

The ABC's of Vitamin D



Michael McClung, MD, FACP

**Department of Medical Education
Providence Portland Medical Center
Director, Oregon Osteoporosis Center**

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

June 2007

ABC's of Vitamin D

Assess:

- Query use of supplements, fortified food
- Measure serum 25(OH)D in patients with
 - Hypocalcemia
 - Malabsorption or small bowel disease or resection
 - Long use of anticonvulsants
 - Unexpectedly low bone mineral density
 - Bone loss while on osteoporosis treatment

ABC's of Vitamin D

Begin supplements

- Up to age 65: 1000 IU D₃ daily
or 100,000 IU D₂ once monthly
- 65 and older: 2000 IU D₃ daily
or 50,000 IU D₂ once weekly

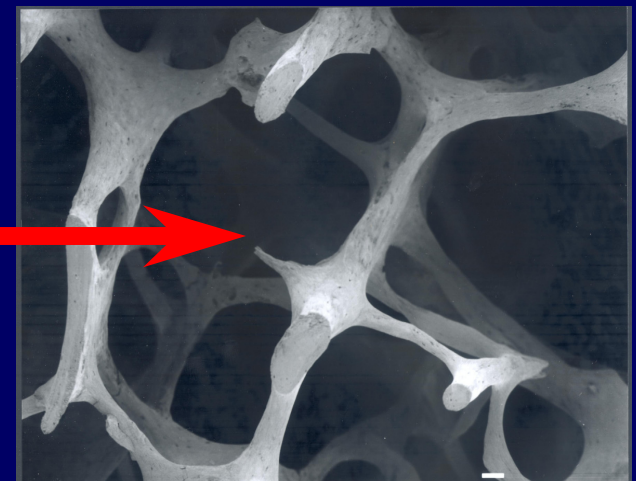
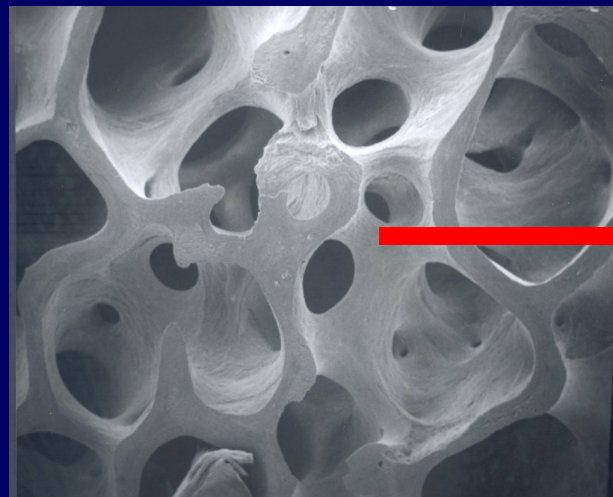
ABC's of Vitamin D

Contraindications

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

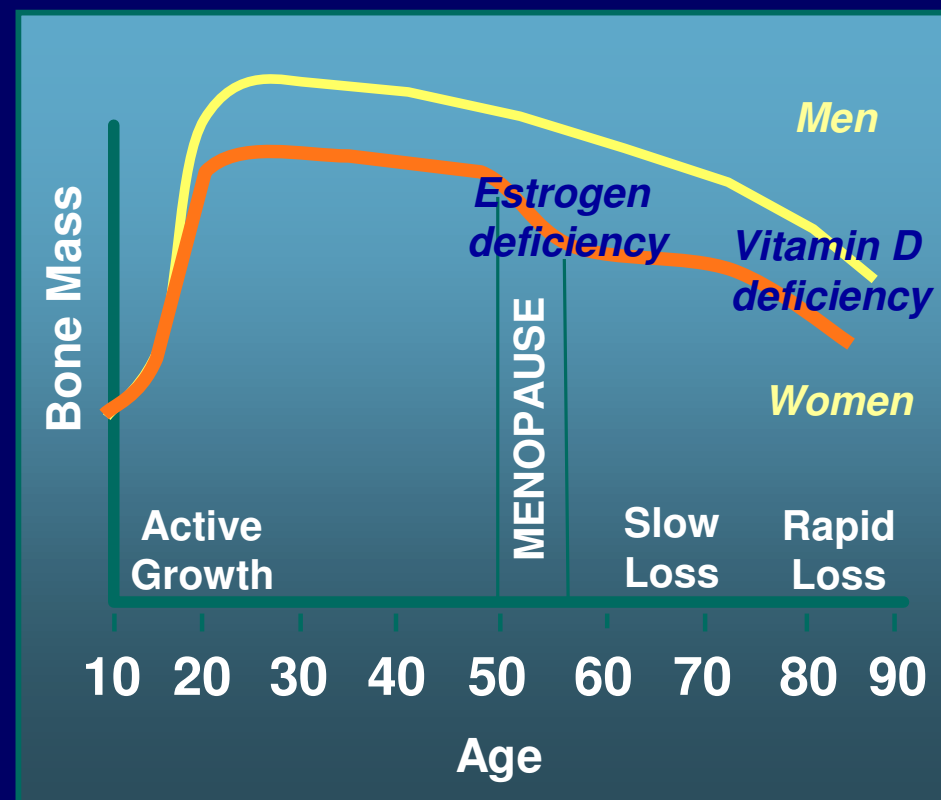
Osteoporosis: The Definition

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



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

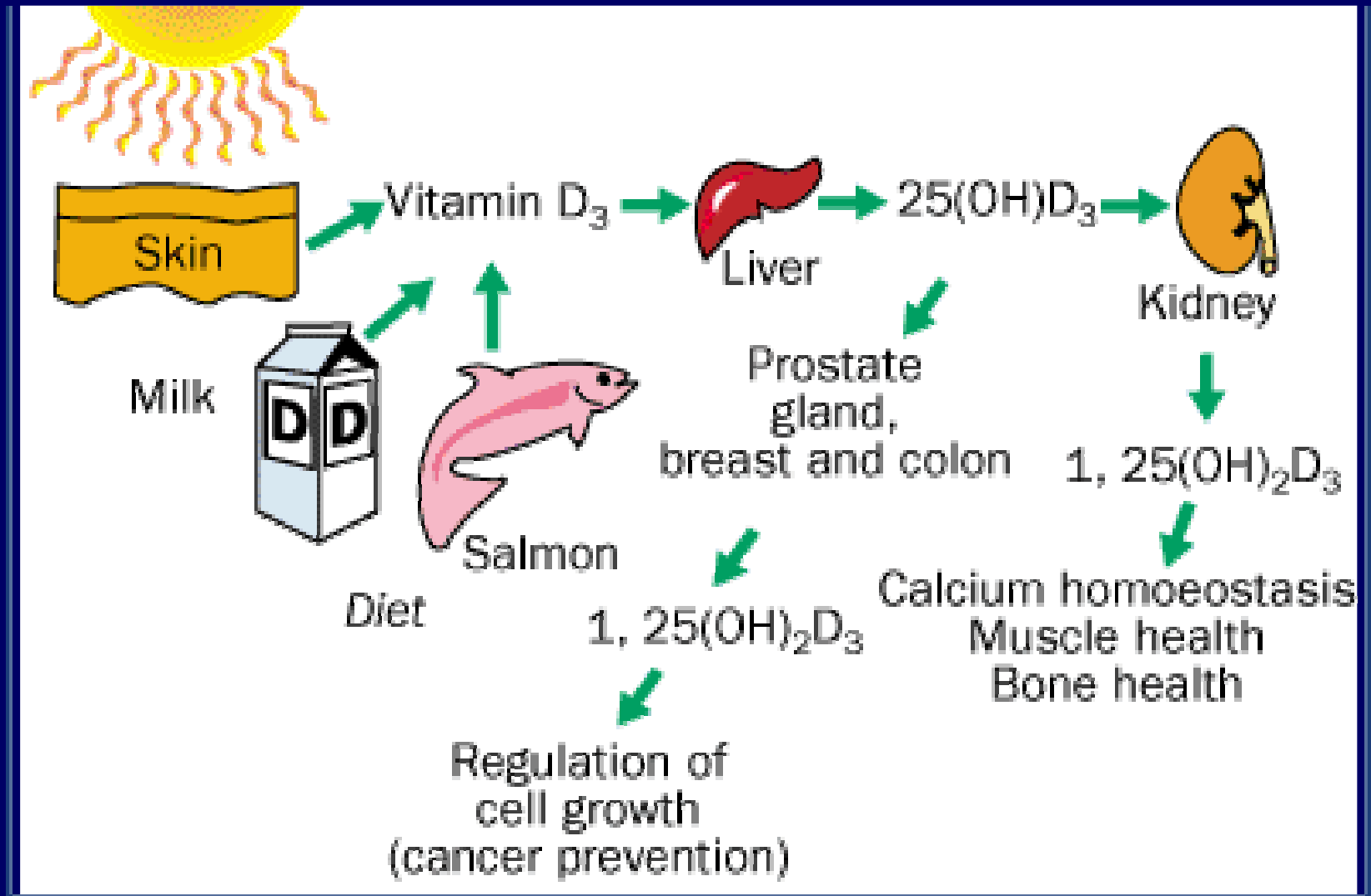


Adapted from Wasnich RD, et al. *Osteoporosis: Critique and Practicum*. Honolulu, Banyan Press, 1989:179-213
Recker R, et al. *J Bone Miner Res*. 2000;15:1965-73

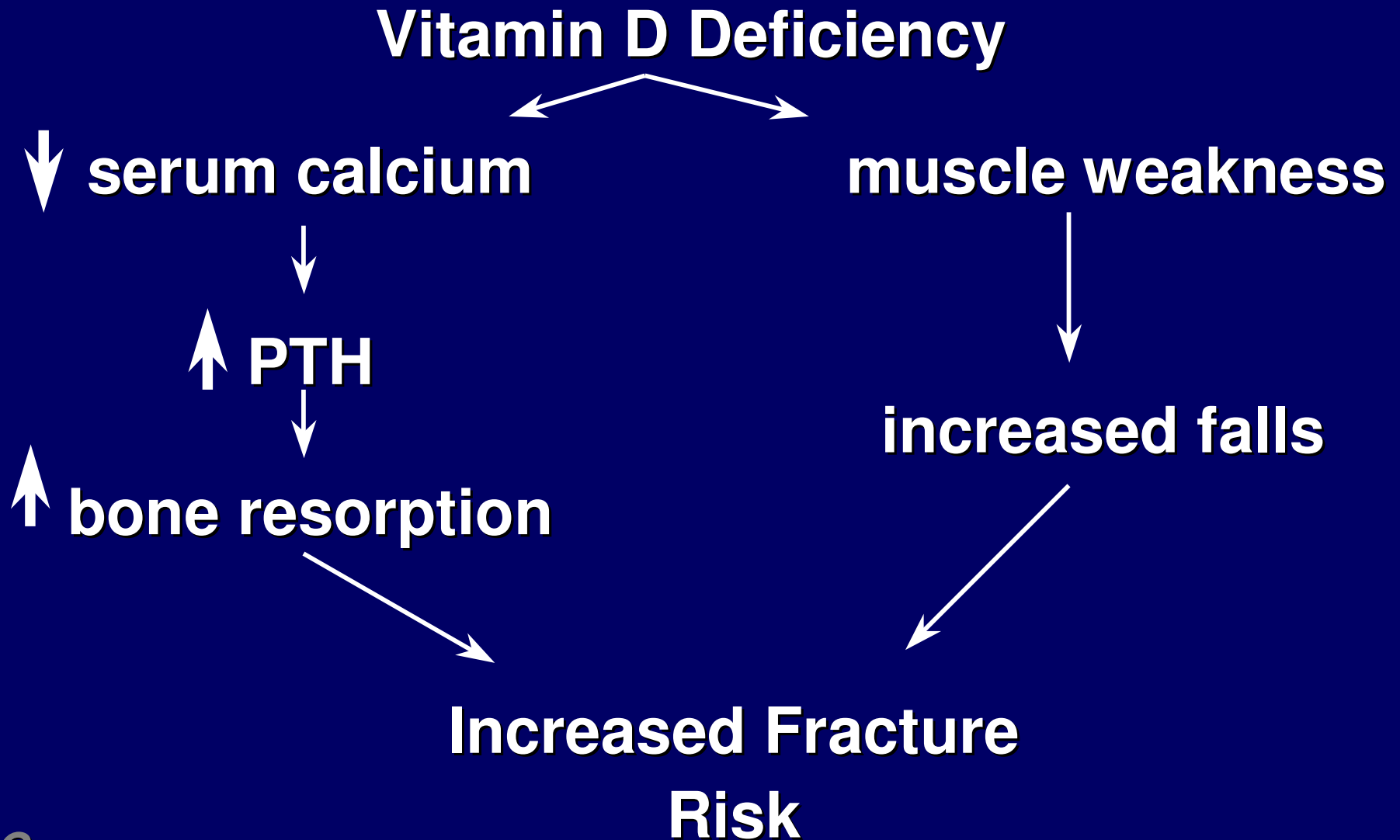
Bone Loss in the Elderly

- **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**

Vitamin D Metabolism

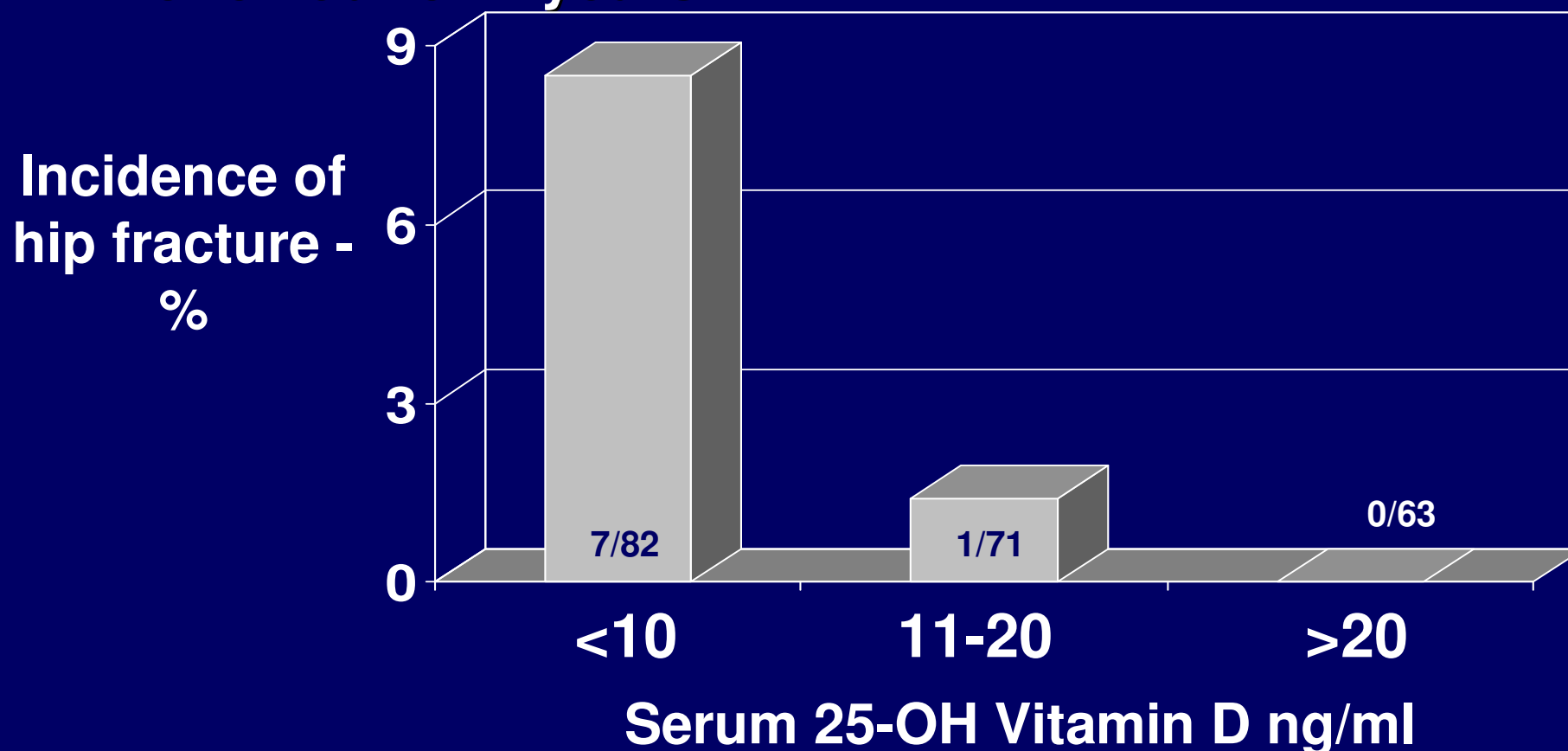


Vitamin D Deficiency and Fracture Risk

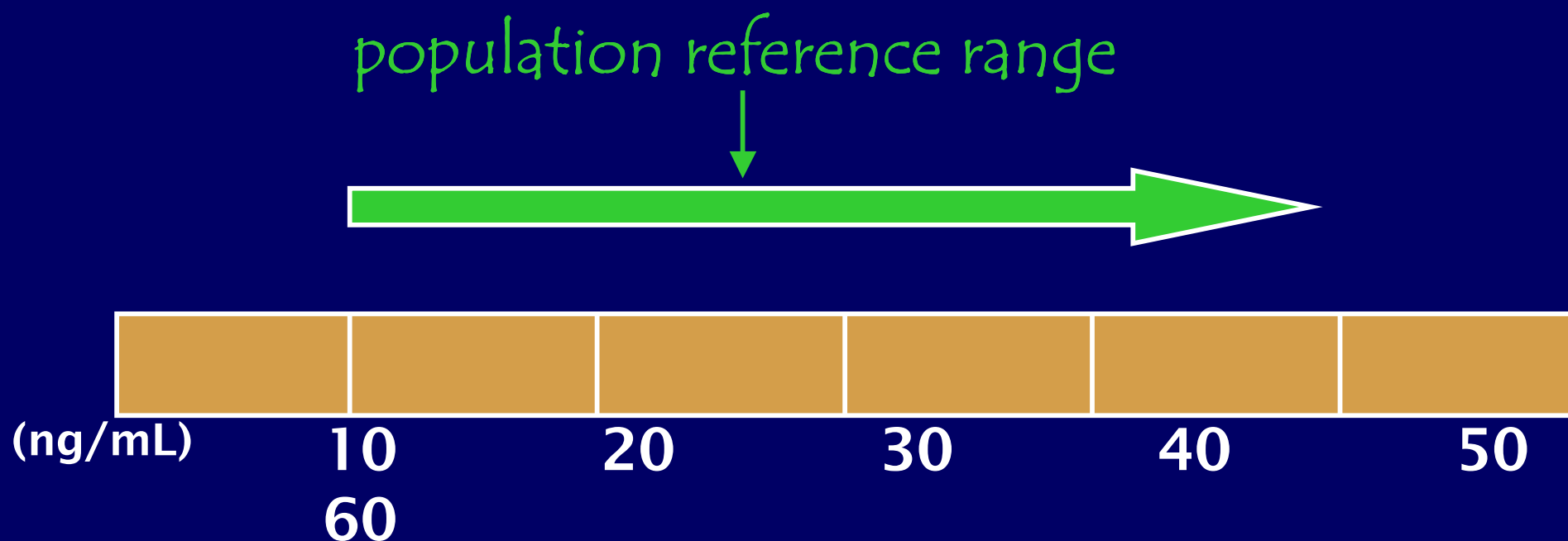


Vitamin D Status and Hip Fracture

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



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.

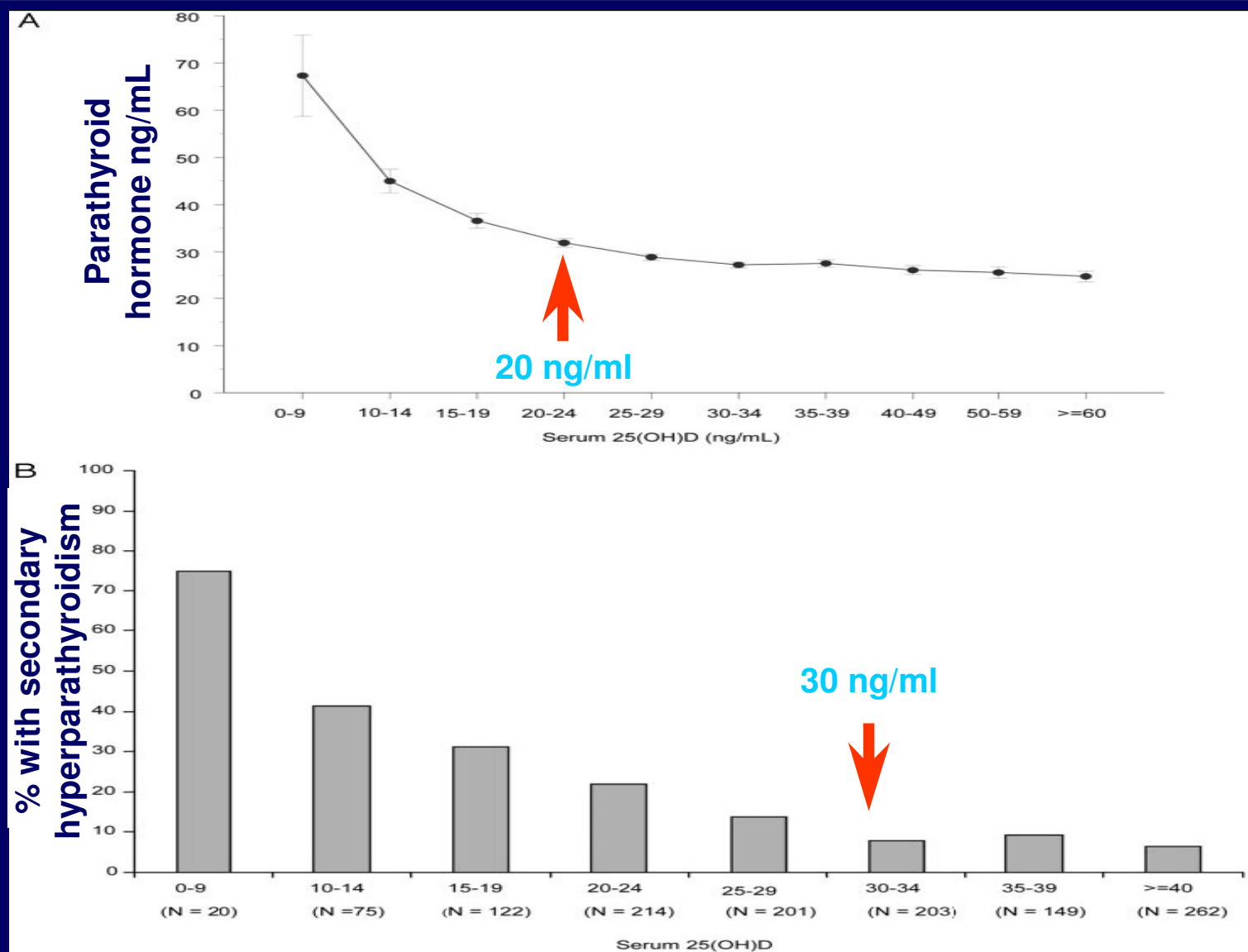
Heaney RP. *Am J Clin Nutr.* 2004;80(suppl):1706S-1709S.

Thomas MK. *NEJM.* 1998;338:777–781.

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

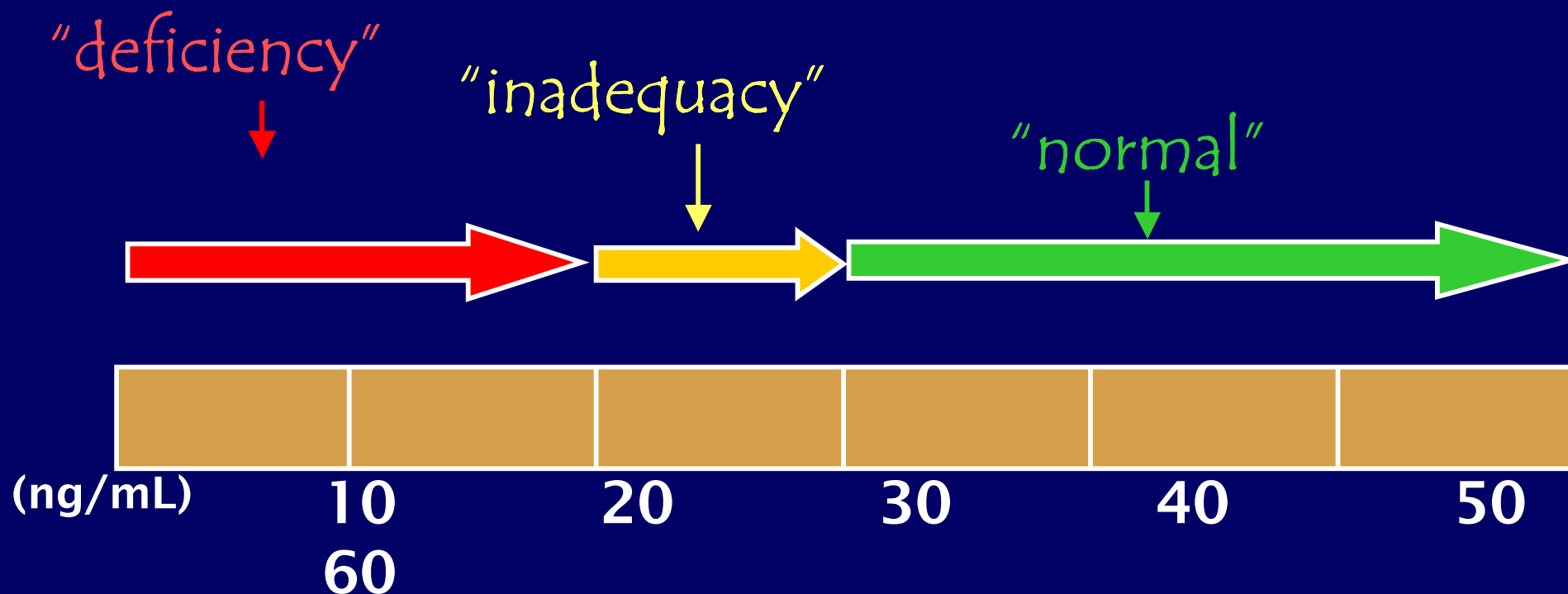
Serum PTH and 25-OH Vitamin D



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

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.

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%

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%

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**

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 D₂ is about 1/3 as effective as vitamin D₃ ²

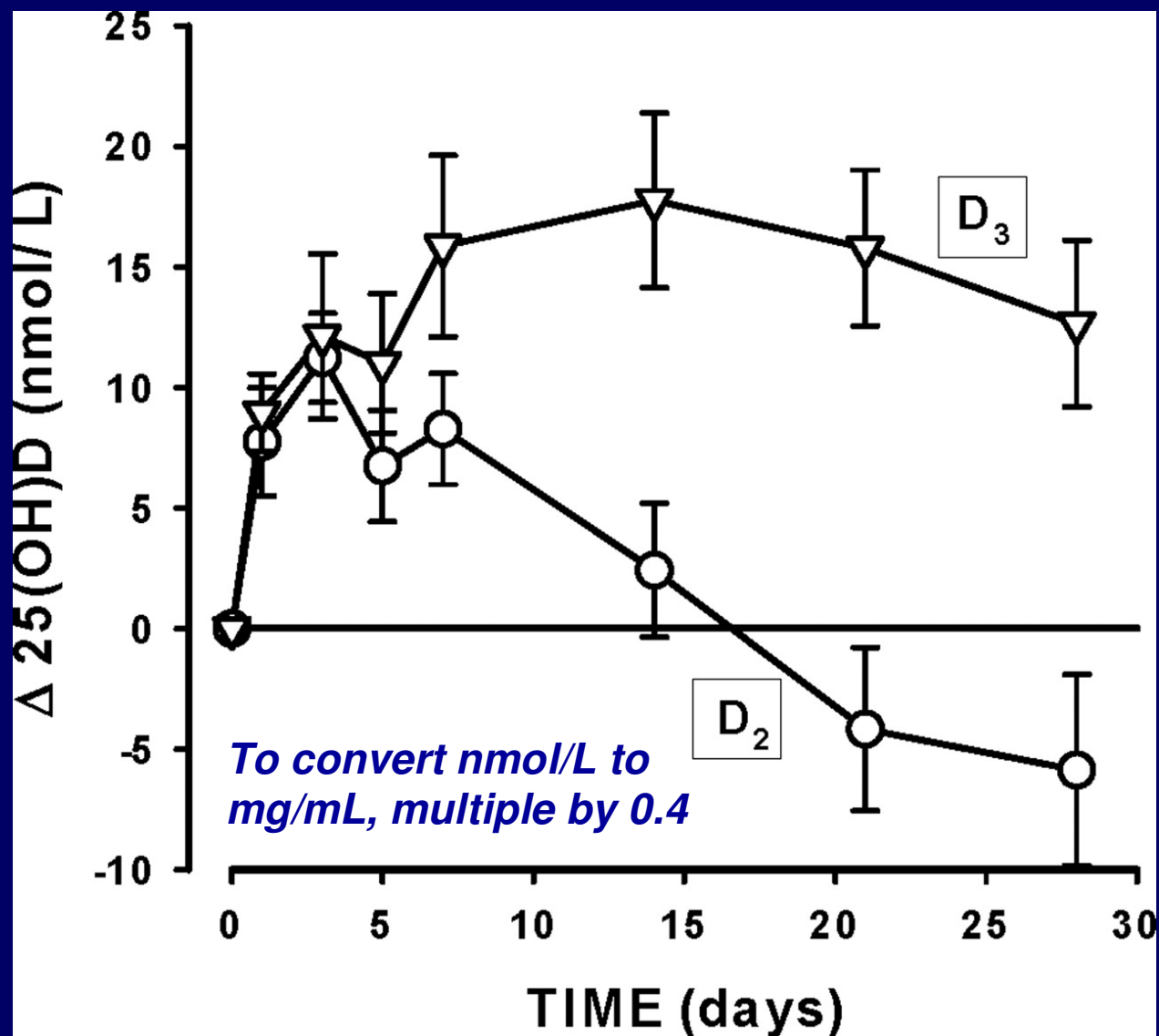
¹ Food and Nutrition Board, Institute of Medicine. Vitamin D. National Academies Press; 1999:250-287.

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

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 D₂ vs Vitamin D₃

Change in serum 25(OH)D to a single dose of 50,000 IU of vitamin D₂ or vitamin D₃ in healthy men



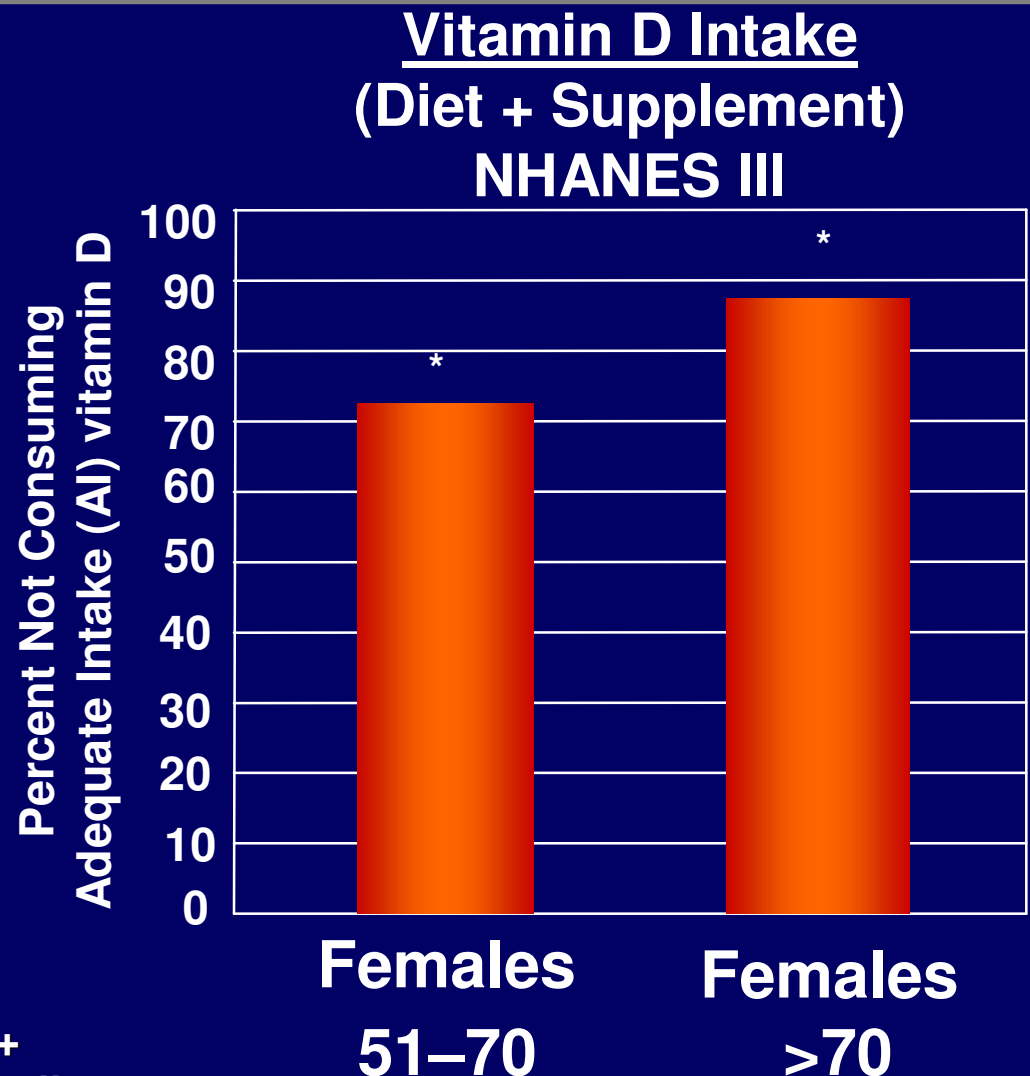
Vitamin D Supplements

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

The Majority of Americans Are Not Receiving Adequate Levels of Vitamin D

- According to an NHANES III survey of 3,444 women aged 51 and older, over 70% of women 51-70 were estimated not to meet adequate intake guidelines for vitamin D based on daily intake from diet and supplements (400 IU).
- Nearly 90% of women over the age of 70 were estimated not to meet guidelines (600 IU).

* Percent consuming AI or above from diet + supplements significantly different from diet alone; $P < 0.05$.

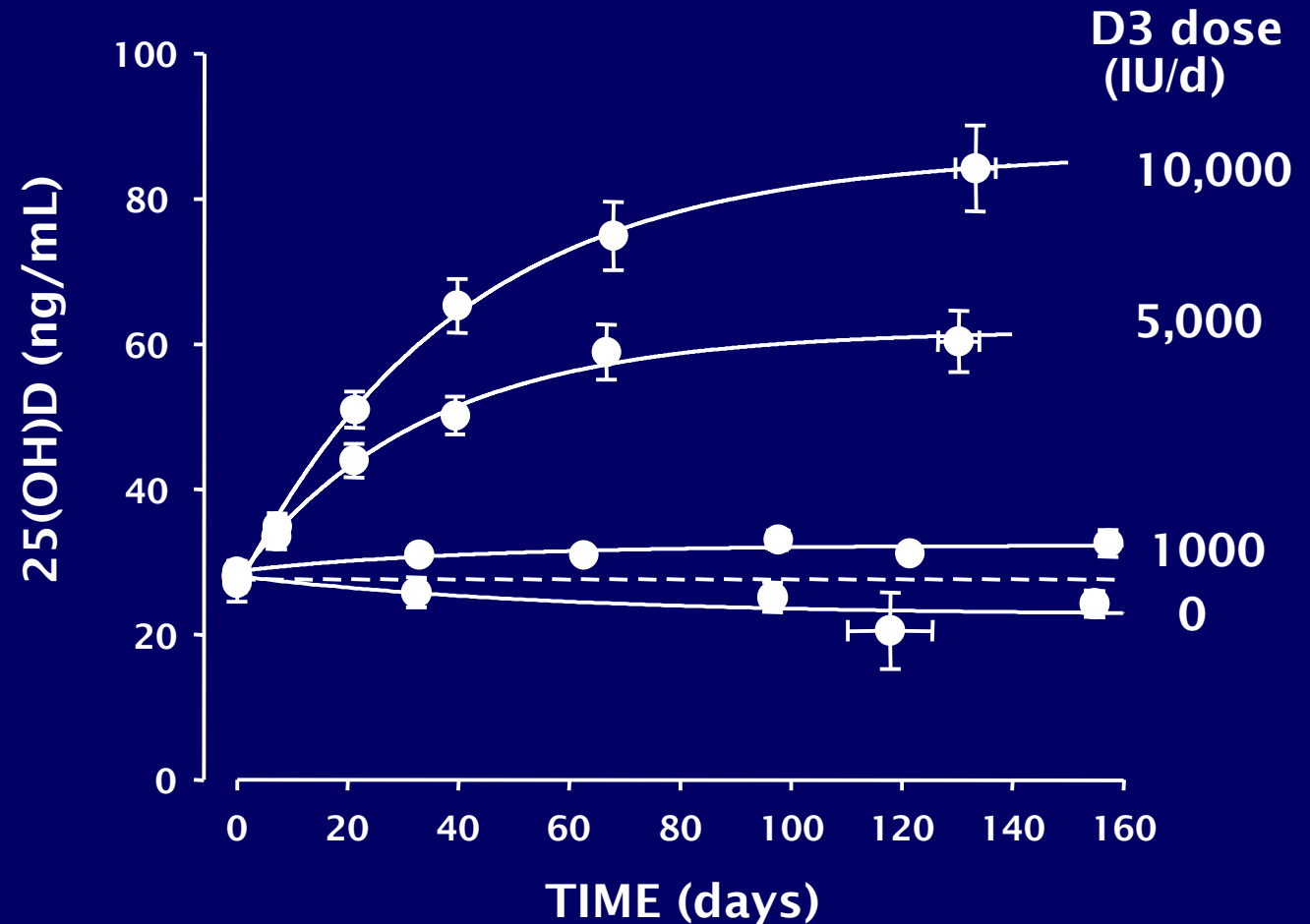


Dietary Sources of Vitamin D

<u>FOOD SOURCE</u>	<u>IU per Serving</u>
• Cod Liver Oil, 1 Tbs	1,360
• Salmon, cooked, 3 1/2 oz	360
• Mackerel, cooked, 3 1/2 oz	345
• Sardines, canned in oil, drained, 3 1/2 oz	270
• Milk, vitamin D fortified, 1 cup	98
• Margarine, fortified, 1 Tbs	60
• Liver, beef, cooked, 3 1/2 oz	30
• Egg, 1 whole (vitamin D is present in the yolk)	25

25(OH)D Response to Oral Vitamin D₃

- 66 males
- aged 38.7 yr (± 11.2)
- dosed with vit D₃ from October through February



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

Effects of Vitamin D Supplements

	Calcium		Calcium + D ₃ 2000 IU daily	
	<u>Baseline</u>	<u>3 years</u>	<u>Baseline</u>	<u>3 years</u>
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*

Vitamin D “Toxicity”

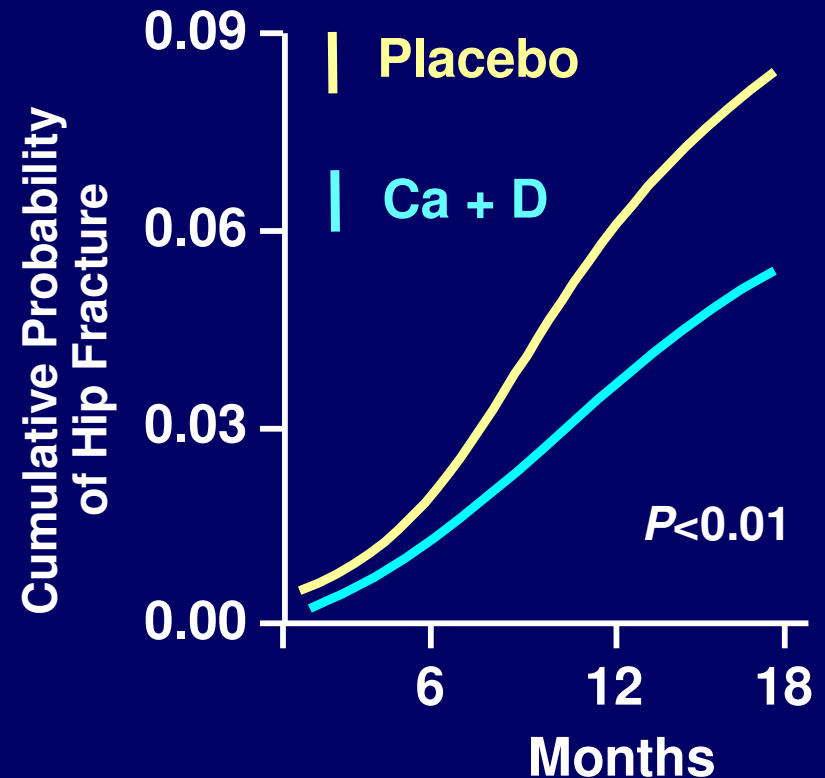
- No “toxic” effects of vitamin D. “Toxicity” is extension of normal physiologic effect
- No case of hypercalcemia with doses of <10,000 IU daily
- Tolerable Upper Intake Level (UL) for vitamin D₃ revised to 10,000 (250 ug) IU daily¹
- Patients at risk:
 - Hyperparathyroidism
 - Granulomatous diseases

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



Vitamin D: Clinical Fracture Risk

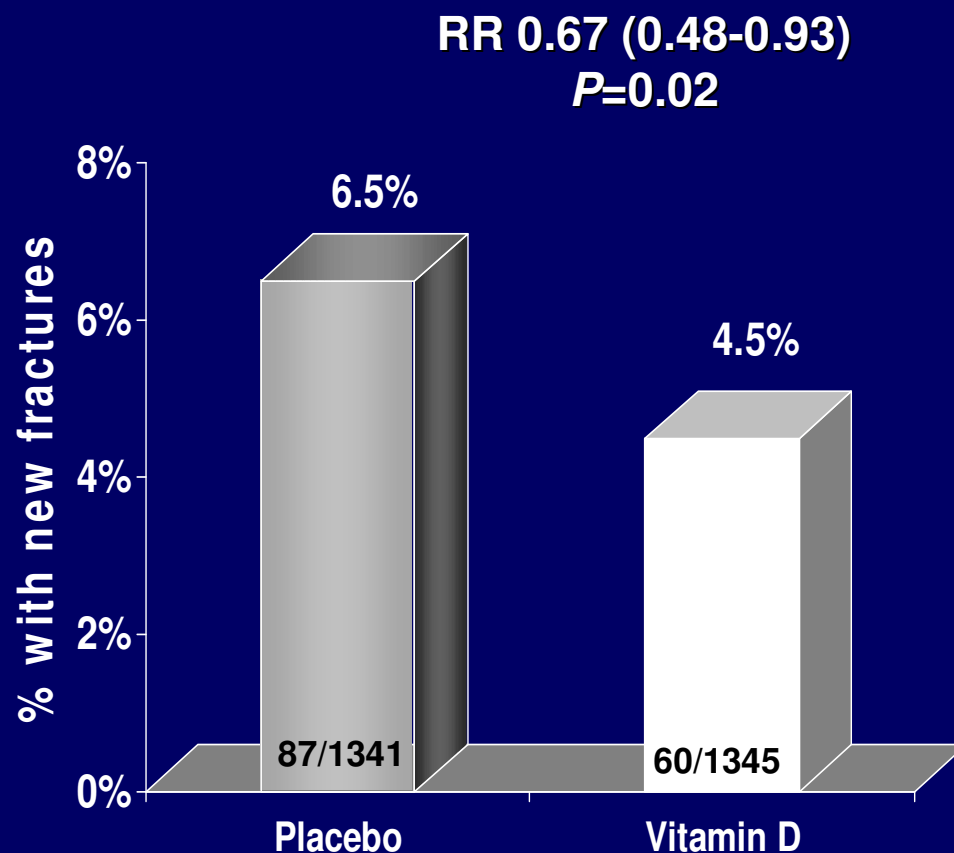
N=2686: Men and women 65-85

Mean age: 74.7

Placebo or vitamin D 100,000 IU
PO every 4 months

Fractures: Hip, wrist, spine and
forearm

Treatment interval: 5 years



Vitamin D Supplements and Fracture Risk

- **Recent meta-analyses conclude that vitamin D₃ 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

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%

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**

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**

When to Use Calcitriol vs Vitamin D

Inability to synthesize calcitriol

- **Renal insufficiency/failure**
 - **NOTE: These patients may also need vitamin D**
- **Hypoparathyroidism**

Other

- **Hypophosphatemic rickets**
 - **to optimize phosphate absorption**

Extra-skeletal Effects of Vitamin D

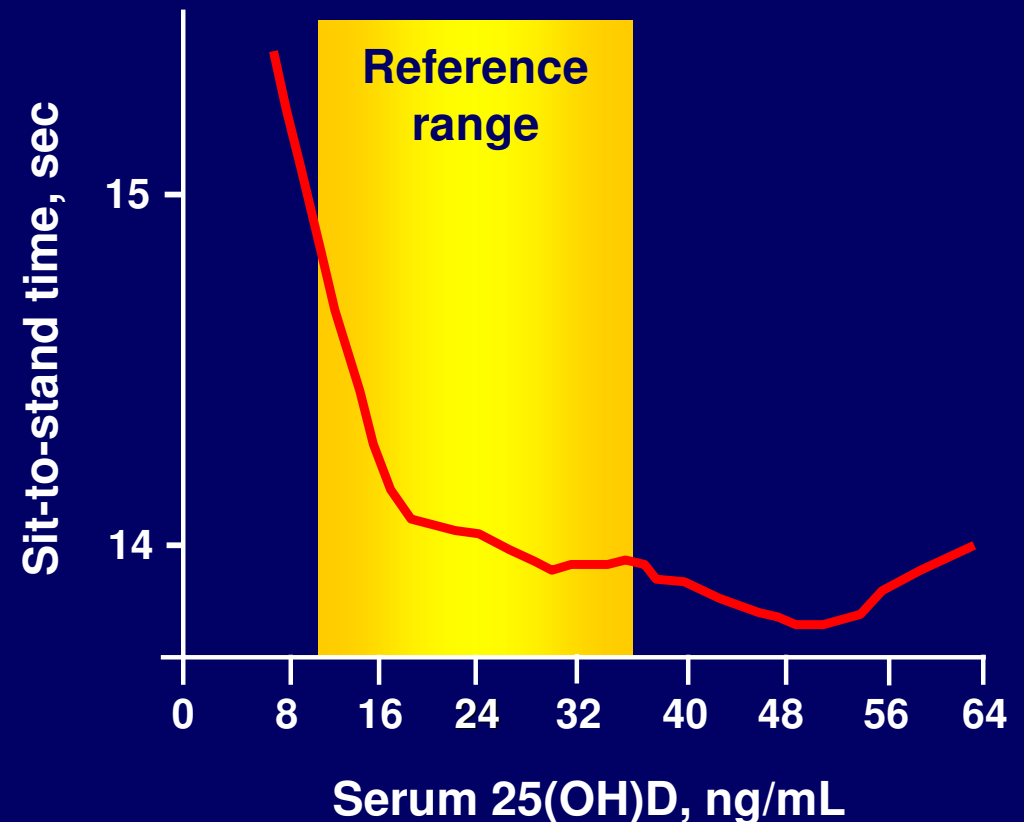
- **Decreased incidence of**
 - **falls in elderly subjects**
 - **colon polyps**
 - **death from colon, ovarian, breast and prostate cancer**
 - **type 1 diabetes in children**
 - **multiple sclerosis**

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

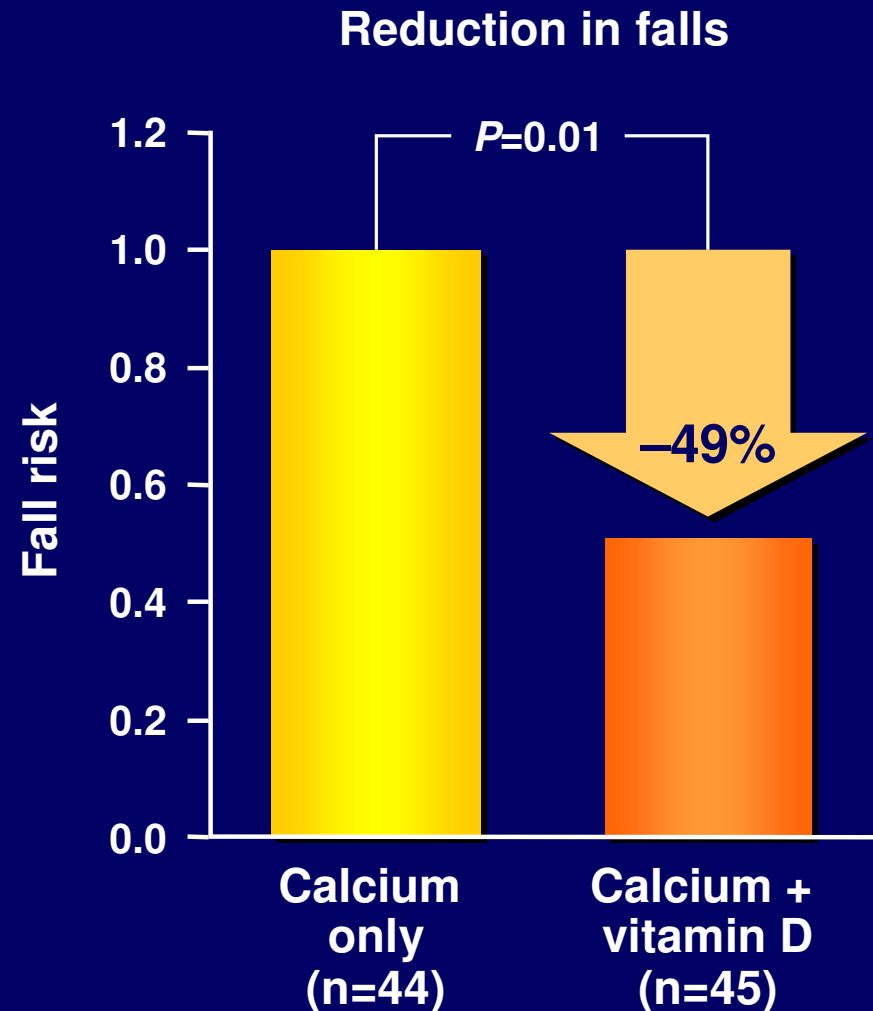
Timed Sit-to-Stand Test

LOWESS regression plot of lower extremity function vs vitamin D levels



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



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 calcium intake of more than 800 mg/day¹**

ABC's of Vitamin D

Assess:

- Query use of supplements, fortified food
- Measure serum 25(OH)D in patients with
 - Hypocalcemia
 - Malabsorption or small bowel disease or resection
 - Long use of anticonvulsants
 - Unexpectedly low bone mineral density
 - Bone loss while on osteoporosis treatment

ABC's of Vitamin D

Begin supplements

- Up to age 65: 1000 IU D₃ daily
or 100,000 IU D₂ once monthly
- 65 and older: 2000 IU D₃ daily
or 50,000 IU D₂ once weekly
- *Total daily calcium intake 800-1000 mg daily*

<i>dairy-free diet</i>	<i>300 mg</i>
<i>dairy servings</i>	<i>300 mg each</i>
<i>supplements</i>	<u><i>xxx</i></u>
TOTAL	

ABC's of Vitamin D

Contraindications

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

Summary

- **Vitamin D deficiency is more common than once thought**
- **Currently recommended doses are inadequate for most older adults**
- **Supplementation is beneficial in older, fall-prone, vitamin D-deficient adults**