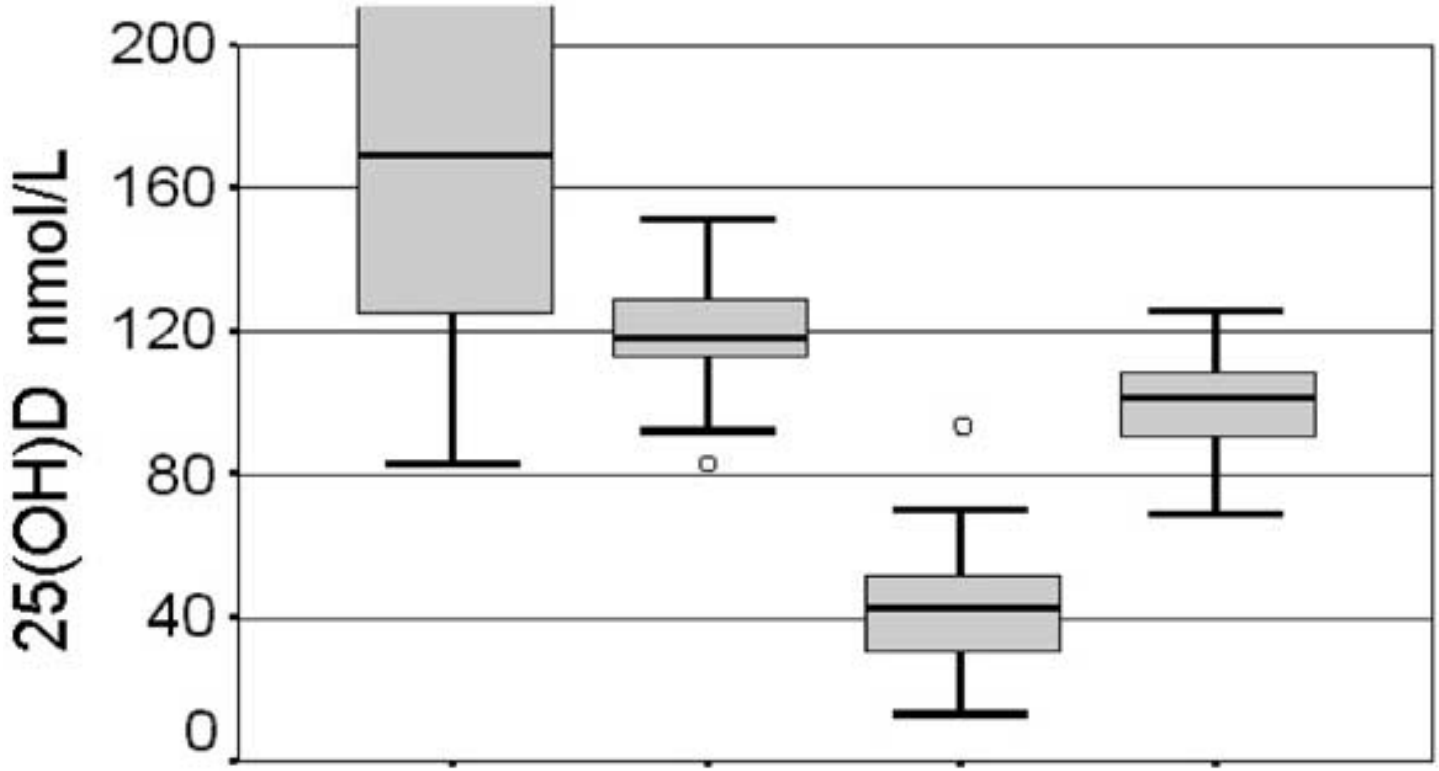
- A merry heart is like a medicine, but a broken spirit drieth the bones. (Proverbs 17:22)

Nutrition Factors and Fracture Risk: What's New?

- Vitamin D: More Important Than Imagined
- Calcium: New Twists on Old Story
- Vitamin K: A New Player

Vitamin D: What's New and Clinically Relevant?




25(OH)D nmol/L
200
160
120
80
40
0
Non-Human Primates
Modern Adults with Abundant Skin-Surface to Sun Exposure
Normal Modern Adults in Winter
Latitude 43°N
Modern Adults on Long-term Oral Vitamin D, 100 µg/day (4000 IU/day)

Vitamin D and Fractures

- Meta-analysis by Papadimitropoulos and colleagues looked at vitamin D studies (using varying doses of vitamin D and varied populations).

- As a whole, with vitamin D intervention:

  Vertebral fractures reduced by 37%.
  Non-vertebral fractures reduced by 23%.

- Papadimitropoulos, E., et al. 2002. VIII: Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. *Endocrinology Review*, 23:560-569.

Vitamin D & Fracture Reduction

Boston community-dwelling residents, 65 yrs+, 3-yr study, no selection by risk, N 389. Study of non-vertebral factures. Intervention with 700 IU D_3 and 500 mg calcium.

Result:

- Non-vertebral factures reduced by 50%.
- One hip fracture in placebo group out of 276 new fractures.

-Dawson-Hughes, B. et al. 1997. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *New England Journal of Medicine,* 337(10): 670-676.

Only 2 Studies Used 700-800 IU Vitamin D_3 and Calcium

French nursing home residents:

- Non-vertebral fractures reduced by 32%.
- 43% fewer hip fractures.

-Chapuy, M.C. et al. 1992. Vitamin D_3 and calcium to prevent hip fractures in elderly women. *New England Journal of Medicine,* 327(23):1637-1642.

Vitamin D Repletion Reverses Osteopenia in Vitamin D Deficient Women

- 12 subjects with low vitamin D (14ng/ml or less) and hip BMD –1.5 SD or greater
- Given 50,000 IU D_2 2x/wk for 5 weeks (total of 500,000 IU D_2), and 1,000 mg calcium carbonate.
- Vitamin D level went up to 24 ng/ml.
- **Significant 4-5% annualized increase in bone mineral at spine and femoral neck.**
- **Reversal of osteopenia.**

-Adams, J. S., et al. 1999. Resolution of vitamin D insufficiency in osteopenic patients results in rapid recovery of bone mineral density. *Journal of Clinical Endocrinology and Metabolism,* 84:2729-2730.

Institute of Medicine Vitamin D Guidelines 2011

Raising the RDA:

- Tripled the RDA for ages 1 to 70
  200 IU to 600 IU a day
- Doubled the RDA for those 71 and older
  400 IU to 800 IU a day
- Doubled recs from birth to 1 year
  200 IU to 400 IU

http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx

Institute of Medicine Vitamin D Guidelines 2011

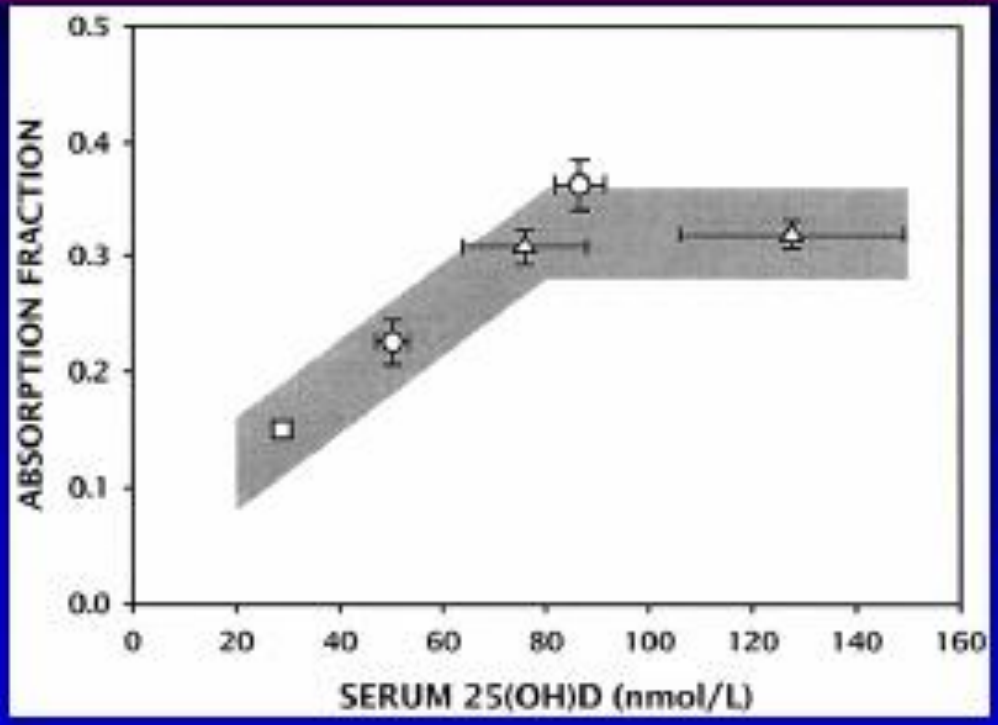
New Upper Tolerable Level:

Doubled from 2000 IU to 4000 IU for all over 9 years of age

http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx

Calcium: What's New and Clinically Relevant?

Relation between Serum 25(OH)D and Calcium Absorption in Vitamin D Insufficiency



Calcium absorption fraction as a function of serum 25(OH)D3 concentrations (combined results of 3 studies)

□ Bischoff et al. J Bone Miner Res 2003; 18: 343–51.

○ Heaney et al. J Am Coll Nutr 2003; 22: 142–6.

△Barger-Lux et al. J Clin Endocrinol Metab 2002;87:4952–6.

Error bars indicate ± 1 SEM

From Heaney RP Am J Clin Nutr 2005; 80: 1706S-9S.

Calcium Absorption and Vitamin D

- In a vitamin D deficient state, the small intestine absorbs no more than 10 -15% of dietary calcium.
- In a vitamin D sufficient state, the small intestine absorbs 30-40% of dietary calcium.

Bischoff, H.A. et al. 2003. Effects of vitamin D and calcium supplementation on falls: A randomized controlled trial. *Journal of Bone and Mineral Research,* 18(2):343-351.

Heaney, R.P. et al. 2003. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. *Journal of American College of Nutrition,* 22(2):142-146.

Barger-Lux, M.J. and R.P. Heaney. 2002. Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. *Journal of Clinical Endocrinology and Metabolism,* 87(11):4952-4956.

Calcium: High Intake Does Not Prevent Fracture

- Pooled results from prospective cohort studies suggest that dietary calcium intake is not significantly associated with hip fracture risk in women or men.

-Bischoff-Ferrari, H.A. et al. 2007. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. *American Journal of Clinical Nutrition,* 86:1780-1790.

Calcium: High Intake Does Not Prevent Fracture

- Pooled results from randomized controlled trials show no reduction in hip fracture risk with calcium supplementation and an increased risk is possible. For any non-vertebral fractures, there was a neutral effect in the randomized trials.

-Bischoff-Ferrari, H.A. et al. 2007. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. *American Journal of Clinical Nutrition,* 86:1780-1790.

Calcium: Needed Less Than Expected

- Data from the U.S. National Health and Nutrition Examination Survey (NHANES 111) published early 2009 found that calcium intakes of **566 mg per day** among women and **626 mg per day** among men are likely adequate for those not burdened by low vitamin D levels.

-U.S. National Health and Nutrition Examination Survey (NHANES 111), 2009.

-Bischoff-Ferrari, H.A., et al. 2009. Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U.S. adults. *Journal of Bone and Mineral Research*, 24(5):935-942.

)

U.S. National Health and Nutrition Examination Survey, 2009

- Among women with low vitamin D levels (20 ng or less) there was a positive association between calcium intake and bone density.
- Among men, calcium intake was not associated with bone density at any vitamin D level studied.

-U.S. National Health and Nutrition Examination Survey (NHANES 111), 2009.

-Bischoff-Ferrari, H.A., et al. 2009. Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U.S. adults. *Journal of Bone and Mineral Research*, 24(5):935-942.

High Calcium Intake May Be Problematic

The calcium-vascular calcification link:

The calcium link to vascular calcification has long been seen in patients with CKD given calcium phosphate to control hyperphosphatemia.

Calcium Supplementation: CVD Link in Osteoporosis

- New research from New Zealand by Bolland and colleagues in 2008 with 1,471 postmenopausal women given a gram of calcium citrate for 5 yrs.
- Results of this and other studies by Boland et al. suggest a modest increase in risk of cardiovascular events with calcium supplementation.

-Miller, P.D. 2011. Vitamin D, calcium and cardiovascular mortality: A perspective from a plenary lecture given at the Annual Meeting of the Am. Assoc. of Clinical Endocrinologists. DOI: 10.4158/EP11203.RA

High Calcium–CVD Link Is Controversial

The IOM, however, in their 2010 review of the literature concluded that:

> "Overall the majority of analysis showed no significant association between calcium intake and CV events."

IOM Calcium Intake Guidelines 2011

- 1,200 mg/day
  for women 51 years and older
- 1,000 mg/day for men ages 50-70
- Safe Upper Limit of 2,000-3,000mg/day

http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx

Is Vitamin K . . . the Missing Link?

- Could it be that low vitamin K levels increase the risk of arterial calcification found with calcium supplementation?
- Is the vitamin K dependent protein GLA part of the answer?

The Function of All Forms of Vitamin K

- Serve as co-factor or carboxylation of certain protein-bound glutamate residues. These are converted into GLA (gamma-carboxy glutamate).
- GLA residues form calcium-binding sites essential for activity of the protein in which they are found.
- With adequate Vitamin K, GLA residues are properly carboxylated.

GLA containing proteins include:

- Blood coagulation factors synthesized in liver.
- Osteocalcin, synthesized in the bone: Undercarboxylated osteocalcin is a known risk factor for fracture.
- Matrix GLA primarily synthesized in cartilage and in the vessel wall.

Undercarboxylated matrix GLA contributes to arterial calcification.

-Adams, J. and J. Pepping. 2005. Vitamin K in the treatment and prevention of osteoporosis and arterial calcification. *American Journal of Health-System Pharmacy*, 62(15):1574-1581.

.

Vitamin K and Osteoporosis

- Vitamin K is required to manufacture osteocalcin (via the vitamin K dependent carboxylation of glutamic acid into gamma-carboxlyglutamic acid, GLA).
- Osteocalcin is a unique GLA protein found in bone that attracts calcium to sites of bone crystallization.
- Without adequate vitamin K, osteocalcin is not adequately carboxylated and bone mineralization is impaired.
- Without adequate vitamin K, bone is weak and more susceptible to low-trauma fracture.

Iwamoto, J. et al. 2009. High-dose vitamin K supplementation reduces fracture incidence in postmenopausal women: a reviewof the literature. *Nutrition Research,* 29(4):221-228.

Vitamin K and Arterial Calcification

- When GLA is again properly carboxylated (by adequate supply of vitamin K) there is a strong inhibition of calcium deposition in the walls of blood vessels.
- When GLA is undercarboxylated (due to low vitamin K supply) calcium is allowed to drift from bone into arteries and other soft tissue. These calcium deposits in the artery increase the risk of heart attack.

-Braam, L. et al. 2004. Beneficial effects of vitamins D and K on the elastic properties of the vessel wall in postmenopausal women: a follow-up study. *Thrombosis and Haemostasis,* 91(2):373-380.

Vitamin K and Arterial Calcification

- Vitamin K dependent matrix GLA when fully activated is one of the most potent inhibitors of arterial calcification.
- Circulating levels of inactive matrix GLA protein has been proposed as a biomarker for cardiovascular calcification.

-Cranenburg, E., et al. 2008. The circulating inactive form of matrix GLA protein (ucMGP) as a biomarker for cardiovascular calcification. *Journal of Vascular Research,* 45:427-436.

-Braam, L. et al. 2004. Beneficial effects of vitamins D and K on the elastic properties of the vessel wall in postmenopausal women: a follow-up study. *Thrombosis and Haemostasis,* 91(2):373-380.

Dietary Vitamin K Reduces Arterial Calcification

- Population studies show aortic calcification, myocardial infarction, and CV mortality are inversely associated with the intake of Vitamin K, notably as K2.

-Geleijnse, J.M. et al. 2004. Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: The Rotterdam study. *Journal of Nutrition,* 134:3100-3105.

Supplementation with Vitamin K2 Reduces Arterial Calcification

Rat study in Netherlands from the Cardiovascular Research Institute:

- Induced arterial calcification with vitamin K antagonist warfarin.
- Rats given high amount of vitamin K experienced a 50% reduction in arterial calcium content, and dispensability was restored.

-Schurgers, L.J. et al. 2007. Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. *Blood,* 109(7):2823-2831.

Vitamin K and Fracture Risk

Higher Level Vitamin K Reduces Fracture Risk

- The large European EPIDOS Study found under-carboxylated osteocalcin (the measure of vitamin K adequacy) to be a major independent risk factor for hip fracture among healthy elderly women.
- Further, those women with both low BMD and high ucOC had a 5.5 risk of hip fracture, as compared to those with only low BMD or high ucOC levels.

-Vergnaud, P. et al. 1997. Undercarboxylated osteocalcin measured with a specific immunoassay predicts hip fracture in elderly women: the EPIDOS study. *Journal of Clinical Endocrinology and Metabolism*, 82(3):719-724.

Higher Level Vitamin K Reduces Fracture Risk

- This study of elderly French institutionalized women found ucOC, but not conventional calcium metabolism parameters, predicts the subsequent risk of hip fracture.

-Szulc, P. et al. 1993. Serum undercarboxylated osteocalcin is a marker of the risk of hip fracture in elderly women. *Journal of Clinical Investigation*, 91(4): 1769-1774.

Preventing Fractures with Vitamin K2 as MK-4

Extensive Japanese research was done using 45 mg of synthetic MK-4 daily to treat osteoporosis and prevent fracture.

-Cockayne, S. et al. 2006. Vitamin K and the prevention of fractures: Systematic review and meta-analysis of randomized controlled trials. *Archives of Internal Medicine*, 166:1256-1261.

Meta-Analysis of Vitamin MK-4 and Fracture Reduction

7 RCTs using MK-4 (6 using 45 mg and 1 using 15 mg):

- 77% reduction in hip fractures
- 60% reduction in vertebral fractures
- 81% reduction in all non-vertebral fractures

-Cockayne, S. et al. 2006. Vitamin K and the prevention of fractures: Systematic review and meta-analysis of randomized controlled trials. *Archives of Internal Medicine*, 166:1256-1261.

Bone Drug Therapy: What's New?

- Rethinking real benefits
- Realizing real risks seen over the long haul
- New suggestion to reserve bone drugs for those at high risk of fracture

Rethinking Benefits of Bone Drugs

Pooled data from 31 bisphosphonate drug studies, involving a total of 376,134 post-menopausal women:

- **Overall, the total "real world" fracture reduction potential of this leading class of osteoporosis drugs was 22%.**

-Wilkes, M.M. et al. 2010. Bisphosphonates and osteoporotic fractures: a cross-design synthesis of results among compliant/persistent postmenopausal women in clinical practice versus randomized controlled trials. *Osteoporosis International*, 21(4):679-688.

Possible Fracture Risk With Osteoporosis Drugs

Search Consumer Updates

go

Get Consumer Updates by E-mail

Consumer Updates RSS Feed

Printer-friendly PDF (332 KB)

The Food and Drug Administration (FDA) is warning there is a possible risk of a rare type of thigh bone (femoral) fracture in people who take drugs known as bisphosphonates to treat osteoporosis.

The agency warned patients and health care professionals of this risk on Oct. 13, 2010, because the rare type of femoral fracture has been predominantly reported in patients taking these prescription medications.

FDA says the possible risk of thigh fracture will be reflected in a labeling change for bisphosphonate medications that treat osteoporosis and in a medication guide that will be required to be given to patients when they pick up their prescription.

Bisphosphonates are a class of drugs that slow or inhibit the loss of bone mass. They have been used successfully since 1995 to prevent and treat osteoporosis and similar diseases. Osteoporosis is a disease in which the bones become weak and are more likely to break.

FDA says it is not clear whether bisphosphonates are the cause of the unusual bone breaks known as subtrochanteric femur fractures, which occur just below the hip joint, and diaphyseal femur fractures, which occur in the long part of the thigh.

Medication Guide, Labeling Change

The changes to labeling and the medication guide will affect only bisphosphonates approved for osteoporosis. These include

- oral bisphosphonates such as Actonel, Actonel with Calcium, Atelvia, Boniva, Fosamax, Fosamax Plus D, and their generic products
- injectable bisphosphonates such as Boniva and Reclast and their generic products

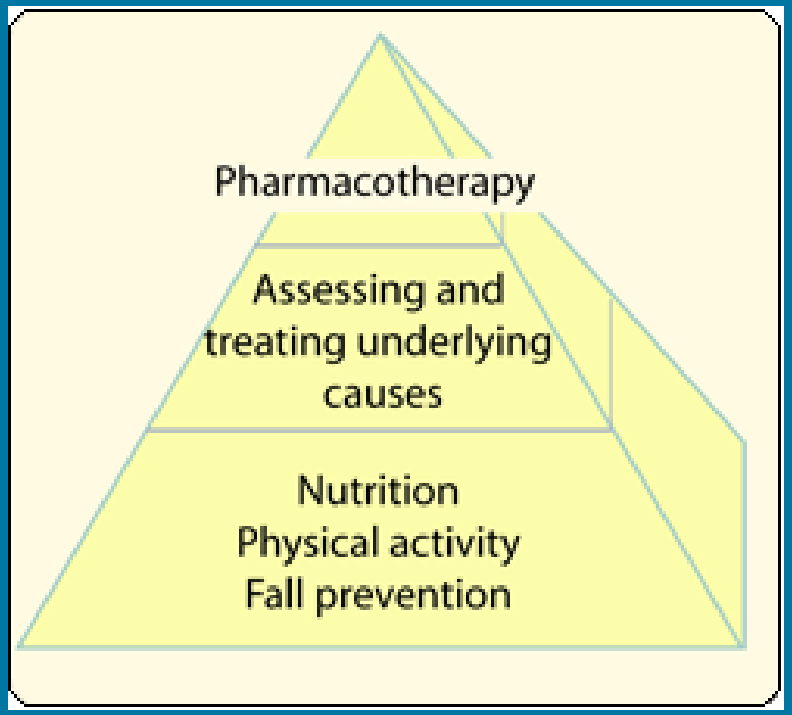
Labeling and the medication guides for bisphosphonates that are used for other conditions will not change.

FDA says the optimal duration of bisphosphonates treatment for osteoporosis is unknown—an uncertainty the agency is highlighting because these fractures may be related to use of bisphosphonates for longer than five years.

FDA medical officer Theresa Kehoe, M.D., says the agency continues to evaluate data about the safety and effectiveness of bisphosphonates when used long-term for osteoporosis treatment.

"In the interim, it's important for patients and health care professionals to have all the safety information available when determining the best course of treatment for osteoporosis," she says.

Reserving Bone Drugs for Those at High Risk



- Thrust of the New Osteoporosis Canada Guidelines
- In some countries bone drugs are given only after first fracture
- Associated with increased attention to initial fractures and the prevention of recurrent fractures

Bisphosphonates More Effective with Adequate Vitamin D

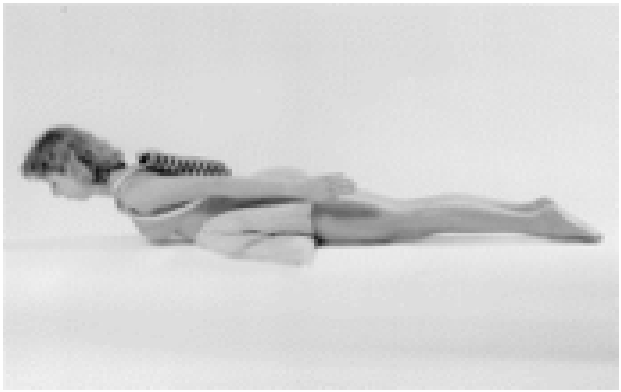
- Women whose 25(OH)D was at least 33 ng were almost 5x more likely to benefit from bisphosphonates.

-Carmel, A. et al. 2011. ASBMR Annual Meeting, Abstract 1137.

The Better Bones Blog

By Dr. Susan E. Brown, PhD

Stronger back muscles can lower future fracture risk



From Sinaki M, Wahner HW, Offord KP, Hodgson SF. Efficacy of nonloading exercises in prevention of vertebral bone loss in postmenopausal women: a controlled trial. Mayo Clin Proc. 1989;64(6):762-769. Used with permission.

Exercise builds muscle and bone, but the benefits are held to disappear upon exercise cessation — or so it appeared, anyway. A recent exercise study from the Mayo Clinic, however, **documented powerful spinal fracture reduction eight years after cessation of a back strengthening program**. Eight years after stopping this two-year exercise program, past exercisers had significantly greater bone density, and nearly a 2.7 times lower vertebral compression fracture incidence, than non-exercising controls.

This study found that **healthy postmenopausal women can reduce their 10-year risk of vertebral fracture by nearly 300% with one simple back exercise performed 5 days a week**. As suggested by this study, back-strengthening exercise is far more effective at reducing spinal fracture than any drug therapy and is totally safe — a true Better Bones, Better Body® Approach. Let's look at the study in detail.

Thank You