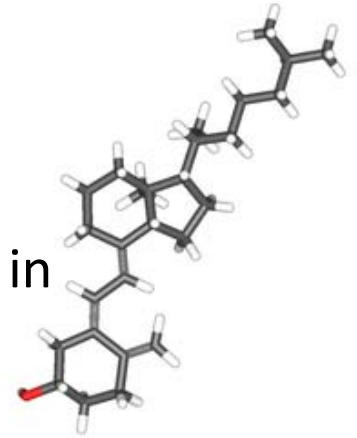


Let the Sunshine In

The evidence, or lack thereof,
regarding Vitamin D

What is Vitamin D?



- Fat-soluble vitamin (ADEK)
- Production of it evolved over 750 million years ago in phytoplankton
- Produced in the skin in most vertebrates
 - Except the naked mole rat!
 - Furry and feathered secrete oils that make it, that they then ingest while grooming
- Secosteroid (one of the steroid rings is broken), structure clarified by Adolf Windaus, who received Nobel Prize in Chemistry, in 1930's
- Can only be synthesized by a photochemical process, demonstrated by Alfred Fabian Hess in 1923
- 1923 Harry Steenbock at Wisconsin showed that irradiation increased the vitamin D content of food and that you could cure rickets in rats by irradiating their food. He patented his process, which was then used to fortify milk

How do we normally get vitamin D?



- Food sources
 - Fortified milk and cereals
 - Cod liver oil



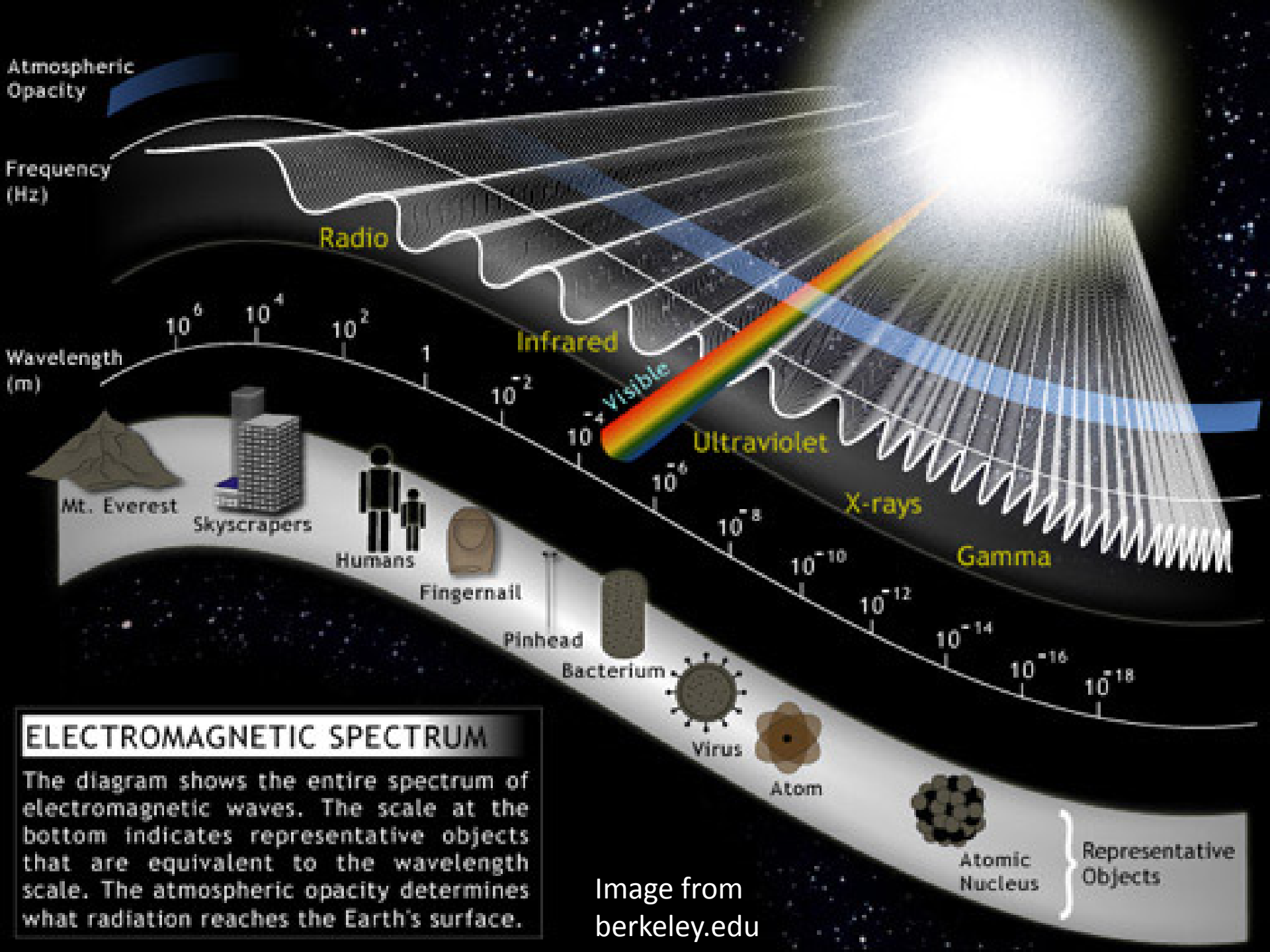
Food Sources

Food	Amount	Vitamin D Content
Salmon	3.5 oz	360 IU
Tuna canned in oil	3.5 oz	235 IU
Eggs	1 egg	20 IU
Cod liver oil	15 ml / 1 tbsp	1360 IU
Mushrooms, regular	3.5 oz	14 IU
Mushrooms, irradiated	3.5 oz	500 IU
Sardines canned in oil	1.75 oz	250 IU
Whole milk	1 cup	97 IU
Lowfat (1%) Milk	1 cup	127 IU
Soy milk	1 cup	100 IU
Fruit Loops	$\frac{3}{4}$ cup	36 IU

How do we normally get vitamin D?



- Production in skin in response to UV light
 - UVB, wavelengths between 270-300 nm, Peak synthesis at 295-297 nm
 - Converts cutaneous 7-dehydrocholesterol to previtamin D₃, which becomes D₃



ELECTROMAGNETIC SPECTRUM

The diagram shows the entire spectrum of electromagnetic waves. The scale at the bottom indicates representative objects that are equivalent to the wavelength scale. The atmospheric opacity determines what radiation reaches the Earth's surface.

Image from
berkeley.edu

Representative
Objects

Sunbathing



- Need approx 5-30 minutes midday sun twice weekly
- Need to be in appropriate season and latitude
- One minimal erythematous dose gives you 20,000 IU in a bikini
- Or can go tanning, if booth/bed has at least 2-6% UVB

Factors Impacting Cutaneous Production

- Latitude
 - No appreciable synthesis above 42° Nov-Feb
 - Year-round synthesis if latitude below 34°
- Sun intensity
 - Cloudy day ↓ by 50%
 - Shade ↓ by 60%
- Melanin content of skin (?)
- Sunscreen
 - SPF 8 or higher blocks all UVB
 - But most of us don't put enough on or reapply as we should
- Glass – cannot absorb UVB through windows
- Time of day – maximal rays between 10 am and 3 pm

Wait, did she say go tanning?!



- Reliable & Safe delivery
 - Not adversely impacted by intestinal factors (vs. oral)
 - Reaches a steady-state, can't over-dose
- Possible mood benefits
- Risk of skin cancer, accelerated skin aging
 - Avoid burns
 - Protect face and hands/arms
 - Risk/benefit ratio

Supplements

- Over-the counter
 - D2 vs D3
 - D2 is made by UV irradiation of ergosterol from yeast
 - D3 is made by UV irradiation of 7-dehydrocholesterol from lanolin and appears to be more bio-available
 - Strengths vary from 400 to 2000 IU
- Prescription
 - Ergocalciferol (D2) 50,000 units once to twice weekly

What do we need it for?

- Promotion of calcium absorption in gut
 - Without D, absorb 10-15%, with it absorb 30-40%
 - Maybe don't need 1000 mg calcium per day if have sufficient vitamin D?!
- Maintenance of adequate serum calcium and phosphate levels
- Bone growth and remodeling
- Neuromuscular function
- Immune function
- Anti-inflammatory action
- Regulation of cell proliferation and apoptosis

Benefits of Vitamin D

- Use of supplements (200-1100 IU) results in statistically significant 7% decrease in overall mortality
- Protective effect against colon cancer (50% reduction)
- Protective against osteopenia, osteoporosis, falls, fractures
- Possible protective effect against breast and prostate cancers
- Probable protection against:
 - Diabetes (type 1 and 2)
 - Hypertension
 - Glucose intolerance
 - Multiple Sclerosis
- Many of these benefits require intakes of >800 IU daily

How much is enough?

- Good question
 - May not be the same for all groups of people
- Recommended dosages:
 - 200 IU daily ages 0-50 (Inst. Of Med. Food Nutrit. Board)
 - 400-600 IU daily over 50 (IOM FNB)
 - AAP & Canada recommends 400 IU for kids and adolescents
- Is that enough?
 - Many benefits require >800 IU daily
 - Up to 46% of persons with deficiency are actually taking the RDA
 - Thomas MK et al. Hypovitaminosis D in medical inpatients. *N Engl J Med.* 1998;338:777-783,
 - Nesby-O'Dell S et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr.* 2002;76:187-192.
 - Vieth R et al. Wintertime vitamin D insufficiency is common in young Canadian women, and their vitamin D intake does not prevent it. *Eur J Clin Nutr.* 2001;55:1091-1097.
 - Drug interactions: prednisone, cholestyramine, orlistat (alli), phenobarbital, and phenytoin all decrease effects of vitamin D

How much is too much?

- Can only overdose from supplements
 - Would need to take 50,000 IU daily to get to toxic levels
 - No toxicity at 10,000 IU daily for up to 5 months
- Hypercalcemia; nausea, vomiting, poor appetite, constipation, weakness, weight loss, mental status changes, arrhythmias, metastatic calcifications
- 17% increase in kidney stones when 400 IU taken with 1000mg calcium in WHI
- ? Increased risk of arterial calcifications in vit D takers?
- Patients with granulomatous disorders need to keep levels less than 30ng/ml (20-30 is recommended) due to risk of hypercalciuria and hypercalcemia (macrophages produce 1-25-Vit D)

Diagnosis of deficiency

- Measure 25-OH Vitamin D (**not** 1-25-OH)
 - ½ life of 25-OH is 15 days (vs 15 hrs for 1-25)
 - 1-25 is tightly regulated by the kidney and will not be decreased unless *severely* deficient
- Reference ranges
 - Less than 15 ng/ml is insufficient
 - Greater than 15 ng/ml considered normal by NIH
 - Many experts say <20 is insufficient
 - Others advocate above 30 ng/ml as normal
 - Levels >200 ng/ml are potentially toxic (can cause hypercalcemia)

Populations at risk for deficiency

- Breast-fed infants
- Poor intestinal absorption (celiac, IBD)
- Patients taking steroids, phenytoin, phenobarbital
- Chronic kidney disease patients
- EVERYONE who lives above 34° or wears protective clothing or sunscreen or doesn't spend much time outside

Prevalence of Deficiency

- NHANES III (1988-1994)
 - 42.2% in African American women
 - 4% in caucasian women
- NHANES (2000-2004) – prevalence increasing
 - age-adjusted mean 2-8 ng/ml lower than '88-'94
 - 8-36% had levels below 20 ng/ml
 - 50-78% had levels below 30 ng/ml
 - Felt to be due to increased BMI's, reduced milk intake, and greater use of sunscreen

Prevalence of Insufficiency (level <20)

- **52% of Hispanic and black adolescents in Boston** (Gordon et al, Prevalence of vitamin D deficiency among healthy adolescents. Arch Pediatr Adolesc Med 2004; 158:531-7)
- **48% of white preadolescent girls in Maine** (Sullivan et al. Adolescent girls in Maine at risk for vitamin D insufficiency. J Am Diet Assoc 2005;105:971-4)
- **32% of med students, physicians, and residents aged 18-29 in Boston**
 - Daily MVI correlated with higher values, but milk-drinking did not
 - (Tangpricha et al. Vitamin D insufficiency among free-living healthy young adults. Am J Med 2002;112:659-62)

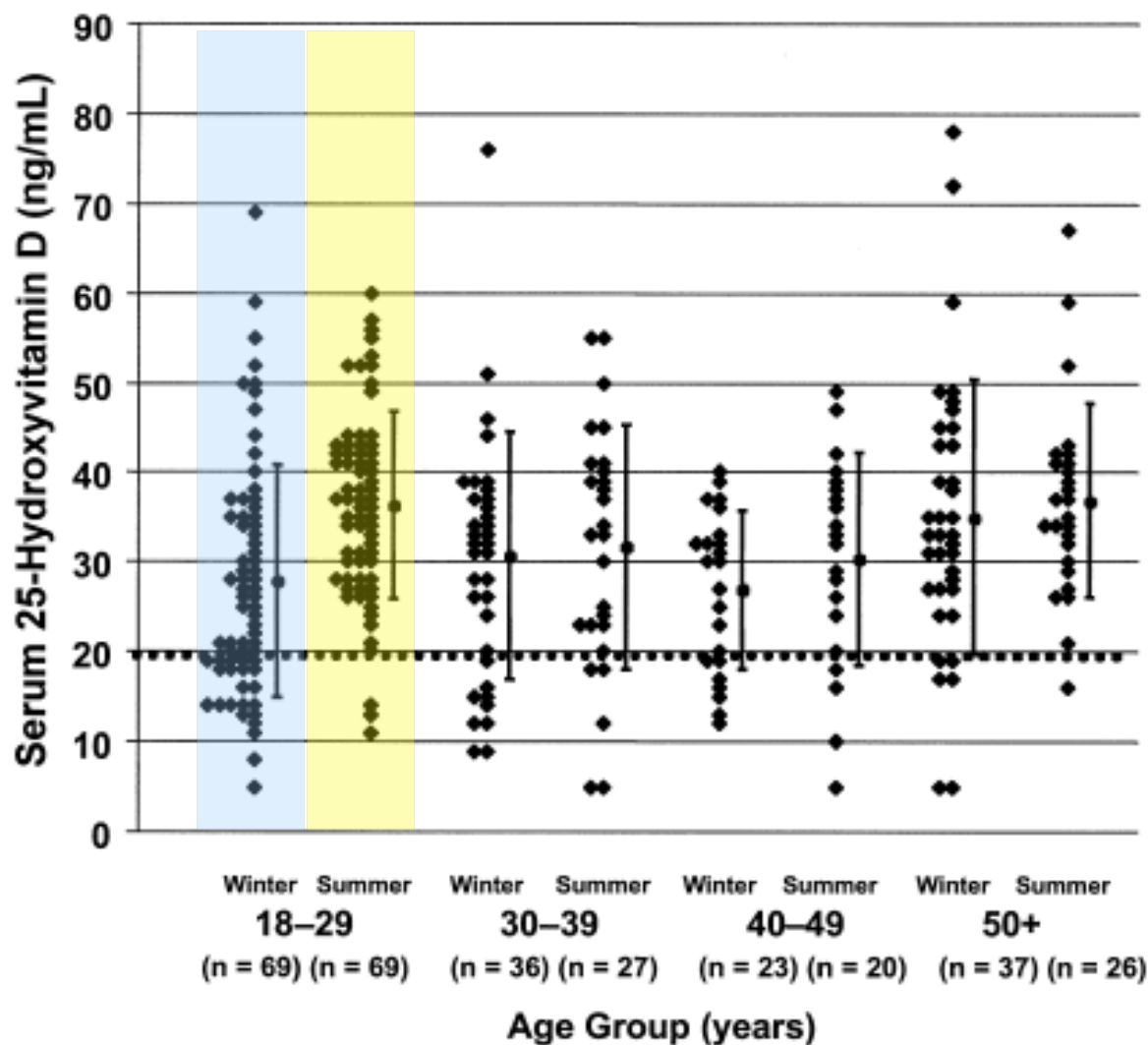


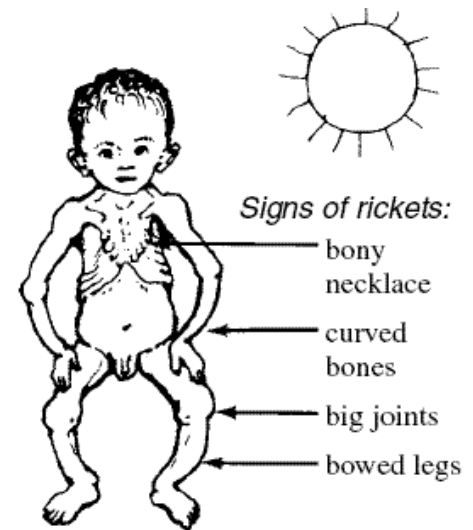
Figure 2. Seasonal variation in 25-hydroxyvitamin D levels by age group. Means are presented with error bars representing the SD. Subjects in the end-of-summer groups had higher 25-hydroxyvitamin D levels. The dashed horizontal line represents the minimum level of 25-hydroxyvitamin D considered to be vitamin D sufficient (12). There was a significant difference in the mean serum 25-hydroxyvitamin D levels in the 18- to 29-year-old group when comparing the end-of-winter with the end-of-summer groups ($P < 0.01$).

Prevalence at Cornell, among students in whom the test was ordered

- Sept 1, 2009 – Aug 31, 2010
- 356 tests ordered (diagnostic, not screening)
- 234 (66%) were abnormal (level less than 32)

Sequellae of Deficiency

- Children: rickets
 - 1930's milk supplementation started and rickets virtually disappeared until recently
 - Growth retardation, bony deformities
- Adults: osteomalacia
 - Bone pain
 - Usually aching, throbbing
 - Can be localized or generalized
 - Press on sternum or tibia with thumb
 - Proximal muscle weakness
 - D Receptors on skeletal muscle
 - Need level above 40 for maximal strength



SUNLIGHT IS THE BEST PREVENTION
AND TREATMENT OF RICKETS

Sequellae of Deficiency

- 93% of outpatients aged 10-65, in Minneapolis, with persistent nonspecific MS pain were vitamin D deficient (<20)
 - deficiency was most severe in those under age 30
 - given wide variety of diagnoses (fibromyalgia, chronic fatigue, depression and others)
 - 100% of Africans, Afr Americans, Hispanics, Native Americans were deficient
- 5 patients had undetectable levels

Plotnikoff & Quigley. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clin Proc 2003;78:1463-70

Sequellae of Deficiency

Patient	Back pain	Weak-ness	Fat-igue	Depr. mood	Insom-nia	Head-ache	Diffuse MS Pain	Dxs given
23F White	+	+	+					Dysthymia, LBP, Non-degen joint disease
26M SE Asian			+		+		+	Dysthymia Stress reaction
27F AfrAm	++	+	+	+	+			3 rd tri preg. Gest DM
35F East Afr.		+	+		+	+	+	MDD PTSD
58M AfrAm	++	+		+	+			Dysthymia/MDD Somatofrom d/o DJD refractory to surgery

Plotnikoff & Quigley. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clin Proc 2003;78:1463-70

Conditions Associated with Vitamin D Deficiency

- Schizophrenia
- Depression
- Colon cancer
- Osteopenia, osteoporosis, & fracture
- Hypertension and congestive heart failure
- Muscle weakness
- Insulin resistance / metabolic syndrome
- Obesity

Benefits of Vitamin D

- Use of supplements (200-1100 IU) results in statistically significant 7% decrease in overall mortality
- Protective effect against colon cancer (50% reduction)
- Protective against osteopenia, osteoporosis, falls, fractures
- Possible protective effect against breast and prostate cancers
- Probable protection against:
 - Diabetes (type 1 and 2)
 - Hypertension
 - Glucose intolerance
 - Multiple Sclerosis
- Many of these benefits require intakes of >800 IU daily

Benefits of Vitamin D

- Vieth et al, Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. Nutrition Journal 2004, 3:8
 - Supplemented 100 patients with either 4000 IU daily or 600 IU daily
 - Measured serum levels, biomarkers, and administered well-being questionnaire
 - All patients had improvements in both serum levels and in well-being scores, but significantly more in the 4000 IU group
 - There were no adverse effects in the 4000 IU group, demonstrating its safety

Benefits of Vitamin D

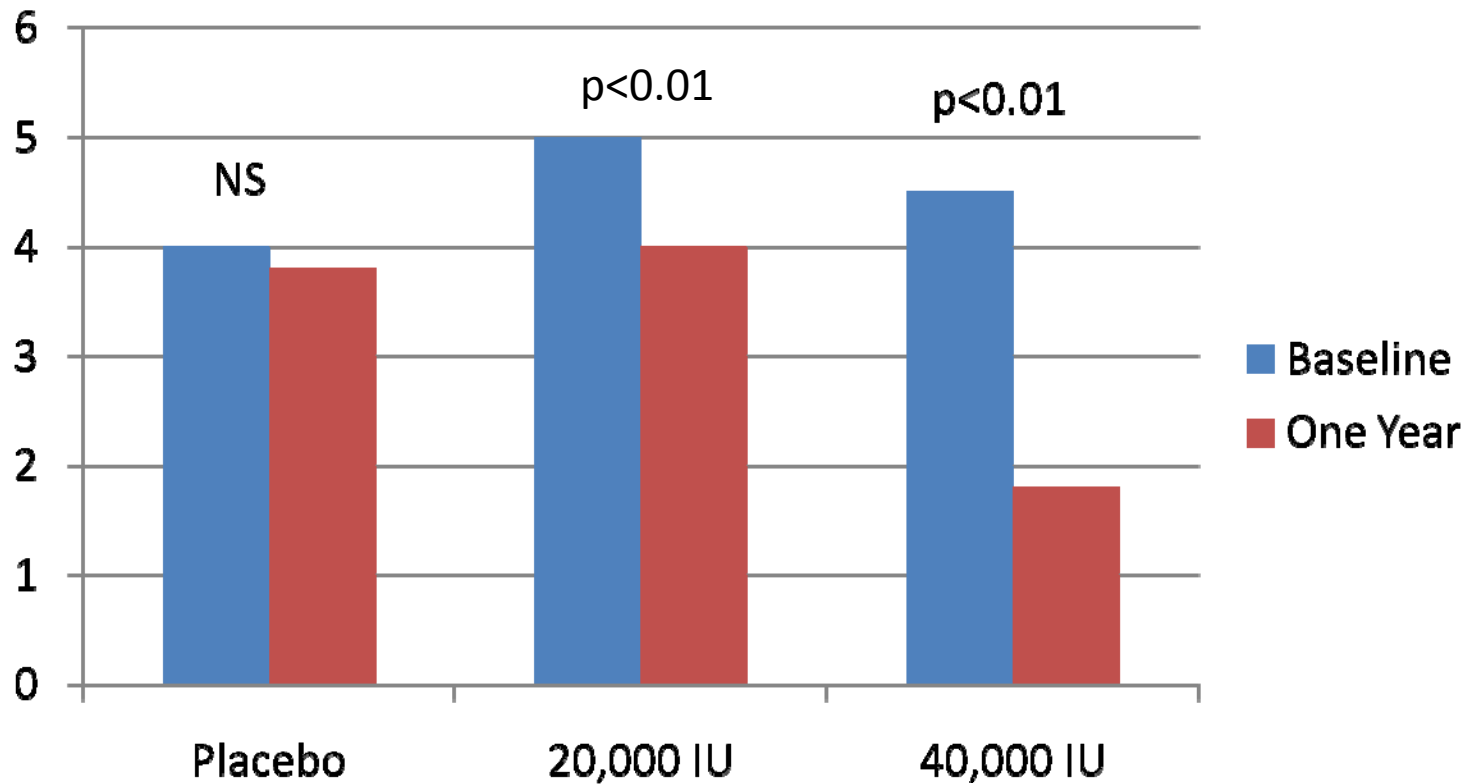
- Gloth and Alam, Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. J Nutr Health Aging. 1999;3(1);5-7
 - 15 patients with SAD randomized to either phototherapy or 100,000 IU vitamin D
 - Administered HAM-D, SIGH-SAD, and SAD-8 at baseline and 1 month
 - Both groups had improved vitamin D levels, but more so in the Vit D group
 - All subjects in Vit D group improved in all outcome measures
 - Phototherapy group had no significant improvement on depression measures

Benefits of Vitamin D

- Jorde et al. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. J Int Med 2008
 - 441 subjects w/BMIs 28-47
 - All subjects had borderline mean baseline Vit D status
 - Randomized to placebo, 20,000 IU Vit D per week, or 40,000 IU Vit D per week for 1 year
 - Administered Beck Depression Inventory

Benefits of Vitamin D

Jorde et al, BDI Scores by Group



Benefits of Vitamin D

- Arvold et al, Correlation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: a randomized controlled trial. *Endocr Pract.* 2009 Apr;15(3):203-12
 - 100 patients with mild-moderate deficiency (10-25 ng/ml)
 - Randomized to 50,000 IU weekly or placebo x 8 weeks
 - 38 severely deficient (<10) patients were treated
 - Patients in RCT treatment group showed significant improvement in fibromyalgia assessment scores (p=0.03)
 - Severely deficient patients did not show improvement at 8 weeks



Take Home Messages

- Vitamin D deficiency is common
- Even when asymptomatic, is associated with worse health outcomes
- Consider testing levels in patients with
 - Fatigue or weakness
 - Insomnia
 - Depressed mood
 - Low back or nonspecific musculoskeletal pain
 - Weird paresthesias (this is my anecdote based on 3 patients)
 - If you're getting a B12 level!

My approach

- If patient found to be deficient (I use <32 ng/dl), treat
 - Rx 50,000 IU ergocalciferol once to twice weekly for 8-12 weeks or
 - Tanning once to twice weekly for 8-12 weeks (no burns)
 - Then recheck level
- If patient borderline normal at the end of summer, supplement
 - 1-2000 IU daily or
 - Tanning
- If level is normal but need maintenance, consider 1000 IUD daily
- Consider taking a supplement yourself, or getting more sun (natural or artificial!)

Thank you!
Questions...