Slide 1

Let the Sunshine In

The evidence, or lack thereof, regarding Vitamin D.

Alexandra Hall MD
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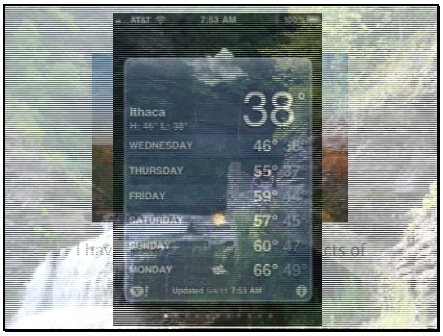
Slide 2



Slide 3

What is Vitamin D?

- Fat-soluble vitamin (ADEK)
- Production 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

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History of Vitamin D

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.

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How do we normally get vitamin D?

Slide 6

Food Sources

- Cod liver oil
- Fatty fish
- Fortified milk and cereals
- Irradiated mushrooms

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Food Sources

Food	Amount	Vitamin D Content
Cod liver oil	15 ml (1 tbsp)	1360 IU
Mushrooms, irradiated	3.5 oz	500 IU
Salmon	3.5 oz	360 IU
Sardines canned in oil	1.75 oz	250 IU
Tuna canned in oil	3.5 oz	235 IU
Lowfat (1%) Milk	1 cup	127 IU
Soy milk	1 cup	100 IU
Whole milk	1 cup	97 IU
Fruit Loops	¾ cup	36 IU
Eggs	1 egg	20 IU
Mushrooms, regular	3.5 oz	14 IU

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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 5000 IU

- Prescription
  - Ergocalciferol (D2) 50,000 units once to twice weekly
- Best absorbed if taken with food that contains fat

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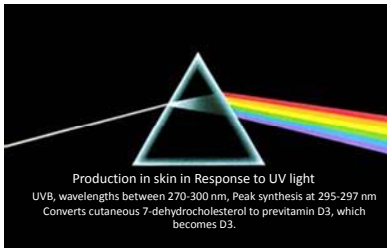
How do we normally get vitamin D?



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.

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Sun Exposure and Sunbathing

- Need approx 5-30 minutes midday sun twice weekly (we think)
- 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

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Wait, did she just say go tanning?!

- Cutaneous production
  - 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

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Factors Impacting Cutaneous Production

- Latitude
  - No appreciable synthesis above 42° latitude from Nov-Feb
    - NY/PA border, Boston, Chicago, CA/OR border
  - Year-round synthesis if latitude below 34°
    - Los Angeles, Columbia SC – Phoenix is 33
- 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

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Risk factors for deficiency

Table 1. Factors contributing to the predictors of age-adjusted plasma 25-hydroxyvitamin D [25(OH)D] level from a multiple linear regression model of 1095 men in the Health Professionals Follow-Up Study

Factor	Change in 25(OH)D, nmol/L
Intercept	90.8
Race	
White	0 (referent)
African American	−12.8
Asian	−13.3
Residence	
South	0 (referent)
Midwest/West	−2.4
Northeast/Mid-Atlantic	−6.4
Quintile of leisure-time physical activity*	
5	0 (referent)
4	−4.5
3	−5.7
2	−9.0
1	−13.2

Journal of the National Cancer Institute, Vol. 98, No. 7, April 5, 2006

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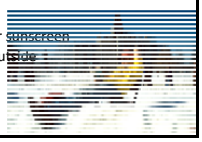
Populations at risk for deficiency

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



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How much is enough?

- Good question
  - Evidence is not conclusive (more to come)
  - May not be the same for all groups of people
- Recommended dosages:
  - Prior to 2010 report:
    - 200 IU daily ages 0-50 (Inst. Of Med. Food Nutrit. Board)
    - 400-600 IU daily over 50 (IOM FNB)
  - Per new IOM RDI report:
    - 400 IU for kids
    - 600 IU for adults
    - 800 IU for adults over 70

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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
- Theoretical increased risk of arterial calcifications with D has been disproven
- 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)
- U-shaped curve of all-cause mortality and cardiovascular disease

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What do we need it for?

- Promotion of calcium absorption in gut
  - Without D, absorb 10-15%, with it absorb 30-40%
- Maintenance of adequate serum calcium and phosphate levels

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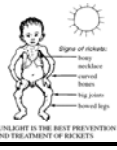
Sequellae of Deficiency

- Children: rickets
  - Growth retardation, bony deformities
  - Incidence very high during industrial revolution
  - 1930's milk supplementation started and it virtually disappeared until recently

- Adults: osteomalacia
  - Bone pain
    - Usually aching, throbbing
    - Can be localized or generalized
  - Proximal muscle weakness
    - D Receptors on skeletal muscle
    - Need level above 40 for maximal strength



SUNLIGHT IS THE BEST PREVENTION AND TREATMENT OF RICKETS

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ARE WE GETTING ENOUGH?

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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
  - Most experts say <20 is deficient
  - Others advocate above 30 ng/ml as normal
  - Levels >200 ng/ml are potentially toxic (can cause hypercalcemia)

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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
  - 50-78% had levels below 30
  - Felt to be due to increased BMI, reduced milk intake, and greater use of sunscreen

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Increasing prevalence of vitamin D deficiency

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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 insufficency among free-living healthy young adults. Am J Med 2002;112:659-62)

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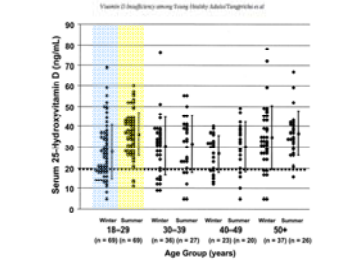

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Sequellae of Deficiency - Osteomalacia

- Outpatients aged 10-65, in Minneapolis, with persistent nonspecific MS pain
  - 93% of were vitamin D deficient (<20)
  - deficiency was most severe in those under age 30
  - given wide variety of diagnoses (fibromyalgia, chronic fatigue, depression, etc.)
- 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

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Sequellae of Deficiency

Patient	Weak-ness	Fatigue	Depr. mood	Insom nia	Back pain	Diffuse MS Pain	Dxs given
23F White	+	+			+		Dysthymia, LBP, Non-degen joint disease
26M SE Asian		+		+		+	Dysthymia Stress reaction
27F AfrAm	+	+	+	+	++		3rd 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

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What do we need it for?

- Promotion of calcium absorption in gut
  - Without D, absorb 10-15%, with it absorb 30-40%
- 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

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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

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NIH 2010 DRI Calcium and Vitamin D

- Evaluated the evidence regarding new health claims for Vitamin D
- Also evaluated calcium data, as the two are inextricably combined
- Expert panel, reviewed thousands of studies, made recommendations using a risk assessment framework

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What is the Evidence?

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Remember, epidemiologic studies can only show correlation, not causation!

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Limitations of Epidemiologic Studies of Vitamin D – Dietary Intake

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Limitations of Epidemiologic Studies of Vitamin D – Serum Levels

Slide 35

RCTs are designed to look for causation.
(attempt to control for confounding factors)

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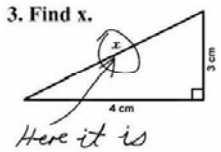

Fuzzy Math

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ALL-CAUSE MORTALITY

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Epidemiologic data – serum levels

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25-hydroxyl Vitamin D Levels and the Risk of Mortality in the General Population *Arch Intern Med.* 2008 August 11; 168(15): 1629–1637.

Michal L. Melamed, MD, MHS[1,*], Erin D. Michos, MD, MHS[2], Wendy Post, MD, MS[2,3], and Brad Astor, PhD[3,4]

- NHANES III
- 13,331 adults followed for median 8.7 years
- Vitamin D < 17.8 was associated with a 26% increase in mortality (RR 1.26, CI 1.08-1.46)
- This was after adjustment for obesity, physical activity, renal function, and low SES (before adjustment the RR was 1.78!)

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Melamed et al 2008

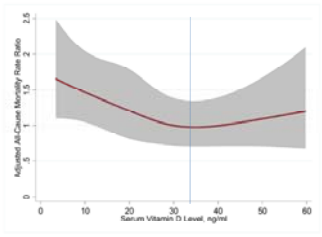

Figure 1.
Restricted cubic spline showing the fully adjusted associations between serum 25(OH)D levels and all-cause mortality in 13,331 participants of NHANES III. Knots are at 10.9, 20.5, 28.9 and 45.9 ng/mL. To convert to SI units (nmol/L), multiply 25(OH)D value by 2.496.

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Randomized Controlled Trials

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Vitamin D Supplementation and Total Mortality

A Meta-analysis of Randomized Controlled Trials

Philippe Autier, MD; Sara Gandini, PhD

Arch Intern Med. 2007;167(16):1730-1737

7 % reduction in all-cause mortality overall
In no individual study were the results statistically significant
Doses ranged from 300-2000 IU of D daily
In no study was mortality the primary endpoint
Almost all of the study participants were age > 60

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Vitamin D and Overall Mortality

- Epidemiologic data shows correlation, but is prone to confounding factors
- But also shows a U-shaped curve: too much is also associated with increased mortality
- RCTs don't show a very large effect
  - Insufficient dosing?
  - Confounding by 'toxicity'?

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CANCER PREVENTION

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Epidemiologic data

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Prospective Study of Predictors of Vitamin D Status and Cancer Incidence and Mortality in Men

Edward Giovannucci, Yan Liu, Eric B. Rimm, Bruce W. Hollis, Charles S. Fuchs, Meir J. Stampfer, Walter C. Willett [J Natl Cancer Inst 2006;98:451–9]

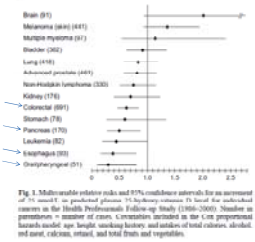

Fig. 1. Multivariable relative risks and 95% confidence intervals for an increment of 75 nmol/L in predicted plasma 25-hydroxy-vitamin D level for individual cancers in the Health Professionals Follow-up Study (1986–2000). Number in parentheses = number of cases. Covariates included in the Cox proportional hazards model: age, height, smoking history, and intakes of total calories, alcohol, red meat, calcium, retinol, and total fruits and vegetables.

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Randomized Controlled Trials

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Effect of four monthly oral vitamin D, (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial

Dakshu P Trivedi, Richard Doll, Kay Tee Khaw

BMJ VOLUME 326 1 MARCH 2003

Table 3 Mortality from all causes, cardiovascular disease, and cancer by death certification 1996-2002 and age adjusted relative risks (Cox regression), according to treatment allocation at randomisation (intention to treat) in 2686 men and women aged 65-85 years. Values are numbers (percentages) unless stated otherwise

Cause of death*	Vitamin D	Placebo	Age adjusted relative risk (95% CI)	P value†
All	(n=1345)	(n=1341)		
All causes	224 (16.7)	247 (18.4)	0.88 (0.74 to 1.06)	0.18
Cardiovascular disease	101 (7.5)	117 (8.7)	0.84 (0.65 to 1.10)	0.20
Ischaemic heart disease	42 (3.1)	49 (3.7)	0.84 (0.56 to 1.27)	0.41
Cerebrovascular disease	28 (2.1)	26 (1.9)	1.04 (0.61 to 1.77)	0.89
Cancer	63 (4.7)	72 (5.4)	0.86 (0.61 to 1.20)	0.37
Lung	7 (0.5)	11 (0.8)	0.62 (0.24 to 1.60)	0.32
Respiratory	10 (0.7)	11 (0.8)	0.89 (0.38 to 2.09)	0.79

100,000 IU every 4 months for 5 years

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Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial[1,2] *Am J Clin Nutr* 2007;85:1586–91.

Joan M Lappe, Dianne Travers-Gustafson, K Michael Davies, Robert R Recker, and Robert P Heaney

- 1179 postmenopausal women
- Nebraska (lat 41.4°N)
- 1400 mgCa + 1100 IU Vit D vs Ca alone vs placebo
- Serum levels of D rose to ≥32
- 4 years
- primary outcome was fracture
- secondary was cancer incidence
- Total of 50 cancers, 13 in year one, 37 thereafter

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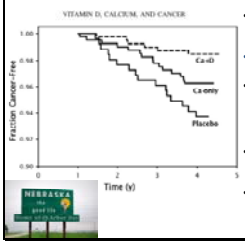
Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial[1,2]

Joan M Lappe, Dianne Travers-Gustafson, K Michael Davies, Robert R Recker, and Robert P Heaney



- When confined to dx s/p first 12 months RR for Ca+D group was 0.232 (0.09-0.6, p<0.005)
- That's a 75% reduction in the incidence of cancer!
- Insufficient power to show difference by individual cancer type, but trends showed reduction for breast, colon, lung, hematologic cancers.
- RR of all cancers in CA+D group was 0.4 (0.2-0.8, p=0.013)
- Ca alone group was NS

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Overall cancer

- One study showed no statistically significant benefit

- One study showed benefit with higher dose of D (1100 IU), and combined with Calcium, in women

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Photo by: Anna Antell

BREAST CANCER

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Breast Cancer and Vitamin D

- In vitro, calcitriol acts on breast cancer cells to cause:
  - Cell cycle inhibition
  - Reduced proliferation
  - Enhanced sensitivity to apoptosis
  - Induction of differentiation markers
- However, achieving these levels in vivo is frequently associated with hypercalcemic toxicity
- Current research ongoing for mutations of the *Vdr* gene in breast cancer

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Epidemiologic studies of intake & exposure

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Epidemiologic studies of intake/exposure

- Rossi 2009, Case-Control study in Italy of dietary D
  - 2569 cases and 2588 controls
  - Small benefit (RR 0.79) seen in highest decile of intake (approx 143 IU) vs. lowest
  - Benefit significant only in postmenopausal women and those in Southern Italy

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Epidemiologic studies of intake/exposure

- John 1999, NHANES cohort study of sun exposure
  - 190 cases in cohort of 5000 white women
  - Small benefit in women who worked outdoors the most, but didn't retain statistical significance after multivariate risk adjustment
  - No benefit based on physician-assessed or self-reported sun exposure

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Epidemiologic studies of intake/exposure

- Shin 2002, Cohort from Nurses Health Study
  - 88 691 women, 3482 incident breast cancers
  - Use of Vit D supplements had no relationship to breast cancer
  - Among pre-menopausal women only, high consumption of low-fat dairy products was associated with a slightly lower incidence of breast cancer

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Epidemiologic studies of Serum Vitamin D

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Vitamin D and prevention of breast cancer: Pooled analysis

Cedric F. Garland[a,*], Edward D. Gorham[a], Sharif B. Mohr[a], William B. Grant[b], Edward L. Giovannucci[c], Martin Lipkin[d], Harold Newmark[e,f], Michael F. Holick[g], Frank C. Garland[a]

Journal of Steroid Biochemistry & Molecular Biology 103 (2007) 708–711

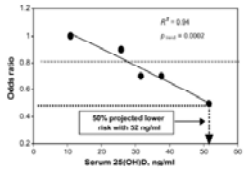

Fig. 3. Dose–response gradient of risk of breast cancer according to serum 25-hydroxyvitamin D concentration, pooled analysis.

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Vitamin D and prevention of breast cancer: Pooled analysis

Cedric F. Garland[a,*], Edward D. Gorham[a], Sharif B. Mohr[a], William B. Grant[b], Edward L. Giovannucci[c], Martin Lipkin[d], Harold Newmark[e,f], Michael F. Holick[g], Frank C. Garland[a]

Table 1
Projected annual number of breast cancer cases prevented, according to serum 25-hydroxyvitamin D level and corresponding Strata

Vitamin D_3		Serum 25(OH)D		Projected	
mcg/day[a]	IU/day[a]	ng/ml[b]	nM[b]	Prevented (%)[b]	Number of cases prevented
25	1000	22	55	21	45,000
50	2000	32	77	31	66,000
60	2400	36	87	35	74,000
75	3000	42	102	40	86,000
95	3800	50	121	48	103,000
100	4000	52	126	50	107,000

- Current total breast cancer in US: 214,000 cases per year
- This chart assumes that baseline population has a serum level below 10 ng/ml, which is not true

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Serum D and Breast CA

- Freedman 2007 – total mortality from Breast CA lower in those in highest stratification, but that was only 8 women, and trend not significant
- Bertone-Johnston 2005, nested case-control in Nurses Health Study – relationship only in women over 60
- Freedman 2008 nested case-control in PLCO Cancer Screening Trial – no relationship

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Any randomized controlled trials?

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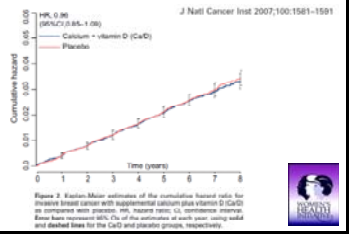
Calcium Plus Vitamin D Supplementation and the Risk of Breast Cancer

Rowan T. Chlebowski, Karen C. Johnson, Charles Kooperberg, Mary Pettinger, Jean Wactawski-Wende, Tom Rohan, Jacques Rossouw, Dorothy Lane, Mary Jo O'Sullivan, Shagufta Yasmeen, Robert A. Hiatt, James M. Shikany, Mara Vitolins, Janu Khandekar, F. Allan Hubbell; for the Women's Health Initiative Investigators

J Natl Cancer Inst 2007;100:1581–1591



WHI, RCT
400 IU of D + Ca
18 000 women
in each group

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Breast Cancer and Vitamin D

- Conflicting epidemiological data
  - Intake/exposure studies show, at best, small effect
  - Serum studies, with few exceptions, mostly show no effect
- Large RCT did not show a protective effect of 400 IU Vitamin D + Calcium against breast cancer
- More RCTs, with higher doses, and of vitamin D alone, would be useful.

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COLON CANCER

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Epidemiologic data – dietary intake

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Colorectal cancer and D, Epi studies

- McCullough, Cancer Cases and Control 2003
  - Cohort study: 127,000 people, 600 incident cases
  - Only association seen was in men who consumed > 525 IU of D daily (diet + supp), who had 30% lower incidence, but barely statistically significant

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Colorectal cancer and D, Epi studies

- Slattery 2004, Int J Cancer
  - 2300 Cases and 2700controls
  - Correlations seen in women only:

- highest calcium intake (1275 mg) had 60% lower incidence
- highest D intake (400 IU) had 40% lower incidence
- 3+ servings of low fat dairy per day had 40% lower incidence

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Epidemiologic data – serum levels

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Prospective Study of Predictors of Vitamin D Status and Cancer Incidence and Mortality in Men

Edward Giovannucci, Yan Liu, Eric B. Rimm, Bruce W. Hollis, Charles S. Fuchs, Meir J. Stampfer, Walter C. Willett **[J Natl Cancer Inst 2006;98:451–9]**

Table 4. Relative risks (RRs) and 95% confidence intervals (CIs) for an increment of 25 nmol/L in predicted plasma 25-hydroxy-vitamin D [25(OH)D] level for digestive system cancer incidence and mortality in the Health Professionals Follow-Up Study (1986–2000)

Endpoint	RR (95% CI)
Digestive cancer incidence (n = 1123)	
Age-adjusted	0.54 (0.44 to 0.66)
Multivariable-adjusted*	0.57 (0.46 to 0.71)
Multivariable + BMI†	0.59 (0.47 to 0.75)
Multivariable + physical activity	0.52 (0.38 to 0.71)
Digestive cancer mortality (n = 564)	
Age-adjusted	0.51 (0.39 to 0.67)
Multivariable-adjusted*	0.55 (0.41 to 0.74)
Multivariable + BMI†	0.54 (0.39 to 0.75)
Multivariable + physical activity	0.45 (0.30 to 0.68)

*The following covariables were included in the Cox proportional hazards model: age, height, smoking history, and intakes of total calories, alcohol, red meat, calcium, retinol, and total fruits and vegetables.

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What about Randomized Controlled Trials?

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Colon Cancer and Vitamin D: RCTs

- **Calcium Plus Vitamin D Supplementation and the Risk of Colorectal Cancer.** Wactawski-Wende et al. Obstetrical & Gynecological Survey: June 2006 - Volume 61 - Issue 6 - pp 389-390
- WHI: 36,000 women randomized to placebo vs Calcium 500 + D 400 for 7 years
- 322 confirmed colorectal cancers
- HR 1.08 [0.86-1.34]
- *No effect of supplementation* on development of colorectal cancer in women

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Colon Cancer and Vitamin D: RCTs

- Grou et al. 2003 JNCI
- Adenoma recurrence in 803 subjects
- Only found effect when considered Ca + D
  - If vit D at/above mean, calcium supplementation mildly protective
  - If taking calcium supplements, higher serum D also slightly protective

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Effect of four monthly oral vitamin D_3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial

BMJ VOLUME 326 1 MARCH 2003

Daksha P Trivedi, Richard Doll, Kay-Tee Khaw

Table 3 Mortality from all causes, cardiovascular disease, and cancer by death certification 1996-2002 and age adjusted relative risks (Cox regression), according to treatment allocation at randomisation (intention to treat) in 2686 men and women aged 65-85 years. Values are numbers (percentages) unless stated otherwise

Cause of death*	Vitamin D	Placebo	Age adjusted relative risk (95% CI)	P value†
All	(n=1345)	(n=1341)		
All causes	224 (16.7)	247 (18.4)	0.88 (0.74 to 1.06)	0.18
Cardiovascular disease	101 (7.5)	117 (8.7)	0.84 (0.65 to 1.10)	0.20
Ischaemic heart disease	42 (3.1)	49 (3.7)	0.84 (0.56 to 1.27)	0.41
Cerebrovascular disease	28 (2.1)	26 (1.9)	1.04 (0.61 to 1.77)	0.89
Cancer	63 (4.7)	72 (5.4)	0.86 (0.61 to 1.20)	0.37
Colon	7 (0.5)	11 (0.8)	0.62 (0.24 to 1.60)	0.33
Respiratory	10 (0.7)	11 (0.8)	0.89 (0.38 to 2.09)	0.78

Slide 75

Colon Cancer and Vitamin D

- Epidemiologic studies, especially those comparing serum levels, seem to show some protective association. May be confounding due to BMI and physical activity.
- RCTs do not support this hypothesis.
- Further studies are needed, especially with higher doses of vitamin D.

Slide 76

Prostate Cancer and Vitamin D

- In vitro studies suggest protective effect
- Mortality rates from prostate cancer appear to be inversely related to sun exposure
- Epidemiologic studies show no correlation with exception of 1 C-rated study of serum levels
- No RCTs have been performed

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CARDIOVASCULAR DISEASE

Slide 78

Potential link between D and CVD?

- 2005, Zittermal et al.
- Higher cardiovascular mortality
  - During the winter
  - In regions with less average exposure to sunlight

Slide 79

Epidemiologic data – serum levels

Slide 80

Vitamin D Deficiency and Risk of Cardiovascular Disease

Thomas J. Wang, MD; Michael J. Pencina, PhD; Sarah L. Booth, PhD; Paul F. Jacques, DSc; Erik Ingelsson, MD, PhD; Katherine Lanier, BS; Emelia J. Benjamin, MD, MSc; Ralph B. D'Agostino, PhD; Myles Wolf, MD, MMSc*; Ramachandran S. Vasan, MD*

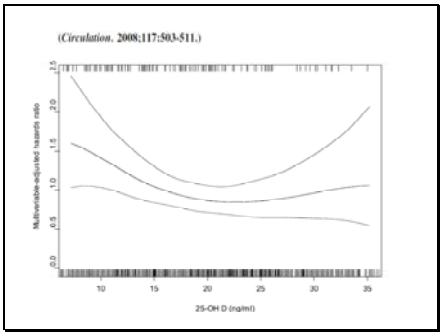
(*Circulation*. 2008;117:503-511.)

Table 3. Results of Multivariable Analyses (n=1739)

	Adjusted for Age and Sex	Adjusted for Clinical Covariates*	Adjusted for Clinical Covariates and CRP
Two-category models			
25-OH D ≥15 ng/mL	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
25-OH D <15 ng/mL	3.04 (1.43–2.94)	1.63 (1.11–2.36)	1.66 (1.13–2.43)
P	<0.001	0.01	0.01
Three-category models			
25-OH D ≥15 ng/mL	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
25-OH D 10 to <15 ng/mL	1.80 (1.18–2.75)	1.53 (1.00–2.36)	1.59 (1.03–2.45)
25-OH D <10 ng/mL	2.63 (1.57–4.38)	1.80 (1.05–3.08)	1.81 (1.03–3.18)
P (linear trend)	<0.001	0.01	0.01

CRP indicates C-reactive protein.
Values are multivariable-adjusted hazard ratios, with 95% CIs in parentheses.
*Clinical covariates are age, sex, systolic blood pressure, antihypertensive treatment, diabetes mellitus, serum creatinine, total-to–high-density lipoprotein cholesterol ratio, cigarette smoking, and body mass index.

Slide 81



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Randomized Controlled Trials?

Slide 83

Effect of four monthly oral vitamin D_3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial

BMJ VOLUME 326 1 MARCH 2003

Dakshi P Trivedi, Richard Doll, Kay Tee Khaw

Table 3 Mortality from all causes, cardiovascular disease, and cancer by death certification 1996-2002 and age adjusted relative risks (Cox regression), according to treatment allocation at randomisation (intention to treat) in 2686 men and women aged 65-85 years. Values are numbers (percentages) unless stated otherwise

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Slide 84

Calcium/Vitamin D Supplementation and Cardiovascular Events (*Circulation*. 2007;115:846-854.)

Judith Hsia, MD; Gerardo Heiss, MD, PhD; Hong Ren, MS; Matthew Allison, MD, MPH; Nancy C. Dolan, MD; Philip Greenland, MD; Susan R. Heckbert, MD, PhD; Karen C. Johnson, MD, MPH; JoAnn E. Manson, MD, DrPH; Stephen Sidney, MD, MPH; Maurizio Trevisan, PhD; for the Women's Health Initiative Investigators

36,000 women

MI or Coronary Death

Stroke

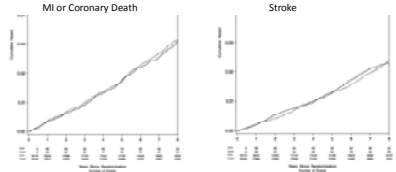


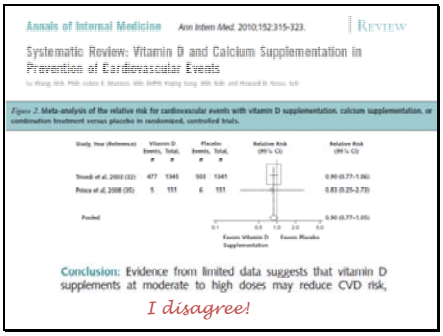
Figure 2. Kaplan-Meier estimates of cumulative hazard rates for CHD (myocardial infarction or coronary death; left) and for stroke (right). HR indicates hazard ratio.

Slide 85

Other RCTs on CVD and D

- Major et al. 2007, 400 IU
- Margolis et al. 2008, 400 IU
- Prince et al. 2008, 1000 IU
- Manson et al. 2010, 400 IU
- NONE found a statistically significant treatment-related effect of vitamin D on cardiovascular disease

Slide 86


Annals of Internal Medicine Ann Intern Med. 2010;152:315-323. REVIEW

Systematic Review: Vitamin D and Calcium Supplementation in Prevention of Cardiovascular Events

Figure 2. Meta-analysis of the relative risk for cardiovascular events with vitamin D supplementation, calcium supplementation, or combination treatment versus placebo in randomized, controlled trials.

Conclusion: Evidence from limited data suggests that vitamin D supplements at moderate to high doses may reduce CVD risk,

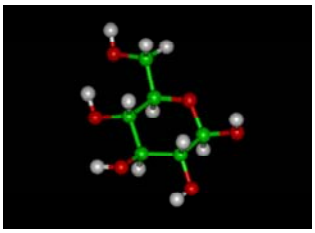
I disagree!

Slide 87

D and CVD

- Epidemiologic data look promising
  - But may be confounded by physical activity levels
- Clinical trials show no effect
  - May be insufficient dose of the D
- Concern about potential U-shaped curve, that too much might be harmful

Slide 88



DIABETES AND METABOLIC SYNDROME

Slide 89

Diabetes and Metabolic Syndrome

- Calcitriol plays a role in
  - Synthesis and secretion of insulin
  - Calcium trafficking in beta-islet cells
  - Action of insulin
- Demonstrated in vitro and in animal models

Slide 90

Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers[1–3]

Am J Clin Nutr 2009;89:1321–7.

- 200 overweight subjects with mean Vit D 12 ng/ml in a weight loss program
- Randomized to Vit D 3332 IU or placebo x 12 mo
- Findings:
  - No impact on weight loss
  - Vit D levels increased to mean of 34 ng/ml (vs 17, p>0.0001)
  - Greater decrease in TGs (-27% vs -19%, p=0.014)
  - Greater decrease in TNF-α (-10% vs -3%, p=0.049)
  - **Increased LDL (+5% vs -2.5%, p<0.001)**

Slide 91

Calcium Plus Vitamin D Supplementation and the Risk of Incident Diabetes in the Women's Health Initiative *Diabetes Care* 31:701–707, 2008

- 33,951 women, mean age 62, w/o DM at baseline
- 400 IU of D + 1000 mg Ca daily vs placebo x 7 yrs
- Hazard ratio for DM was 1.01 (CI 0.94-1.10)
- NO effect on incident diabetes

Slide 92

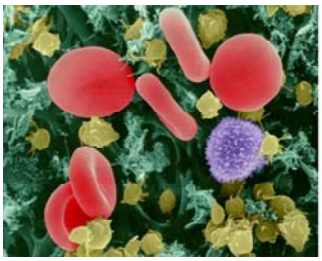
Annals of Internal Medicine | REVIE

Systematic Review: Vitamin D and Cardiometabolic Outcomes

Anastassios C. Pittas, MD, MS; Mei Chung, MPH; Thomas Trikalinos, MD; Joanna Mitri, MD; Michael Brendel, BA; Kamal Patel, MPH; Alice H. Lichtenstein, DSc; Joseph Lau, MD; and Ethan M. Balk, MD, MPH *Ann Intern Med.* 2010;152:307-314.

- 7 other RCTs have been performed re DM/IR
- Doses ranged 400- >8000 IU/day
- NONE show an effect of vitamin D on glycemic control
  - Exception – Pittas et al 2007, subgroup of those with IFG had a small net decrease in FPG of 3 mg/dl, p=0.042)

Slide 93

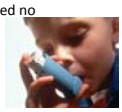


IMMUNE FUNCTION

Slide 94

Asthma and Vitamin D

- Asthma is more common at higher latitudes, New England has the highest prevalence
- Epidemiologic studies of maternal D on kids:
  - 3 studies show that higher maternal intake of during pregnancy is associated with slightly lower risk of wheezing in childhood
  - 1 study of cord blood Vit D showed decreased risk of wheezing with higher levels
  - 1 study of maternal serum levels showed no protection against asthma and in fact showed an increased risk of both eczema and asthma with Vit D levels above 37.5 ng/ml



Slide 95

IDDM and Vitamin D

- Type 1 DM is caused by autoimmune destruction of beta cells in the pancreas
- Genetic and environmental factors
  - Identical twins have only 50% chance of both having the disease
  - Incidence varies with region/latitude, and time of birth
  - Incidence also appears to be increasing

Slide 96

Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis

Arch Dis Child 2008;93:512–517. doi:10.1136/adc.2007.120519

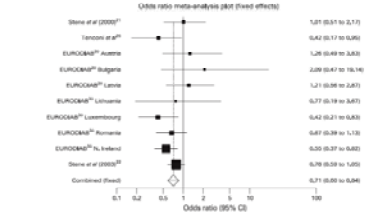


Figure 2 Odds ratios (95% CI) of effect of vitamin D supplementation in infancy on development of type 1 diabetes.

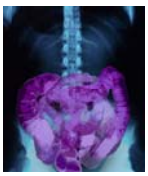
Slide 97

Vitamin D and IDDM in children

- Children who received Vit D supplements had, overall, a 29% reduction in risk of IDDM (OR 0.71, CI 0.60-0.84)
- Greater risk reduction (RR 0.22, CI 0.05-0.89) with regular use of higher dose (2000 IU)
- No studies attempted to identify total D exposure (including diet or sun exposure) nor actual status (serum levels)
- These are all case-control and cohort studies, no randomized controlled trials

Slide 98

Inflammatory Bowel Disease



- Mice who are vitamin D deficient or have a polymorphism in the *Vdr* gene have a higher risk of developing IBD
- Patients who have IBD are often vitamin D deficient (cause vs effect?)
- No case-control studies, no prospective studies, no RCTs have been done

Slide 99

Multiple Sclerosis and Vitamin D

- Administration of calcitriol to rodents exposed to Experimental Allergic Encephalitis (the animal model for MS) can prevent and treat clinical symptoms and pathologic findings
- Low D levels in adolescence are associated with an increased risk of MS, whereas higher outdoor activity is associated with risk reduction
- MS prevalence increases with distance from the equator, also with decreased solar radiation scores
- MS flares often occur at the ends of seasons when people are mostly indoors
- No placebo-controlled studies have been done, but some very small pilot studies (of high to ultra-high doses, 4000 - 40,000 IU per day, leading to serum levels of 175 ng/ml) show potential benefit

Slide 100

Rheumatoid Arthritis

- In mouse model, calcitriol reduces symptoms and halts progression of arthritis
- Iowa Women's Health Study, 29,000 post-menopausal women, supplements of >400 IU were associated with a 34% lower risk, but barely attained statistical significance (RR 0.66, CI 0.43 – 1.0, p=0.03) Merlino et al. ARTHRITIS & RHEUMATISM Vol. 50, No. 1, January 2004, pp 72–77
- No randomized controlled trials for prevention or treatment

Slide 101

MOOD AND WELL-BEING

Slide 102

Mood and Well-Being

- Suicide rates are highest in early spring
- Suicide rates are also higher with increasing latitude
- Seasonal Affective Disorder – is it vitamin D deficiency?

Slide 103

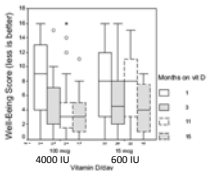
Mood and Well-Being - SAD

- 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

Slide 104

Randomized comparison of the effects of the vitamin D_3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients

Reinhold Vieth*[1], Samantha Kimball[1], Amanda Hu[1] and Paul G Walfish[2,3]



- 82 subjects with baseline Vit D < 24 ng/dL in summer
- Supplemented with either 600 or 4000 IU daily
- Serum levels increased to 32 and 45 ng/dL respectively
- Well-being score, out of 16
- Both groups improved, but the higher dose group had greater improvement

Slide 105

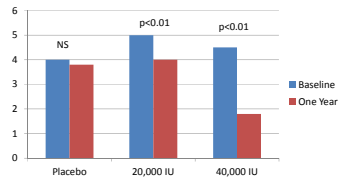
Mood and Well-Being

- 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

Slide 106

Mood and Well-Being

Jorde et al, BDI Scores by Group



Slide 107

Mood and Well-Being

- 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
  - Patients in RCT treatment group showed significant improvement in fibromyalgia assessment scores (p=0.03)
  - 38 severely deficient (<10) patients were treated but did not show improvement at 8 weeks

Slide 108

BONE HEALTH

Slide 109

Calcium and Vitamin D Supplementation Decreases Incidence of Stress Fractures in Female Navy Recruits

Joan Lappe,[1] Diane Cullen,[1] Gleb Haynatzki,[1] Robert Recker,[1] Renee Ahlf,[2] and Kerry Thompson[2]

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 23, Number 5, 2008

- 5200 female Navy recruits
- Randomized to 800 IU D plus 2000 mg Calcium
- 20% reduction in stress fractures (5.3% vs 6.6%, p = 0.0029)

TABLE 3. FRACTURES BY SKELETAL SITE AND TREATMENT GROUP

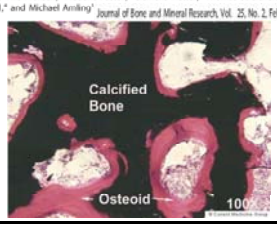
Skeletal site	*Calcium and vitamin D group*	*Placebo group*
Tibia/fibula	138	179
Foot	38	34
Pelvis	3	8
Femur	20	22
Other	27	27
Total	226	270

Slide 110

Bone Mineralization Defects and Vitamin D Deficiency: Histomorphometric Analysis of Iliac Crest Bone Biopsies and Circulating 25-Hydroxyvitamin D in 675 Patients

Matthias Priemel,[1,2] Christoph von Domarus,[1] Till Orla Klatte,[1] Steffen Kessler,[1] Julia Schlie,[1] Simon Meier,[1] Nils Proksch,[1] Frederic Pastow,[1] Clemens Netter,[1] Thomas Streichert,[3] Klaus Püschel,[4] and Michael Amling[1,2]

Journal of Bone and Mineral Research, Vol. 25, No. 2, February 2010, pp 305-312



Slide 111

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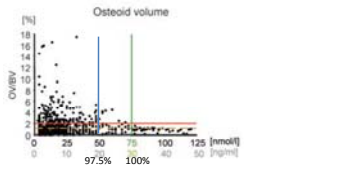

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Vit D levels and Bone Mineral Density

- Observational studies: some association between higher D levels and increased bone density or content.
- RCTs of Vitamin D alone, however, at doses of 200-1000 IU per day, conducted for an average of one year, have not shown an increase in bone density compared with those treated with placebo. In many, the baseline levels of D and of calcium intake were quite low.
- RCTs of calcium plus D do show some small increase in BMD.

Slide 113

Whew!

Slide 114

What's the Conclusion?

How much Vitamin D do average, healthy people need?

Slide 115

Slide 116

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the Nation. Improving Health.

Slide 117

Institute of Medicine DRI Calculations

- Insufficient data to consider anything other than skeletal health for developing the DRI
- Skeletal Health Studies
  - Most studies show that levels of 15-20 ng/ml are associated with optimal calcium absorption
  - Children are at risk for rickets if Vit D <12 ng/dL
  - Adults are at risk for osteomalacia if Vit D <20-30 ng/ml
- The RDA, estimated to provide sufficiency for 97.5% of the population, therefore targets 20 ng/ml, which requires a daily intake of 600 IU

Slide 118

New DRI from IOM FNB

2010 Recommended Daily Allowance	
Children	400 IU
Adults	600 IU
Adults over 70	800 IU

- These are for healthy individuals and assumes no sun exposure
- Very hard to get this much D from diet, need supplements
- Calculated to meet the *skeletal health* needs of 97.5% of the population
- Beware the EAR (Estimated Average Requirement), which is 400 IU and is calculated to be the mean requirement, i.e. it will meet the needs of about 50% of the population (and not meet the needs of the other 50%)

Slide 119

Um, what about that other stuff?

- IOM felt that there was, as yet, insufficient evidence to support increasing vitamin D for any of the other health outcomes
- Also concern over possible increased mortality at higher serum D levels, so didn't want to raise the RDA more than necessary

Slide 120

	Biologic Plausibility	Epidemiologic Studies	RCTs	Comments
All-Cause Mortality	+	+	++/-	U-shaped curve
Cancer	+	+/-	+/-	
Breast cancer	+	+/-	-	
Colon cancer	+	+	-	
Prostate cancer	+	-	0	
CVD	+	+	-	U-shaped curve
DM/Metabolic	+		-	↑LDL, ↓TG
Asthma	+	++/-	0	
IDDM	+	+	0	
RA	+	+	0	One study
MS	+	+	?	Small pilot studies
IBD	+	?	0	Conf. by malabs.
Mood	+	+	+	

Slide 121

Take Home Messages

- Vitamin D deficiency is common (as high as 50%) and so, probably, is osteomalacia.
- 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)

Slide 122

Take Home Messages

- There is some evidence to suggest protective effect of Vitamin D against total mortality and cancer, and efficacy in treatment of depressive symptoms.
- Vitamin D 800 IU and Calcium 2000 mg in female athletes helps to prevent stress fractures.
- There is some epidemiologic evidence to suggest a protective role of maternal D in childhood asthma and of vitamin D supplementation in IDDM

Slide 123

My Strategy

- If patient found to be deficient (< 20 ng/dL)
  - Treat
    - Rx 50,000 IU ergocalciferol once to twice weekly for 8-12 weeks or
    - 15-30 minutes of midday sunshine per day to as much body as possible or
    - Tanning once to twice weekly (no burns)
  - Then recheck level after 8-12 weeks
- If insufficient (20-30 ng/dL), or just at 30 at end of summer
  - 2000 IU daily or treat as above if potentially symptomatic
- If level is normal but need maintenance, consider 600-1000 IU daily
- Consider taking a supplement yourself, or getting more sun (natural or artificial!)

Slide 124

Slide 125

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

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