The ABC's of Vitamin D

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Conflicts of Interest

I receive research grants and/or consulting fees from the following companies:

Amgen	**Pfizer**
Lilly	**Procter & Gamble**
Merck	**Roche**
Novartis	**sanofi-aventis**
	Wyeth

I will not discuss off-label use of medications

Michael McClung, MD October 2007

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Objectives

At the end of the session, attendees will know

1. **the consequences of vitamin D deficiency on bone metabolism and fracture risk**
2. **the effectiveness of vitamin D supplementation on fracture risk in older adults**
3. **the indications for measurement of serum vitamin D levels**
4. **the current recommendations for vitamin D supplementation to optimize bone health**

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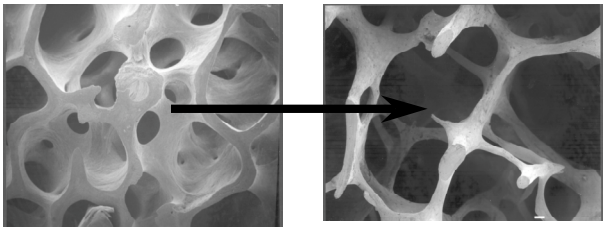
Osteoporosis: The Definition

- **impaired bone strength**
  - **low BMD**
  - **poor bone quality**
- ***increased fracture risk***
- **due to bone loss**



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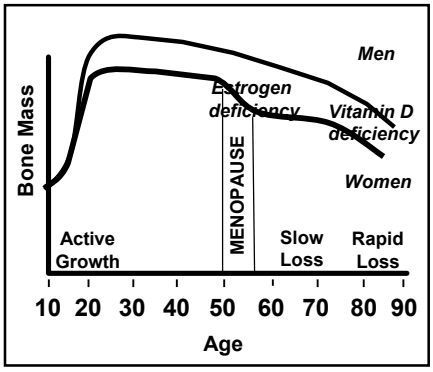
Images Courtesy of Dr. David Dempster

Bone Mineral Density Over the Lifespan

- Minimal in healthy young men and premenopausal women
- Accelerates at menopause due to estrogen deficiency
- Continues throughout life
- Increases in old age
- Influenced by other factors – nutrition, diseases, medications, activity, etc



Adapted from Wasnich RD, et al. *Osteoporosis: Critique and Practicum*. Honolulu, Banyan Press, 1989:179-213
Recker R, et al. J Bone Miner Res. 2000;15:1965-73

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Bone Loss in the Elderly

- Bone loss accelerates with age
- Associated with
  - age-related decrease in vitamin D
  - increase in parathyroid hormone (PTH)
  - increased bone resorption
  - progressive weakness and inactivity
  - increased frequency of falls and fractures

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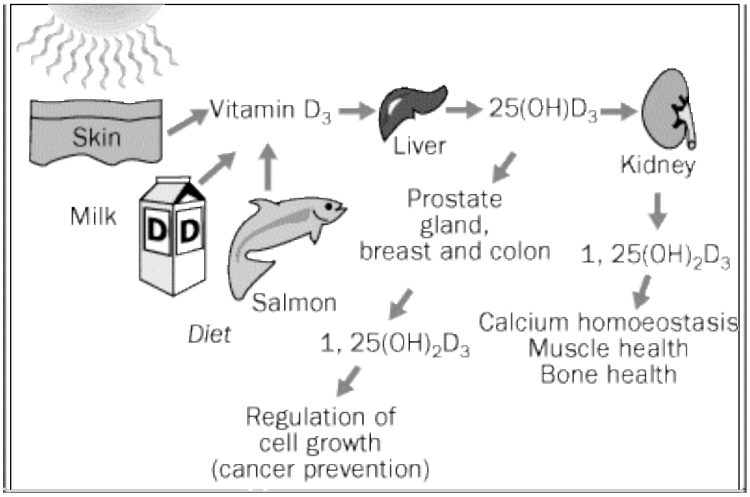
Vitamin D Metabolism



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Holick MF, *Lancet.* 2001;357:2001:4

Vitamin D Deficiency and Fracture Risk

Vitamin D Deficiency

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Increased Fracture Risk

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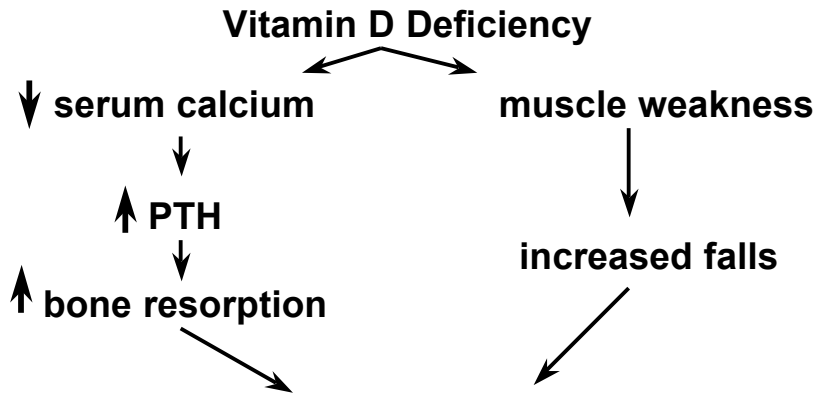
Vitamin D Deficiency and Fracture Risk



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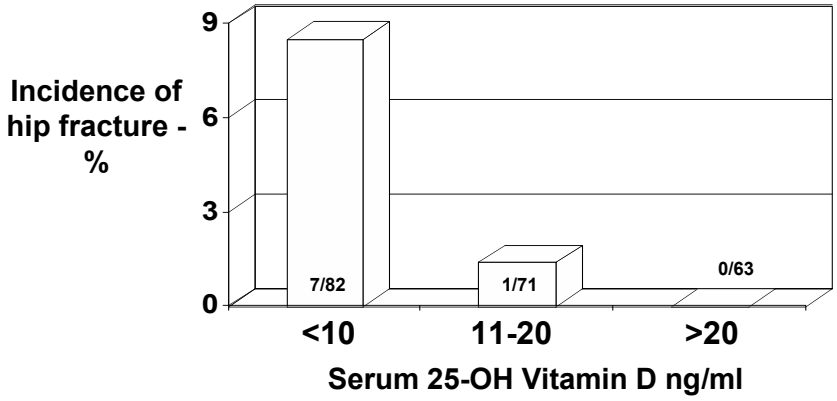
Vitamin D Status and Hip Fracture

- 216 patients 65 and older with previous stroke
- Followed for 2 years



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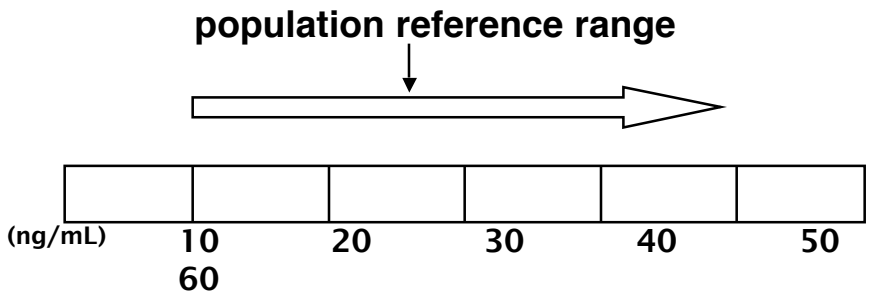
Sato Y et al. *Stroke* 2001;3261673-7

Definitions of Vitamin D Status



Boonen S et al. *Osteoporos Int.* 2004;15:511–519.
Lips P. *Endocr Rev.* 2001;22:477–501.
Heaney RP. *Osteoporos Int.* 2000;11:553–555.
Heaney RP. *Am J Clin Nutr. 2004;80(suppl):1706S-1709S.*
Thomas MK. *NEJM.* 1998;338:777–781.

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Definitions of Vitamin D Status

- **Calcium absorption 65% greater with 25-OH D values of 32 ng/ml vs 20 ng/ml**
- **PTH values rise at levels below 30 ng/ml and are often above normal at levels <20 ng/ml**

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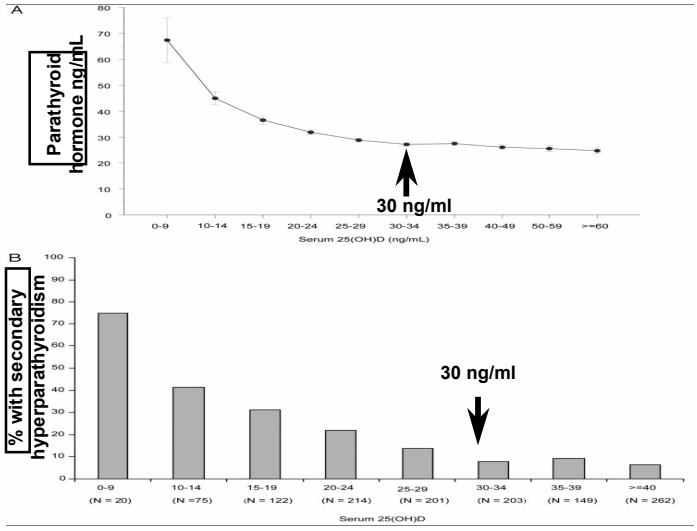
Dawson-Hughes B, et al. *Osteoporos Int* 2005;16:713-6

Serum PTH and 25-OH Vitamin D



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Hollick MF, et al. *J Clin Endocrinol Metab* 90: 3215–24, 2005

Definitions of Vitamin D Status

- **Hip BMD values correlate with 25-OH less than 30 ng/ml but not at higher levels**
- **Increasing serum levels from 15 to 30 ng/ml reduced fall frequency in elderly men and women**
- **Studies in which serum levels are raised to 30 ng/ml or higher reduce fracture risk; smaller treatment effects have not been associated with reduced fracture risk**

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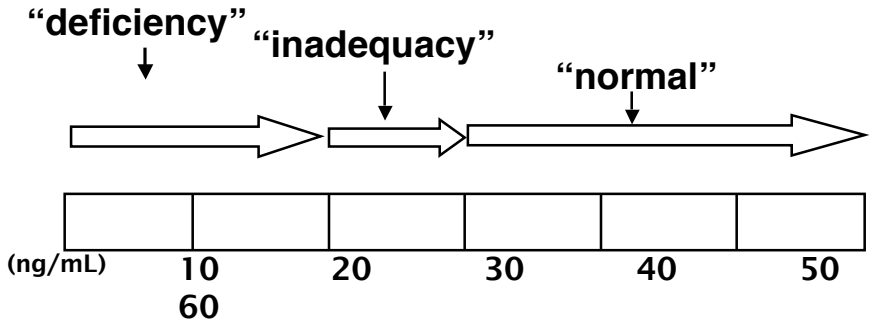
Dawson-Hughes B, et al. *Osteoporos Int* 2005;16:713-6

Definitions of Vitamin D Status



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Heaney RP. *Osteoporos Int.* 2000;11:553–555.
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Vitamin D and Sun Exposure

1 minimal erythema dose of sun (about 20 minutes in summer) is equivalent of 10,000-25,000 IU of vitamin D

Decreased cutaneous production of vitamin D with

- **aging**
- **pigmented skin**
- **sunscreen**
  - **Number 8 sunblock reduces vitamin D synthesis by 95%**

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Prevalence of Vitamin D Deficiency

In USA	% with values <20 ng/ml
Patients with hip fracture	>80%
Nursing home residents	75%
In-patients on Medicine service in Boston hospital	66%
Healthy women 60 years and older in Portland, OR (latitude 45°)	60%
Medical students and residents in Boston	32%
10-13 year old girls in Maine	43%

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Manifestations of Vitamin D Deficiency

- Most are asymptomatic
- Accelerated bone loss, especially in elderly
- Muscle weakness (increased fall and fracture frequency)
- Severe deficiency – osteomalacia with bone pain, hypocalcemia

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Dawson-Hughes B, et al. *Osteoporo Int* 2005;16:713-6

Vitamin D Supplements

- RDA for vitamin D is 400-600 IU daily [1]
- The 400 IU dose based on dose found to prevent rickets in children
- 1000 IU daily increases serum 25-OH vitamin D by about 10 ng/ml [2]
- Vitamin D_2 is about 1/3 as effective as vitamin D_3 [2]

[1] Food and Nutrition Board, Institute of Medicine. Vitamin D. National Academies Press; 1999:250-287.

[2] Armas LA, Hollis BW, Heaney RP. J Clin Endocrinol Metab. 2004;89:5387-91.

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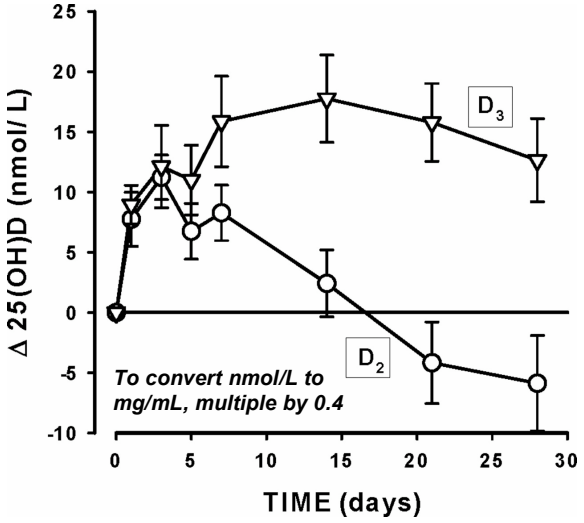
FIG. 2. Time course of the rise in serum 25OHD after a single oral dose of 50,000 IU of either cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2) to two groups of 10 normal men each

Vitamin D_2 vs Vitamin D_3

Change in serum 25(OH)D to a single dose of 50,000 IU of vitamin D_2 or vitamin D_3 in healthy men



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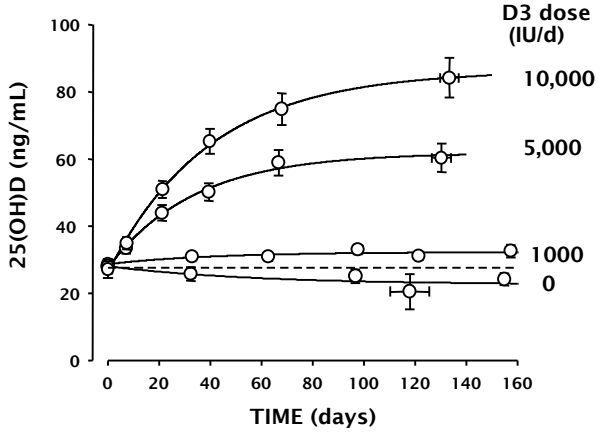
Armas, L. A. G. et al. *J Clin Endocrinol Metab* 2004;89:5387-5391

25(OH)D Response to Oral Vitamin D_3

- 66 males
- aged 38.7 yr (± 11.2)
- dosed with vit D_3 from October through February



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Hathcock JN, Shao A, Vieth R, Heaney R. *Am J Clin Nutr.* 2007;85:6-18.

Vitamin D Supplements

- To achieve serum levels of at least 30 ng/ml in 97.5% of elderly patients would require intake of 2600 IU daily

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Heaney RP. *J Nutr.* 2006;136:1123-5.

Effects of Vitamin D Supplements

	Calcium		Calcium + D_3 2000 IU daily	
	Baseline	3 years	Baseline	3 years
Serum Ca	8.96	9.39	8.96	9.51
Urine Ca	92	100	86	113
25(OH)D	17.2	no change	18.2	34.8*

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Aloia JF et al. *Arch Intern Med* 2005:165:1618-23.

Vitamin D "Toxicity"

- No "toxic' effects of vitamin D. "Toxicity" is extension of normal physiologic effect
- No case of hypercalcemia with doses of <10,000 IU daily
- Tolerable Upper Intake Level (UL) for vitamin D_3 revised to 10,000 (250 ugm) IU daily [1]
- Patients at risk:
  - Hyperparathyroidism
  - Granulomatous diseases

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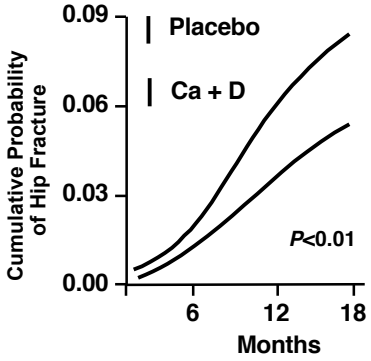
[1] Hathcock JN, Shao A, Vieth R, Heaney R. *Am J Clin Nutr.* 2007;85:6-18

Calcium and Vitamin D Reduce Hip Fractures

Subjects: elderly women in French nursing home (n=3270)

Therapy: Calcium 1200 mg and vitamin D 800 IU daily

Outcome: 30% decrease in hip fracture risk over 18 months



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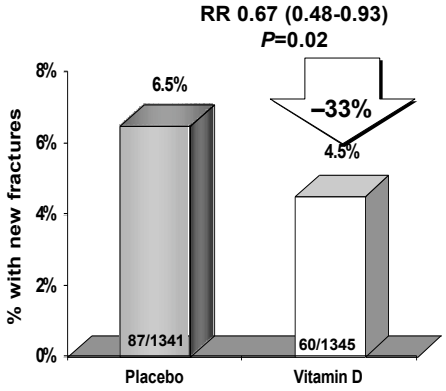
Chapuy MC, et al. *BMJ*. 1994;308:1081–1082.

Vitamin D_3: Clinical Fracture Risk



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Trivedi D, et al. *BMJ.* 2003;326:469-474

Vitamin D Supplements and Fracture Risk

- **Recent meta-analyses conclude that vitamin D_3 in doses of 800 IU daily or more reduce fracture risk**

Boonen S et al. *Osteoporos Int.* 2004;15:511–519
Bischoff-Ferrari HA, et al. *JAMA* 2005;293:2257-64

- **Studies with smaller doses or poor compliance did not demonstrate effect of treatment on fracture incidence**

Lips P, et al. *Ann Intern Med* 1996;124:400-6
Grant AM, et al. *Lancet* 2005;365:1621-8

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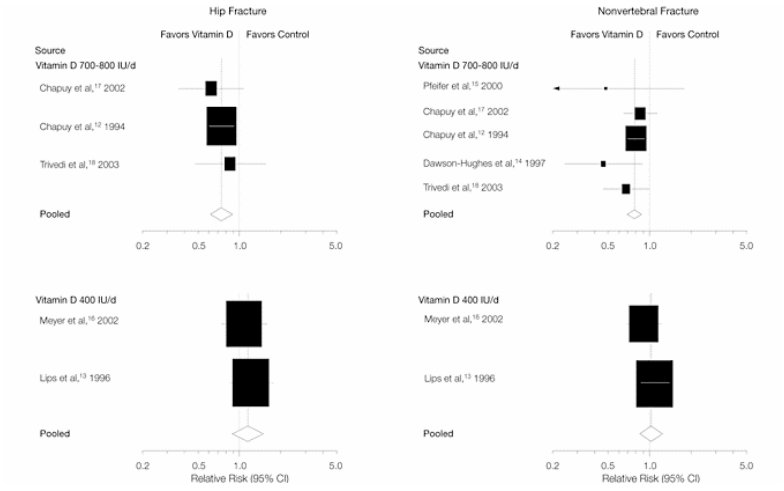
Meta-analysis of Vitamin D Therapy and Fractures



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JAMA

Bischoff-Ferrari HA, et al. *JAMA* 2005;293:2257-64

WHI Calcium-Vitamin D Study

- 36,000 postmenopausal women ages 50-79 randomly assigned to receive 1000 mg calcium and 400 IU D3 daily or placebo
- With treatment,
  - Total hip BMD increased 1%
  - No effect on hip fracture risk
  - Renal stones increased 17%

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Jackson RD, et al. *N Engl J Med.* 2006;354:669-83

WHI Calcium-Vitamin D Study

- Limitations
  - Baseline calcium intake >800 mg daily in more than half
  - Supplements allowed in all subjects
  - More than half were on estrogen therapy
  - Average age 62 – low fracture rates
  - Hip fractures decreased by 29% in compliant subjects

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Jackson RD, et al. *N Engl J Med.* 2006;354:669-83

WHI Calcium-Vitamin D Study

- **Conclusions**
  - **Calcium and vitamin supplements of no benefit** [1]
  - **Calcium and vitamin supplements of limited benefit in calcium-replete adults at low risk of fracture** [2]
  - **Results do not preclude beneficial effect in older subjects with vitamin D deficiency** [2]
  - **Kidney stone data not consistent with other findings – may reflect high calcium intake in the study** [2]

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[1] Jackson RD, et al. *N Engl J Med*. 2006;354:669-83

[2] McClung M. Personal opinion

Vitamin D and Bone Health in Young Adults

- **Prevalence of vitamin D deficiency is high among several populations of premenopausal women.**
- **Some but not all studies demonstrate a weak correlation between vitamin D or PTH levels and BMD values.**

Correlation of PTH and BMD: R^2 = 0.039-0.048

Nakamura K et al. Nutrition, mild hyperparathyroidism, and bone mineral density in young Japanese women. *Am J Clin Nutr* 2005;82:1127–33.

Falch JA, Steihaug S. Vitamin D deficiency in Pakistani premenopausal women living in Norway is not associated with evidence of reduced skeletal strength. *Scand J Clin Lab Invest* 2000;60:103–9.

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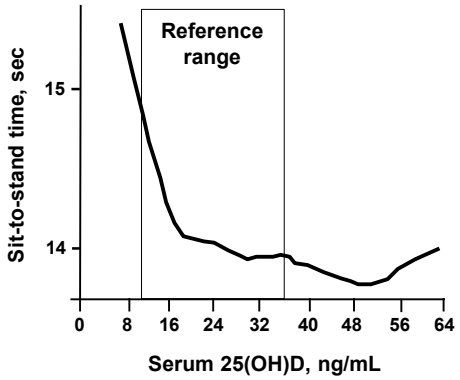
Higher 25(OH)D Levels Are Associated With Better Lower Extremity Function in Ambulatory Women

- 4,100 ambulatory adults included in NHANES III
- 60 to ≥90 years
- Functional measurements used to assess lower extremity function:
  - 8-ft walking speed test
  - Timed sit-to-stand test

Timed Sit-to-Stand Test

LOWESS regression plot of lower extremity function vs vitamin D levels



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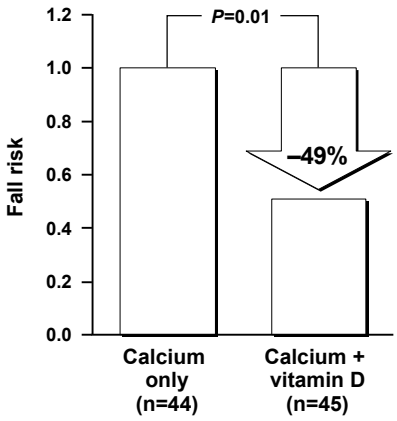
Bischoff HA, et al. *J Bone Miner Res.* 2003;18:343–351

Lower Levels of Vitamin D May Be Associated with the Risk for Falling

- N =122
- Ages: 63–99
- Randomized, double-blind, controlled trial
  - Calcium 1200 mg/d
  - Calcium 1200 mg/d + vitamin D 800 IU/d
- 12-week duration
- Mean serum 25(OH)D 12 ng/mL at baseline
- Women living in long-term care units

Reduction in falls



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Bischoff HA, et al. *J Bone Miner Res.* 2003;18:343–351

Calcium vs Vitamin D

- **Calcium infusion will heal rickets in children without vitamin D**
- **Vitamin D without calcium has little effect on calcium homeostasis**
- **In vitamin D-replete adults, there is no advantage of total calcium intake of more than 800 mg/day [1]**

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Steingrimsdottir L et al. *JAMA*. 2005;294:2336-41.

Summary

- **Vitamin D deficiency is an important determinant of poor skeletal health in older adults**
- **Currently recommended doses are inadequate for most older adults**
- **Supplementation reduces fall frequency and fractures in older, fall-prone, vitamin D-deficient adults**
- **Doses to achieve serum levels of 25 OH vitamin D of at least 30 ng/ml (at least 800 IU daily) are required to observe skeletal effects.**

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Vitamin D Supplements

Up to age 65: 1000 IU D_3 daily
or 100,000 IU D_2 once monthly

65 and older: 2000 IU D_3 daily
or 50,000 IU D_2 once weekly

Contraindications

- **Hypercalcemia**
- **History of renal stones**
- **Granulomatous diseases**

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Discussion

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