Vitamin D, Health, & CVD

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Prevalence of Inadequate Vitamin D

- 50-60% of the older population in the world do not have satisfactory vitamin D status
  - Urbanization
  - Decreased outdoor activities
  - Air pollution and global dimming
  - Age-related decreases in cutaneous vitamin D production
  - Dietary sources of vitamin D are generally too insignificant
- Dobnig H, et al. 2008. Independent association of low serum 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D levels with all-cause cardiovascular mortality. *Arch Int Med 268(12)*:1390.

Prevalence of Inadequate Vitamin D

- 36% of otherwise healthy young adults
- Pregnant women and neonates
  - 90% taking prenatal vitamins
  - 54% pregnant black women and 46% black neonates
  - 42% pregnant white women and 56% white neonates
  - Bodnar, L. M., H. N. Simhan, et al. (2007). "High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates." J Nutr **137(2): 447-52.**
- up to 57% of general medicine inpatients in the United States
  - Holick, M. F. (2006). "High prevalence of vitamin D inadequacy and implications for health." Mayo Clin Proc **81(3): 353-73.**

Proposed ranges of 25(OH)D3

- Proposed ranges:
  - **Severely deficient**
    < 10 ng/mL
  - **Deficient**
    < 30 ng/mL
  - **Suboptimal (insufficiency)**
    30–50 ng/mL
  - **Optimal**
    50–80 ng/mL
  - **Excess – > 100 ng/mL**

- *Nefrologia* 2003;23 Suppl 2:73-7.
  - **>40 desirable**
  - **20-40: hypovitaminosis D**
  - **10-20: insufficiency**
  - **<10 deficiency**
- Other studies
  - **<20 ng/ml: deficient**
  - **20-30 (to 35) ng/ml: insufficient**
  - **>30 (to 35): sufficient**

Disorders produced or aggravated by low 25(OH) vitamin D status

Heaney, Robert P. 2008. Vitamin D in Health and Disease. Clin J Am Soc Nephrol 3:1535-1541.

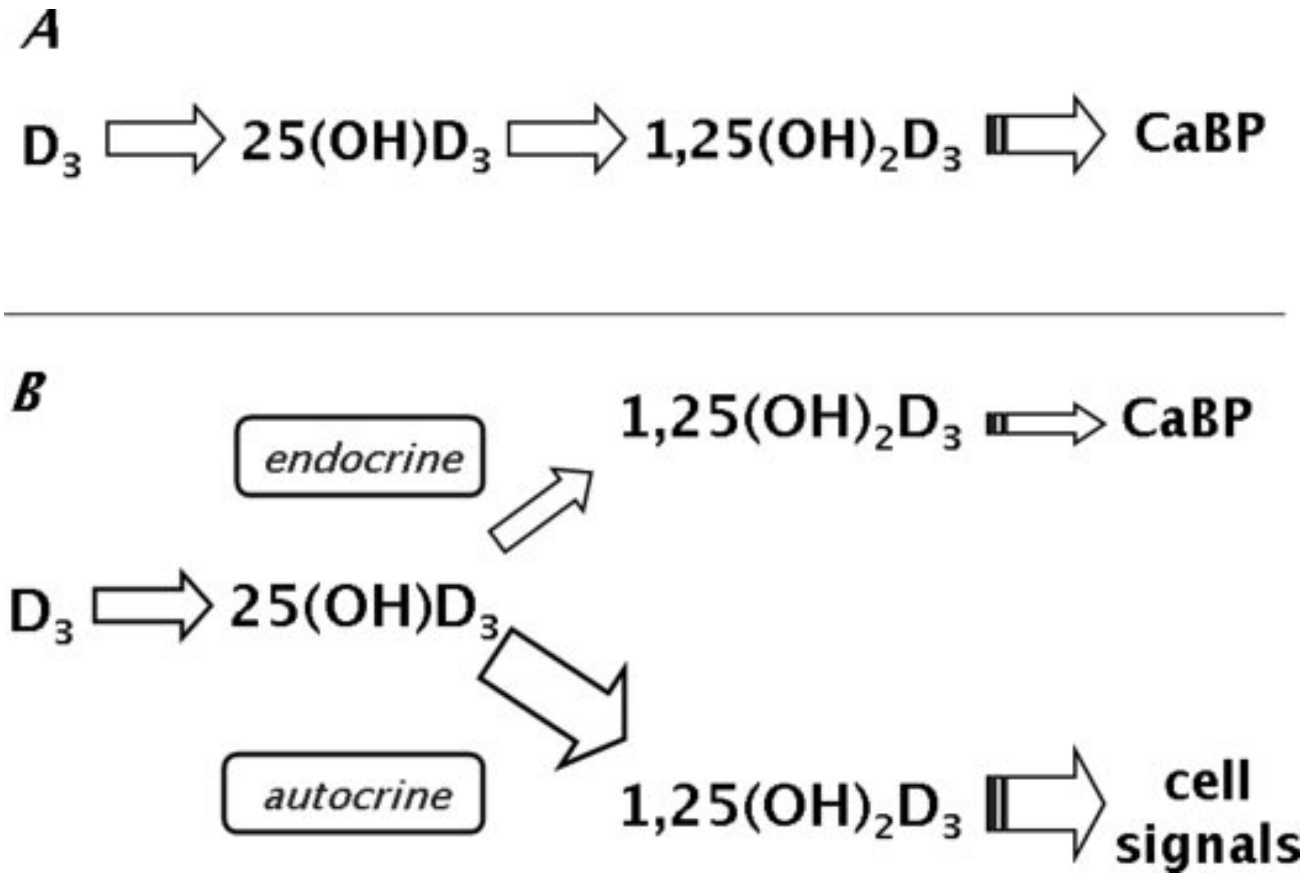
Disorder	Strength of Evidence
Osteoporosis	++++
Falls	++++
Type 1 DM	++
Cancer	++++
Autoimmune diseases	++
Hypertension	+++
Periodontal disease	++++
Multiple sclerosis	++
Susceptibility/poor response to infection	++++
Osteoarthritis	++

What is Vitamin D? Cast of players

- **Cholesterol:** Sunlight breaks the 9-10 bond to produce
- **Cholecalciferol (D3), the naturally occurring form of Vitamin D in the skin and in food.** In the liver , a hydroxide molecule is added to produce:
- **Calcidiol (calcifediol or 25 hydroxy Vitamin D) is considered a "prehormone," and calcidiol blood level is measured to assess Vitamin D stores in the body.** Hydroxylation yields:
  - in the kidneys, (endocrine)
  - In the breast, prostate, ovary, pituitary, brain, etc (autocrine)
- **Calcitriol 1,25 hydroxy Vitamin D, which maintains calcium in the blood and has an array of effects in the body's organs**
  - Calcitriol is marketed under various trade names including **Rocaltrol** (Roche), **Calcijex** (Abbott) and **Decostriol** (Mibe, Jesalis).
- **Ergocalciferol (D2) is a form of Vitamin D used as a supplement, that is not as effective as Vit D3.**

Calcitriol, (D 1,25 dihydroxy Vitamin D) the most biologically active form of vitamin D does the following:

- Controls bone metabolism
- Modulates neurotransmitter and neurological function
- Has immunoregulatory function and can decrease inflammation (Autoimmune disease such as multiple sclerosis)
- Modulates transcription of 200 genes, particularly those effecting differentiation and proliferation (Cancer mortality)



A. Old scheme. B. The current scheme, explicitly incorporating **extra-renal 1 alpha-hydroxylation**, with the resulting calcitriol appearing mainly intracellularly, where it is **clinically unmeasureable**. Heaney, Robert P. 2008. Vitamin D in Health and Disease. *Clin J Am Soc Nephrol* 3:1535-1541.

Extra-renal production of 1,25(OH)2 Vit D

- 1 alpha-hydroxylase detected in
  - skin (basal keratinocytes, hair follicles)
  - vascular smooth muscle cells
  - monocytes/macrophages
  - lymph nodes (granulomata)
  - colon (epithelial cells and parasympathetic ganglia)
  - pancreas (islets)
  - adrenal medulla
  - brain (cerebellum and cerebral cortex)
  - placenta (decidual and trophoblastic cells)
  - prostate cells
  - breast cells

Extra-renal production of 1,25(OH)2 Vit D

- 1 alpha-hydroxylase in the tissues functions well below its kM (maximum rate)
- The amount of calcitriol that enzyme can produce locally depends on the availability of the precursor compound--*25(OH)D*
- *Thus, serum concentration* of 25(OH)D becomes a critical factor in ensuring optimal functioning of the various systems that require vitamin D as a part of their signaling apparatus.
- Heaney, RP. 2008. Vitamin D in Health and Disease. *Clin J Am Soc Nephrol* 3:1535-1541.

CVD and Vitamin D Summary

- Low levels of 25-hydroxyvitamin D have been recently linked to the presence of cardiovascular disease, hypertension and the metabolic syndrome.
- Results of recent nationwide investigations showed an association of low 25-hydroxyvitamin D levels with important cardiovascular risk factors
- We don't know if supplementing with vitamin D will alter this risk.
- Preclinical and clinical investigations demonstrate positive effects of vitamin D and its analogues on fibrinolysis, blood lipids, thrombogenicity, endothelial regeneration, and smooth muscle cell growth.

CVD & Vitamin D meta-analysis

- 28 studies, 99,745 participants
- moderate variation between the studies in their grouping of 25OHD levels, design and analytical approach
- highest levels of serum 25OHD were associated with a 43% reduction in cardiometabolic disorders [OR 0.57, CI 0.48–0.68]
- High levels of vitamin D among middle-age and elderly populations are associated with a substantial decrease in cardiovascular disease, type 2 diabetes and metabolic syndrome
- “If the relationship proves to be causal, interventions targeting vitamin D deficiency in adult populations could potentially slow the current epidemics of cardiometabolic disorders.”
- Parker, J., O. Hashmi, et al. (2010). "Levels of vitamin D and cardiometabolic disorders: Systematic review and meta-analysis." Maturitas **65(3): 225-236.**

Specific Vitamin D & CVD related studies

- CVD
  - LURIC study, Germany
  - Health Professionals Follow-up Study
  - Framingham Offspring Study
  - Women's Health Initiative
  - Australian Study
- Hypertension
  - Nurses Health Study
  - Prospective cohort studies (serum 25-OH Vit D)
  - Prospective cohort studies (dietary intake of Vit D)
- Diabetes
  - NHANES study
  - Finish study

LURIC Study, Germany

- **Low 25-OH D and 1,25 (OH)2 D levels are independently associated with all-cause and cardiovascular mortality**
  - 3258 male & female patients,
  - Mean age 62 yrs
  - High risk group, scheduled for coronary angiography
  - Prospective study, D levels taken monthly over median of 7.7 years
  - Although the lowest levels were associated with much less physical exercise, the effects were independent of coronary artery disease, physical activity level, Charlson Comorbidity Index, variables of mineral metabolism, and New York Heart Association functional class.
  - Dobnig H et al. 2008. Independent Association of Low Serum 25-Hydroxyvitamin D and 1,25-Dihydroxyvitamin D Levels With All-Cause and Cardiovascular Mortality. *Arch Int Med 168(12)*:1341-1349.

LURIC Study, Germany

- **Twice the all-cause mortality** in patients with the lowest 25% for 25(OH)D (median 7.6) versus highest 25%. HR 2.08, CI 1.6 to 2.7.
- **Twice the CV mortality** patients with the lowest versus highest quartile (median 28.4 ng/mL). HR 2.22, CI 1.57-3-13.
- **53% greater all-cause mortality** in patients in 2nd lowest quartile (median 13.3 ng/mL) than highest. HR 1.53, CI 1.17-2.01.
- **82% more CV mortality** in patients in 2nd lowest quartile than those in the highest quartile. HR 1.82, CI 1.29-2.58.
- Similar results were obtained for patients in the lowest 1,25-dihydroxyvitamin D quartile.

LURIC Study, Germany

- Even insufficiency has an effect on all-cause mortality (trend)
  - For vitamin D insufficiency—levels of >20 to 30 ng/mL, all cause mortality was 1.54 (CI .99-2.41) versus >30 ng/mL.
- 25(OH)D and 1,25(OH)2D levels **were not significantly different between patients taking versus not taking vitamin D supplements**. Range of 25(OH)D: 5.8 to 33.5 ng/mL.

LURIC Study, Germany

- Low 25(OH)D levels were significantly correlated with:
  - variables of inflammation
    - C-reactive protein and
    - interleukin 6 levels)
  - oxidative burden
    - serum phospholipids
    - glutathione levels
  - cell adhesion
    - vascular cell adhesion molecule 1
    - intercellular adhesion molecule 1
- 25-hydroxyvitamin D has beneficial effects, some involving the cardiovascular system, that are **independent of calcium metabolism**.

Health Professionals Follow-up Study: Serum 25(OH)D & MI

- 18,225 men aged 40-75 years, free of diagnosed CVD
- Prospective study with 10 years of follow-up
  - **2.42 X increase in MI for individuals <15ng/ml versus >30 ng/mL** after adjustment for matched variables. (CI 1.53-3.84)
  - **Relationship still significant even after adjustment** for family history of myocardial infarction, body mass index, alcohol consumption, physical activity, history of diabetes mellitus and hypertension, ethnicity, region, marine -3 intake, low and high-density lipoprotein cholesterol levels, and triglyceride levels (RR, 2.09; 95% CI, 1.24-3.54; *P*=.02 *for trend)*.
- **Even men with intermediate 25(OH)D levels (22.6-29.9 ng/mL) had 60% more MIs than men with sufficient levels.**

Framingham Offspring Study

- Vitamin D deficiency associated with incident CVD
- 1739 participants, mean age 59 years, 55% women, white
- No prior CVD
- Pre-specified thresholds: <10ng/mL (9%) and < 15ng/Ml (28%)
- Follow-up mean 5.4 years
- There was an effect on participants with hypertension, but not in those without HT
- **More than double the CV events for hypertensives with Vit D <15 ng/ML compared with those >=15 ng/mL** [Hazard Ratio of 2.13 (CI 1.30-3.48)]
- Trend for a graded increase in CV risk across all vitamin D categories.
- **Adjustment for C-reactive protein, physical activity, or vitamin use did not affect findings.**

Australian study

- 1471 health-community dwelling women with a mean age of 74 years
- 5 year trial of calcium supplementation
- 25(OH)D was measured at baseline in all women. Skeletal and nonskeletal outcomes were evaluated according to seasonally adjusted vitamin D status at baseline.
- 50% of women had a seasonally adjusted 25(OH)D concentration <50 nmol/L. These women were significantly older, heavier, and less physically active and had more comorbidities than women with a seasonally adjusted 25(OH)D concentration > or =50 nmol/L.
- Women with a seasonally adjusted 25(OH)D concentration <50 nmol/L had an increased incidence of stroke and cardiovascular events **that did not persist after adjustment for between-group differences in age or comorbidities.**

Does too high 25(OH)D cause CVD?

- **Serum 25-hydroxyvitamin D3 levels are elevated in South Indian patients with ischemic heart disease**
  - **Rajasree, *et al*, reported a world record high for 25(OH)D levels (4X the average in India) due to sun exposure in a country where low, not high, 25(OH)D levels are the problem**
  - **Unexplained high occurrences of both hypercalcemia and hyperphosphatemia, in subjects as well as controls**
  - **Analytical methods most likely inaccurate**
  - **Eur J Epid probably published as it fit in with current vit D hysteria of the times.**

Women's Health Initiative

Hsia, J., G. Heiss, et al. (2007). "Calcium/vitamin D supplementation and cardiovascular events." Circulation **115(7): 846-54.**

- Looked at CV mortality (fracture risk trial)
- 400 IU vitamin D and 500 mg calcium did not alter CV events in a randomized study of 36,282 post-menopausal women during a 7-year period.
  - Unlikely that the 400 IU had a significant effect on vitamin D levels. The LURIC study showed that those with vitamin D supplementation had levels similar to those without supplementation. Vitamin D levels were not measured.
  - Both calcium and 400 IU vitamin D supplementation was allowed in both groups.
    - Mean calcium intake was already 1150 mg daily.
    - Mean vitamin D intake was close to 400 IU daily.

HT: Nurses Health Study

Forman, J. P., G. C. Curhan, et al. (2008). "Plasma 25-hydroxyvitamin D levels and risk of incident hypertension among young women." Hypertension **52(5): 828-32.**

- Plasma 25(OH)D levels are inversely and independently associated with the risk of developing hypertension
- 1484 women aged 32-54 years
- No hypertension at outset
- Matched case control for age, race, and month of blood collection and further adjusted for body mass index, physical activity, family history of hypertension, oral contraceptive use, and plasma levels of parathyroid hormone, calcium, phosphorous,creatinine, and uric acid
- **Almost 50% more HT in women with <30 ng/mL** (65.7% of the study population) [OR of 1.47 (CI: 1.10 to 1.97)]

HT: Prospective cohort studies

Forman, J. P., H. A. Bischoff-Ferrari, et al. (2005). "Vitamin D intake and risk of incident hypertension: results from three large prospective cohort studies." Hypertension **46(4): 676-82.**

- Plasma 25(OH)D levels are inversely associated with risk of incident hypertension
- 613 men from the Health Professionals' Follow-Up Study
  - During 4 years of follow-up, RR of hypertension in men <15 ng/mL plasma 25(OH)D was 6.13 (CI 1-37.8) versus those >= 30 ng/mL.
- 1198 women from the Nurses' Health Study
  - RR of 2.67 (95% CI: 1.05 to 6.79) (same comparison)
- In addition, 2 prospective cohort studies including 38,388 men and 77,531 women with predicted 25(OH)D levels were followed for 16 to 18 years.
  - Compare lowest to highest decile: 2.31 (CI: 2.03 to 2.63) in men and 1.57 (CI: 1.44 to 1.72) in women.

HT and vitamin D intake

- Higher intake of vitamin D is not associated with a lower risk of incident hypertension
  - Nurses Health Study I (NHS I; n=77,436), NHS II (n=93,803), and Health Professionals' Follow-up Study (HPFS; n=38,074).
  - When we compared participants who consumed > or =1600 to <400 IU per day and those who consumed > or =1000 to <200 IU per day, no association was found.
  - Forman, J. P., H. A. Bischoff-Ferrari, et al. (2005). "Vitamin D intake and risk of incident hypertension: results from three large prospective cohort studies." *Hypertension* ***46(4):*** **676-82.**

Vitamin D and DM: NHANES

Scragg, R., M. Sowers, et al. (2004). "Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey." Diabetes Care **27(12): 2813-8.**

- Doubled OR for diabetes mellitus among the participants in the first 25% compared with the fourth 25%
- Ethnicity: inverse association between vitamin D status and DM in non-Hispanic whites and Mexican Americans. Lack of an inverse association in non-Hispanic blacks may reflect decreased sensitivity to vitamin D and/or related hormones such as the parathyroid hormone.

Vitamin D and Diabetes

- Administration of 1,25-dihydroxyvitamin D3 prevents the development of type 1 DM in animal models.
- Vitamin D deficiency (<20 ng/mL) has been associated with decreased beta-cell function
- Insulin sensitivity is as much as 60% higher in individuals with serum level 30 ng/mL vs 10 ng/mL
- Vitamin D deficient participants without DM had higher and post glucose challenge blood glucose values than those with adequate levels
- Consistent with the established literature
- Suggests a potential role for the serum level of 25(OH)D in the promotion of insulin sensitivity and the prevention of diabetes mellitus.
- Teegarden, D. and S. S. Donkin (2009). "Vitamin D: emerging new roles in insulin sensitivity." Nutr Res Rev **22(1): 82-92.**

Serum Vitamin D and Type 2 DM

- Finnish study
  - 1st prospective study demonstrating that low 25(OH)D levels predict incident diabetes.
- Nested case-control design of 412 incident diabetes cases and 986 age/sex matched controls
- Aged 40 years and over
- Followed for up to 22 years
- In men, although not in women, higher baseline 25(OH)D reduced the risk of incident diabetes by 72%
- adjustment for smoking, body mass index, physical activity, and education.
- Knekt, P., M. Laaksonen, et al. (2008). "Serum vitamin D and subsequent occurrence of type 2 diabetes." Epidemiology **19(5): 666-71.**

Does Vitamin D supplementation prevent Type 2 DM?

- "Evidence from trials with vitamin D and/or calcium supplementation suggests that **combined vitamin D and calcium supplementation may have a role in the prevention of type 2 DM only in populations at high risk** (i.e. glucose intolerance). The available evidence is limited because most observational studies are cross-sectional and did not adjust for important confounders, whereas intervention studies were short in duration, included few subjects, used a variety of formulations of vitamin D and calcium, or did post hoc analyses."
- Pittas, A. G., J. Lau, et al. (2007). "The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis." J Clin Endocrinol Metab **92(6): 2017-29.**

Mechanisms of CVD prevention

- Inhibition of vascular smooth muscle proliferation
- Suppression of vascular calcification
- Down regulation of pro-inflammatory cytokines
- Up regulation of anti-inflammatory cytokines
- Action of vitamin D as a negative endocrine regulator of the renin-angiotensin system.

- Zittermann, A., S. S. Schleithoff, et al. (2005). "Putting cardiovascular disease and vitamin D insufficiency into perspective." Br J Nutr **94(4): 483-92**

Mechanisms of Calcitriol & CVD

- Calcitriol decreases vascular calcification
  - Vascular smooth muscle cells express vitamin D receptors. **Calcitriol inhibits proliferation** of these cells by an acute influx of Ca into the cells
  - Matrix Gla protein is synthesized by chondrocytes and vascular smooth muscle cells and **decreases vascular calcification**; vitamin D increases Gla.
  - Excess PTH levels due to deficiency may at least in part promote CVD by increased cardiac contractility, chronic atherosclerosis via insulin resistance, Ca and phosphate deposition in vessel walls, chronic myocardial calcification, and chronic heart valve calcification
  - Calcitriol dose-dependently suppresses the release of the pro-inflammatory cytokines TNF-a and IL-6
  - Zitterman. 2005. Putting cardiovascular disease and vitamin D insufficiency into perspective. Br. J Nutr. 94:483-492.

Does vitamin D supplementation prevent CVD?

- A causal relationship has yet to be proved by intervention trials using adequate amounts of vitamin D.
  - Intakes of "ordinary" doses of vitamin D supplementation (300-2000 IU) are associated with decreased mortality rates [meta-analysis]
  - No indication yet that Vitamin D supplementation prevents HT, MIs, or CVD.
  - Early supplementation Vitamin D appears to help prevent Type 1 DM.
  - May reduce risk of Type 2 DM in at-risk populations.

Could Vitamin D supplementation help the very sick?

- "In patients with advanced chronic diseases such as end-stage heart failure, however, **circulating calcitriol predicts mid-term mortality better than 25(OH)D does.** Available data indicate that these patients may enter a vicious cycle of low calcitriol, increased inflammation markers, and renal impairment, **which may be difficult to escape by simple vitamin D supplementation.**"
- Zittermann, A., J. F. Gummert, et al. (2009). "Vitamin D deficiency and mortality." Curr Opin Clin Nutr Metab Care **12(6): 634-9.**

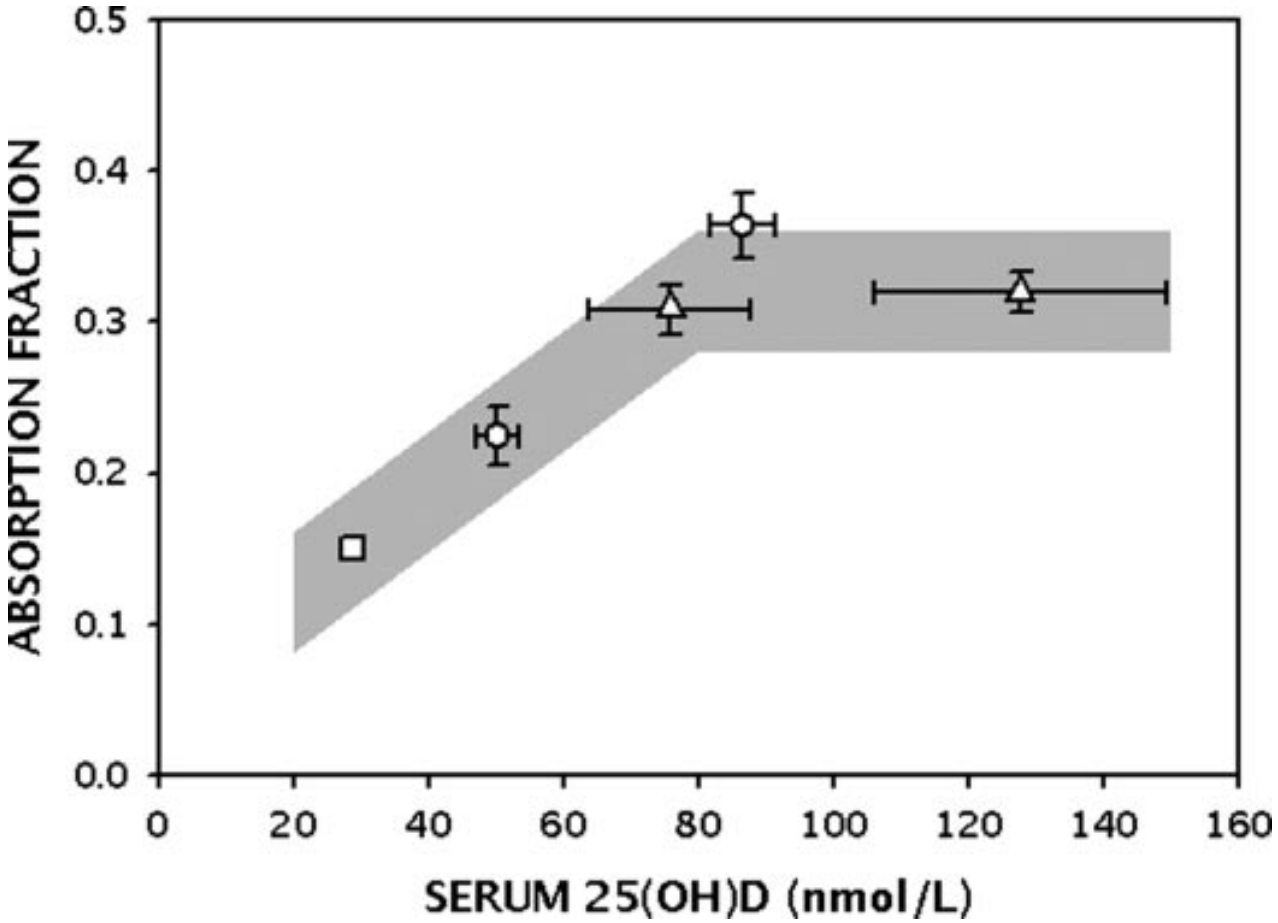
How much Vitamin D do we need?

- RDA (Recommended Daily Allowance) vs. **DRI (Dietary Reference Intake,** i.e., Optimal Intake)
- DRIs recognize the difference between only reducing deficiency diseases and reducing disease risk.
- "A key component of this new approach is establishing reliable **functional indicators of nutrient status that may predict disease risk before a severe nutrient deficiency ensues.** The identification and use of functional indicators is also important in the determination of nutrient intakes adequate to support key metabolic functions."
- Rampersaud G et al **Genomic DNA methylation decreases in response to moderate folate depletion in elderly women .** American Journal of Clinical Nutrition, 2000. Vol. 72, No. 4, 998-1003,

Calcium absorption and serum D

Heaney, RP. 2008. Vitamin D in Health and Disease. *Clin J Am Soc Nephrol* 3:1535-1541.

Vitami n D blood levels of > 80 nmol/L (about 33 ng/L) are needed for optimal absorption



NIH scientists are over a decade behind the times in their recommendations, in spite of a wealth of info, including Heaney's calcium absorption data.

- **Serum 25-Hydroxyvitamin D [25(OH)D] Concentrations and Health: NIH Recs ≥15 ng/mL (≥37.5 nmol/L)**
- **"Generally considered adequate for bone and overall health in healthy individuals ."**
  - Dietary Supplement Fact Sheet: Vitamin D Office of Dietary Supplements • National Institutes of Health http://dietary-supplements.info.nih.gov/factsheets/vitamind.asp
  - Reference cited: Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington, DC: National Academy Press, 1997.

Vitamin D protects the frail elderly

- **a low level of serum vitamin D is associated with a greater risk of being admitted to a nursing home and increase the risk of dying within six years**
- **due primarily to increased muscle weakness and risk of falls, as well as a greater risk of osteoporosis.**
  - **Visser, et al . Low serum concentrations of 25-hydroxyvitamin D in older persons and the risk of nursing home admission.** ***American Journal of Clinical*** Vol. 84, No. 3, 616-622, September 2006

Dental Caries and Peridontal Disease

- **Peridontal Disease: In 6,700 people ages 13 to 90, the gums of patients with higher blood levels of vitamin D were 20 percent less likely to bleed**
- **"The evidence on gingivitis and tooth loss suggests that vitamin D influences oral health by decreasing inflammation."** Dawson-Hughes. *American Journal of Clinical Nutrition* (80:108-13). July 2004.
- **Dental Caries: Dozens of studies were conducted in the 1930's and 1940's. More than 90% of the studies concluded that supplementing children with vitamin D prevents cavities**.

Vitamin D and Cancer Mechanisms

- **Vitamin D's most profound gene-influenced activity appears to be in keeping healthy the broad category of epithelial cells.**
- **Calcitriol switches on and off at least 200 genes.**
- **Reduces the unregulated growth of cancer cells by promoting normal cell death (apoptosis)**
- **Prevents new cells from becoming cancerous (promoted differentiation).**
- **Helps regulate the production of E-Cadherin, a type of biological glue that holds cells together.**
- **Helps prevent cancer cells from spreading (metastasis)**
- **Inhibits cancer cells from developing new blood supply (angiogenesis).**
- **In short, calcitriol seemed like the perfect anticancer drug.**

Vitamin D and Cancer Risk

- **Breast Cancer**
  - **Women with vitamin D >50ng/ml had a *6-fold reduction* in breast cancer risk compared to women <50ng/ml. EurJCanc2005;41p1164**
- **Melanoma**
  - **Higher Vitamin D was associated with a *46% reduction in relapse* of melanoma.**
  - **It works by blocking cancer cell duplication and prevention of cancer blood vessel growth.**
  - **FPN 12/15/06 p.23**

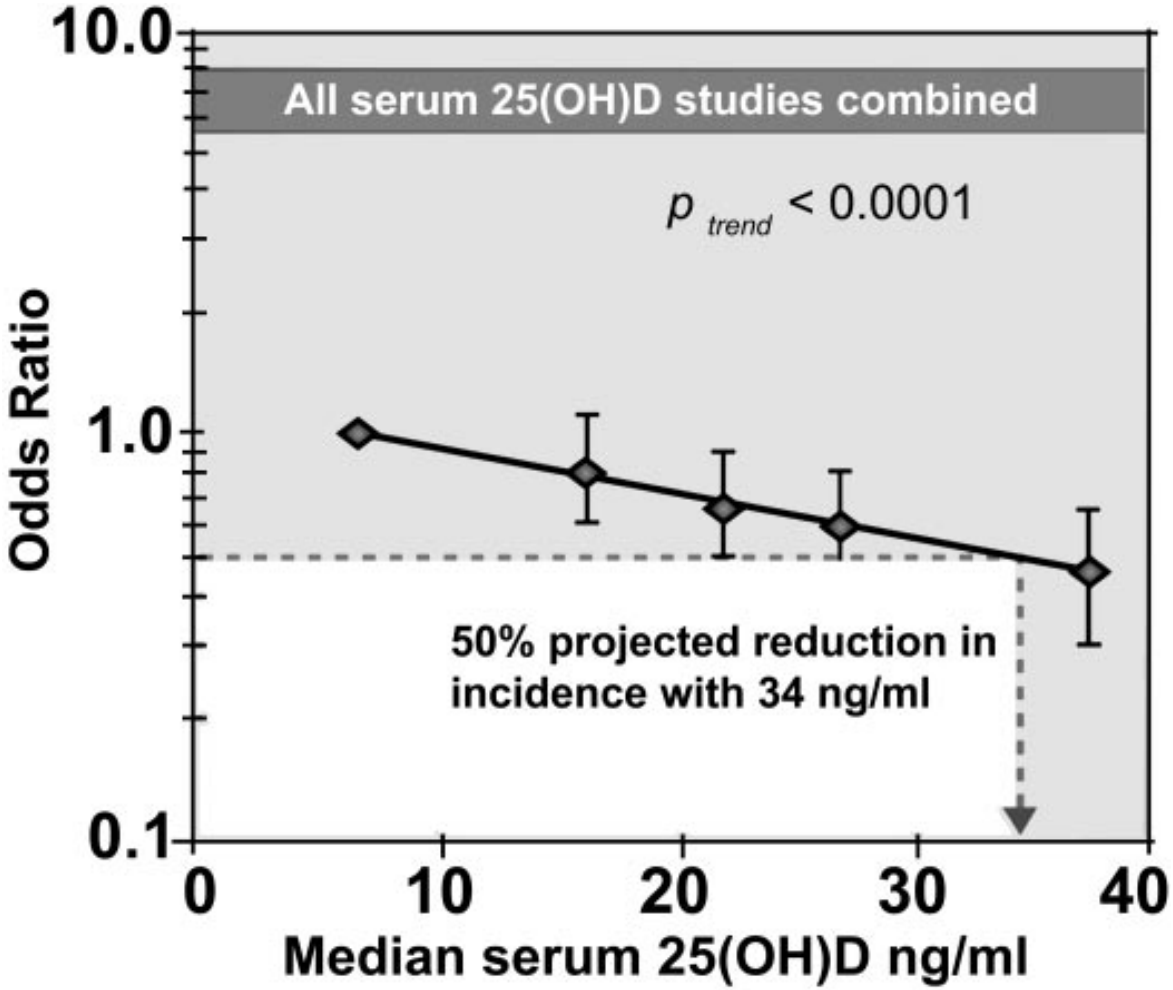
Vitamin D and Cancer Risk

- **Non-Hodgkin's Lymphoma**
  - **Sun exposure (& presumably improved vitamin D levels) reduced non-Hodgkin's lymphoma by 35-63% in one study;**
  - **a second study confirmed findings.**
    - **IntJCancer12/10/2004p865, Cancer Causes Control10/06p1045**
- **Kidney Cancer**
  - **Ultraviolet B (from sunshine, suspect vitamin D) reduced risk of kidney cancer, while high altitude, cloud cover, & calories from animal sources increased risk.**
    - **IntJCancer2006;119(11)p2705**

Vitamin D and Cancer Risk

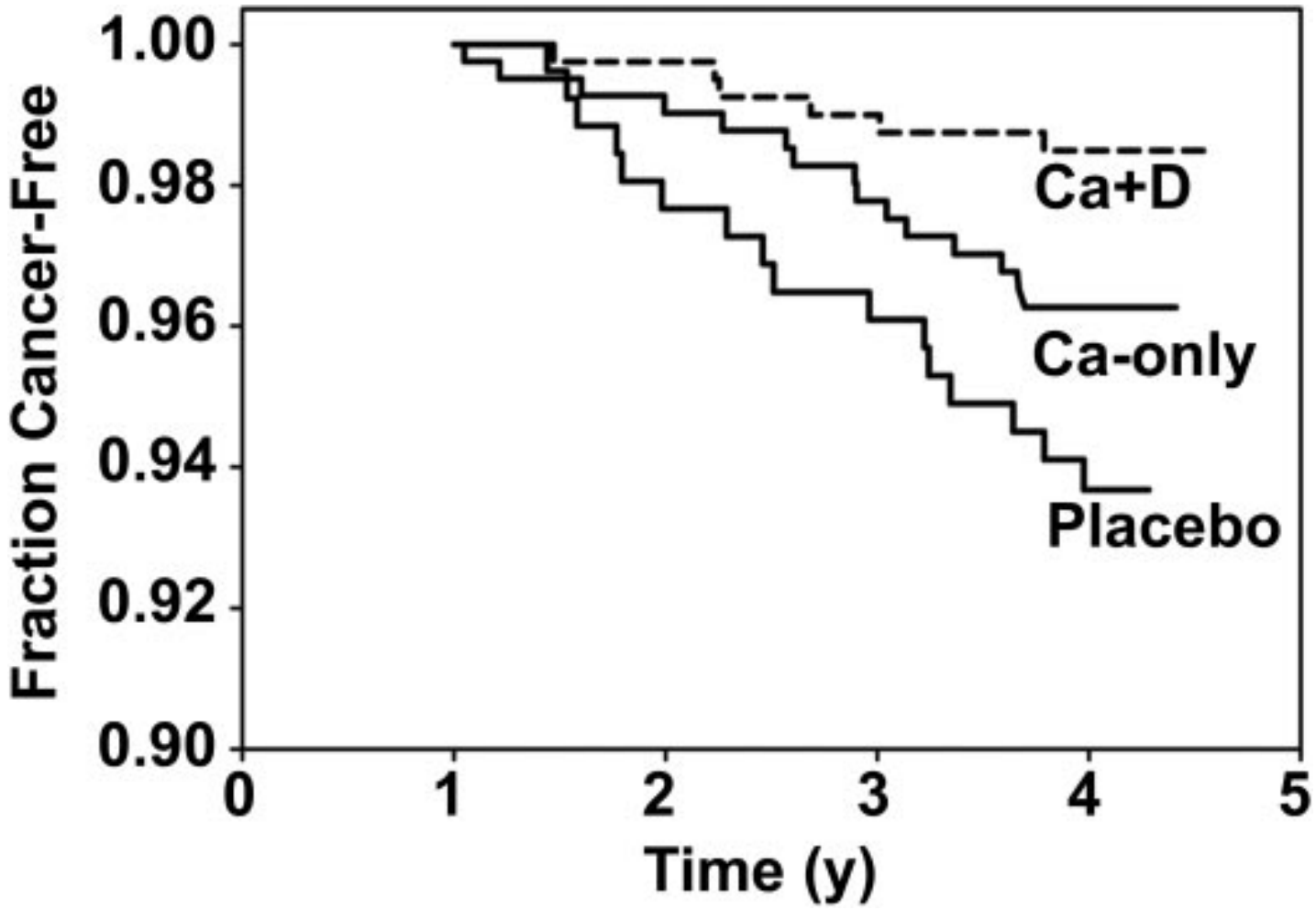
- **Colorectal Cancer:**
  - **In a meta-analysis, the optimal dose of vitamin D to prevent colorectal cancer is 1000-2000u daily;**
  - **Blood levels of 25OH vitamin D of 33ng/ml had a 50% lower colorectal cancer risk vs 12ng/ml**
  - ***1000-2000IU of vitamin D from sunlight, supplements, or diet would reduce colon cancer risk in half.*** **AmJPrevMed2007;32p210**
  - ***Increasing Vitamin D intake by 1500u daily could prevent 45% of digestive cancers*** **(study by Dr. Walter Willett, Harvard) Vitamin D and Hypertension**

Dosage-response gradient for colorectal cancer. Sumary of 5 Studies: Clin J Am Soc Nephrol 3: 1548–1554, 2008.



Kaplan-Meier survival curves in colon cancer

Clin J Am Soc Nephrol 3: 1548–1554, 2008



Vitamin D and Cancer Risk

- **Pancreatic Cancer: D 400 IU daily reduced pancreatic cancer risk by 43% in a large epidemiology study. *CancEpidBiom&Prev* 9/06**
- **Vitamin D supplementation would reduce a wide variety of cancers 30-50%. *AmerJPublicHealth* 2006;96 p252**
- **50,000-63,000 in America annually die prematurely from cancer due to vitamin D deficiency. *PhytochemPhotobio* 2005;81 p1276**

Prostate Cancer

- Higher levels of D 25OH and D1,25: 45 percent lower risk of developing aggressive prostate cancer than those with lower levels.
- Genotype homozygous FokI FF and high vitamin D levels lowered overall risk by 55 percent, and aggressive disease by 77 percent
- **“Our findings suggest that vitamin D plays an important protective role against prostate cancer, especially clinically aggressive disease. This research underscores the importance of obtaining adequate vitamin D through skin exposure to sunlight or through diet, including food and supplements.“**
  - Presentation by Haojie Li MD, PhD of Harvard University School of Public Health at the 2005 Multidisciplinary Prostate Cancer Symposium Orlando, Florida

Vitamin D and Cancer Prevention

- **"It is projected that raising the minimum year-around serum 25(OH)D level to 40 to 60 ng/mL (100-150 nmol/L) would prevent approximately *58,000 new cases of breast cancer and 49,000 new cases of colorectal cancer each year*, and three fourths of deaths from these diseases in the United States and Canada, based on observational studies combined with a randomized trial."**
- Garland, C. F., E. D. Gorham, et al. (2009). "Vitamin D for cancer prevention: global perspective." Ann Epidemiol **19(7): 468-83.**

Vitamin D, Vitamin A, & Cancer Risk

- Vitamin A (as preformed retinol, not beta-carotene) may attenuate the positive effect of vitamin D in colorectal, prostate, breast, lung, and pancreatic cancer.
- Dr. John Cannell , in his review of studies containing evidence of this association, hypothesized that the retinol most likely came from cod-liver oil supplementation. Cannel, J. Remarkable Paper in British Medical Journal. *The Vitamin D Newsletter*, February 28, 2010.
- In a prospective study of 48,000 women, a high vitamin D and low retinol intake further decreased the risk of colorectal cancer over the opposite extreme. The authors suggest, "the actions of vitamin D may be attenuated by high retinol intake." Oh, K., W. C. Willett, et al. (2007). "Calcium and vitamin D intakes in relation to risk of distal colorectal adenoma in women." Am J Epidemiol **165(10): 1178-86.**

Increasing sun exposure and cancer risk

Increase:

- Squamous cell cancer (1500 deaths/year)

Decrease

- Breast Cancer (50,000 deaths per year)
- Colon Cancer (57,000 deaths per year)
- Prostate Cancer (40,000 deaths/year
- Ovarian Cancer (14,000 deaths/year)

No Change

- Lung Cancer

Sun exposure and Melanoma

Review of 14 published studies,

- **two found a positive association between solar UV exposure and melanoma;**
- **seven found no association; and**
- **five studies found an inverse association, that is, the more sun-exposure the less melanoma.**
  - **Godar DE, Landry RJ, Lucas AD. Increased UVA exposures and decreased cutaneous Vitamin D(3) levels may be responsible for the increasing incidence of melanoma. *Med Hypotheses*. 2009 Apr;72(4):434-43.**
- **Intermittent and occupational sun exposure has been found to reduce the risk of malignant melanoma**
  - **Holick M. Deficiency of sunlight and vitamin D. *British Medical Journal* 2008; 336:1318–1319.**

Schizophrenia

- **latitude and cold climate strongly determine the prevalence of schizophrenia.**
  - **skin color only mattered away from the equator,**
- **adjuvant Vitamin D**
  - **does not reduce hallucinations, paranoia, or psychosis**
  - **improves mood, reduces tremors,**
  - **may reduce the amount of antipsychotic medications needed and helps prevent diabetes and the metabolic syndrome, (common side-effects of "modern" antipsychotic medications.)**
  - **Cannell:** The Vitamin D Newsletter August 2009

Type 1 Diabetes

- Low levels of 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 were found in patients with newly diagnosed type 1 diabetes
- D3 supplementation at birth protects individuals from type 1 diabetes later in life
- 1,25-(OH)2D3 may act as an immunomodulator, facilitating the shift from a Th1 to a Th2 immune response,
  - Low levels of 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 in patients with newly diagnosed type 1 diabetes. Pozzilli et al Hormone and metabolic Research 2005, vol. 37, n°11, pp. 680-683

Type 1 DM & Vit D supplements

- Meta-analysis: Zipitis, C. S. and A. K. Akobeng (2008). "Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis." Arch Dis Child **93(6): 512-7.**
  - 5 observational studies (4 case-control studies and 1 cohort study); no RCTs
- Risk of type 1 diabetes was significantly reduced in infants who were supplemented with vitamin D compared to those who were not supplemented (pooled odds ratio 0.71, 95% CI 0.60 to 0.84).
- Evidence of a dose-response effect--those using higher amounts of vitamin D being at lower risk of developing type 1 diabetes.
  - Children who regularly took the recommended dose of vitamin D (2000 IU daily) had a RR of 0.22 (0.05-0.89) compared with those who regularly received less than the recommended amount.—Finnish study
- Timing of supplementation might also be important for the subsequent development of type 1 diabetes.
- Need RCTs with long-term follow-up to establish causality and the best formulation, dose, duration and period of supplementation.

Polycystic Ovary Sydrome

- **In a study involving 120 untreated women with polycystic ovarian syndrome (median age: 28 years), low levels of vitamin D were found to be associated with insulin resistance and obesity. In all the subjects, concentrations of 25-OH-VD were inversely associated with body mass index, body fat, HOMA-IR, hyperinsulinemia, and levels of leptin, while being positively associated with HDL cholesterol levels.**
- **Additional analysis found 25-OH-VD levels to be significantly correlated with sex hormone-binding globulin and the free androgen index.**
- **Hahn S, Haselhorst U, et al, Experimental and Clinical Endocrinology and Diabetes, 2006; 114(10): 577-583**

Lung Function and Asthma

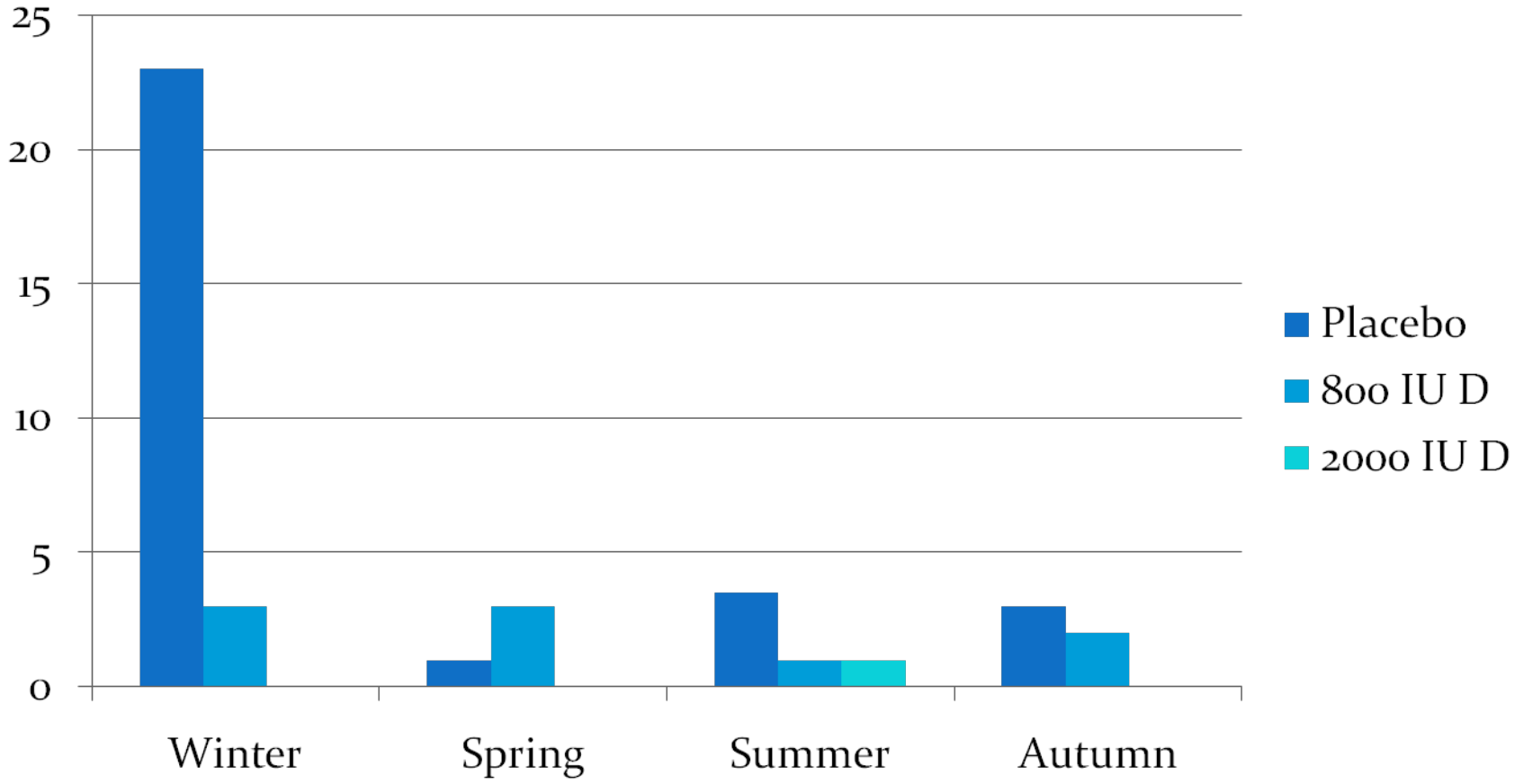
- A report published in the December 2005 issue of the journal Chest, the journal of the American College of Chest Physicians, revealed that **higher levels of vitamin D are correlated with improved lung function** compared to individuals whose levels of the vitamin are lower.
- **Childhood asthma** is associated with vitamin D deficiency. At least two researchers at Harvard think it is the result of maternal vitamin D deficiency.
  - Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? J Allergy Clin Immunol. 2007 Nov;120(5):1031-5.
  - Weiss ST, Litonjua AA. Maternal diet vs lack of exposure to sunlight as the cause of the epidemic of asthma, allergies and other autoimmune diseases. Thorax. 2007 Sep;62(9):746-8.

Sunlight and Multiple Sclerosis

- There is a genetic component to MS risk, with Northern Europeans being at higher risk.
- You are 5 times more likely to get MS if you live in Europe or North America than in the tropics.
- The prevalence rate for MS is twice as high in the US above the 37th parallel, then below. (The 37th parallel runs through Virginia)
- Exposure to the sun before age 15 reduces the risk of MS.
- Norwegians who live along the coast have a lower risk of MS than those who live inland. (Coastal inhabitants eat more fish,)
- Eskimos who eat a traditional diet (bear liver, whale, seal blubber, oily fish) have almost no MS.
- Identical Twin Study Conclusions: Early sun avoidance seems to precede the diagnosis of multiple sclerosis (MS). This protective effect of sunlight is independent of genetic susceptibility to MS.
  - **Islam T, Gauderman WJ, Cozen W, Mack TM. Childhood sun exposure influences risk of multiple sclerosis in monozygotic twins. Neurology. 2007 Jul 24;69(4):381-8.**

Epidemic influenza and vitamin D

(104 subjects) Epidemiol Infect 2007; 135:1095–1096.



Pearls


WHEN FISH GO OFF
I DON'T WANT ANY TROUBLE...JUST HAND OVER THE PEARL!
search ID: mly0384
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Pearls: 1

- Testing: Use 25-OH vitamin D
- Conversion:
  - ng/mL to nmol/L – multiply by 2.496
  - nmol/L to ng/mL – divide by 2.496
- Supplementation: D3 (cholecalciferol) is better absorbed and utilized than D2 (ergocalciferol, an irradiated plant sterol source).

Testing can easily be justified in all patients given the prevalence of deficiency.

But at a minimum, testing should be done on patients with or at increased risk for:

- Prostate, breast, colon, & ovarian cancer
- Hypertension
- Schizophrenia
- Depression
- PCOS
- Migraine
- Epilepsy
- Osteoarthritis
- Diabetes (types 1 & 2)
- Fibromyalgia
- Autoimmune conditions such as SLE, ankylosing spondylitis, MS, RA
- Osteoporosis/ osteopenia

Patients with symptoms of:

- Musculoskeletal pain and low back pain
- Muscle weakness and loss of balance
- Systemic inflammation

Resources

- Vitamin D council: http://www.vitamindcouncil.org/
- *T he New England Journal of Medicine* July 19, 2007. **Progress:** Vitamin D Deficiency. Michael F. Holick, M.D., Ph.D.
  - N Engl J Med 2007;357:266-81.
  - Address reprint requests to Dr. Holick at Boston University School of Medicine, 715 Albany St., M-1013, Boston, MA 02118, or at mfholick@bu.edu.
- **Cell Defenses and the Sunshine Vitamin** By Luz E. Tavera-Mendoza and John H. White Scientific American Magazine November 2007

Pearls: Vitamin D supplementation

- Cautions with vitamin D supplementation – the following predispose to hypercalcemia :
  - Granulomatous disease,
  - sarcoidosis,
  - hydrochlorothiazide Rx
- Check serum calcium before starting high dose Vitamin D. Toxicity may occur if serum calcium is elevated.

Vitamin D Toxicity: 1948 report

- 10 patients with Vitamin D intoxication, Dosage prescribed for arthritis ranged from 150,000 IU/day to 600,000 IU/day
- clinical toxicity resulted in 2 to 18 months
- weight loss, malaise and fatigue, followed by anorexia, nausea and vomiting.
- high blood *calcium*: 12.4 - 15 mg/dL—anemia; kidney impairment
- Seven of the ten patients insisted their arthritis was improved by Vitamin D toxicity and most complained their arthritis returned several months after withdrawal of Vitamin D,
  - 1948 paper from Johns Hopkins: J Clin Endocrinol Metab. 1948 Nov;8(11):895-910. **Intoxication with vitamin D.**HOWARD JE, MEYER RJ. PMID: 18101618

Vitamin D Rx of all infants in East Germany: 1955 to 1990: Slide 1

- Infants received 600,000 IU of Vitamin D every three months for a total of 3,600,000 IU at age 18 months.
  - average of 6,000 IU per day
- Before the first dose, at 3 months of age, the average infant was extremely deficient (median 25(OH)D of 7 ng/ml)
- Two weeks after the first dose the average 25(OH)D level was 120 ng/ml, the second dose 170 ng/ml, the third dose, 180 ng/ml, the fourth dose, 144 ng/ml, the fifth dose, 110 ng/ml and after the sixth and final dose, 3.6 million total units, at age 18 months, the children had mean levels of 100 ng/ml.

Vitamin D Rx of all infants in East Germany From 1955 to 1990: Slide 2

- Thirty-four percent of the infants had at least one episode of hypercalcemia but only 3 had an elevated serum 1,25(OH)D.
- The authors reported that "all the infants appeared healthy," even the infant with a level of 408 ng/m
- No clinical toxicity was noted in any of these infants.
- No study has been done of morbidity or mortality of these children.

- Am J Clin Nutr. 1987 Oct;46(4):652-8. **Intermittent high-dose vitamin D prophylaxis during infancy: effect on vitamin D metabolites, calcium, and phosphorus.** Markestad T, et al. PMID: 3499065

The Great Vitamin D Panic

- Affected subsequent U.S. Food and Nutrition Board (FNB) Vitamin D recommendation for 50 yrs after England had a “.”it of hysteria,
- Williams syndrome is a genetic malformation that causes, among other things, infantile hypersensitivity to Vitamin D, elevated 1,25 levels even without supplemental Vitamin D, and often hypercalcemia in response to supplemental Vitamin D
- Great Britain reduced infant supplementation by one-half in 1957, expecting to see a reduction in infantile hypercalcemia (7.2 cases per month in the country)
- in 1959, the incidence of infantile hypercalcemia in Great Britain was essentially unchanged (6.8 cases per month)
  - Br Med J. 1964 Jun 27;1(5399):1659-61.**INFANTILE HYPERCALCAEMIA, NUTRITIONAL RICKETS, AND INFANTILE SCURVY IN GREAT BRITAIN. A BRITISH PAEDIATRIC ASSOCIATION REPORT.** SAMUEL HS.PMID: 14147742

Led astray by Narang's 1984 Paper

- **Six subjects with hypercalcemia who reportedly consumed increasing amounts of vitamin D, with the highest dose at 3800 IU (95 µg) per day, for up to six months.**
- **The old Narang data suggest error on technical grounds: i.e. the hypercalcemia suggests that Narang, *et al*, did not confirm the accuracy of vitamin D doses given, and the doses were probably many times higher than they thought**
  - Narang NK, Gupta RC, Jain MK J Assoc Physicians India. 1984 Feb;32(2):185–8.
- Although reports of the safety of higher, physiologic doses of vitamin D were available, the FNB instead chose to rely solely upon the data from the Narang study to support their current toxicity levels (LOAEL of 3800 IU)

Adams & Lee: Misinformation of toxic levels

- Four patients with were taking dietary supplements with an "unadvertised" high level of vitamin D.
  - Accompanied by an editorial expressing "a word of caution" about vitamin D.
- **Three cases appeared to be industrial type poisoning with vitamin D, probably from errors in the manufacturing of the supplements.**
  - **The fourth patient misdiagnosed. Had hypercalcuria but only had a 25(OH)D level of 140 nM/L (56 ng/mL). In addition, her calcium to creatinine urinary ratio remained unchanged even after her 25(OH)D levels fell to low, "normal" values, indicating that her hypercalcuria was from another cause**.
  - The upper limit of Adams and Lee's reference lab (140 nM/L or 56 ng/mL)
  - Adams JS, Lee G Ann Intern Med. 1997 Aug 1;127(3):203–6.
- Except for the report of Adams and Lee, all toxicosis from vitamin D reported in the world literature has been associated with serum 25(OH)D levels of more than 200 nM/L (80 ng/mL).

Vitamin D from Food

- *A*

- **The average U.S. adult intake of vitamin D is 230 IUs daily, according to a study reported in the journal *Nutrition Reviews*.**
- **Bruce Hollis, professor of pediatrics at the Medical University of South Carolina, calls the usual supplement of 400 IU a day “a joke”.**

Food Sources Vitamin D

- Apart from fish and milk, there is very little Vitamin D in food. Cheese, yogurt, ice cream, butter, etc. do not contain significant amounts of Vitamin D.
- **saltwater fish**
  - **Wild salmon have more than twice the vitamin D content of other fish**
  - **farmed salmon have 1/4th of wild**
- **egg yolks**
- **cod liver oil**
- **fortified foods include milk, orange juice, cereal, butter, & chocolate mixes.**
  - 1/3 of milk samples contains none or less than stated on the label
- **shitake mushrooms (natural source of D2)**

Food sources of Vit D

Food	IUs per serving
Cod liver oil, 1 tablespoon	1,360
Salmon (sockeye), cooked, 3 ounces	794
Mushrooms that have been exposed to ultraviolet light to increase vitamin D, 3 ounces (not yet commonly available)	400
Mackerel, cooked, 3 ounces	388
Tuna fish, canned in water, drained, 3 ounces	154
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	115-124
Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)	100
Yogurt, fortified with 20% of the DV for vitamin D, 6 ounces (more heavily fortified yogurts provide more of the DV)	80
Liver, beef, cooked, 3.5 ounces	46
Egg, 1 whole (vitamin D is found in yolk)	25

Vitamin D from sun exposure

- Judiciously expose as much skin as possible to direct midday sunlight for **1/4 the time it takes for the skin to turn pink**, during those months when the proper ultraviolet light occurs at their latitude (usually late spring, summer and early fall). Produces 10,000-15,000 units per day.
  - For a caucasian, this might mean only 5-10 minutes daily
  - After this, put on UVA/UVB blocking sunscreen if you plan to remain outside.
- **Do not try to get a tan.**
- **Do not get sunburned.** Vitamin D production is already maximized before your skin turns pink and further exposure does not increase levels of vitamin D but may increase your risk of skin cancer.
- **Black persons may need 5-10 x longer in the sun than whites, depending on skin type.**
- Topical application of an SPF of 8 will reduce the cutaneous production of Vitamin D3 by 97.5%; SPF 15 blocks 99%

To Sun or Not to Sun

- **Not to sun—the American Academy of Dermatology Position** [http://www.aad.org/media/background/factsheets/fact_vitamind.htm]
  - **"Substantially more than 1 million cases of skin cancer are diagnosed in the United States every year."**
  - "**UV rays can cause premature aging of the skin and skin cancer.** There is significant scientific evidence to support this fact, which is why the International Agency of Research on Cancer classifies UV radiation from the sun and tanning devices as a known carcinogen (cancer-causing agent). UV exposure also can lead to cataracts and suppressed immune responses."
  - "**The number of diagnosed cases of skin cancer continues to increase.** Current estimates are that one in five Americans will develop skin cancer during his or her lifetime."
  - "**One person dies from melanoma, the most serious form of skin cancer, almost every hour in the United States.2** Melanoma is the No. 1 cancer for young adults 25-29 years old and the second-most-common cancer for adolescents and young adults 15-29 years old.5 At current rates, a person has a one in 58 chance of developing melanoma during his or her lifetime."
  - Dr. Gilchrest, dermatologist at Boston U: "Any individual or organization that advocates intentional sun exposure as the preferred means of producing vitamin D is doing a tremendous disservice to the public."

To Sun or Not to Sun

- To Sun (judiciously, not tanning or burning)
  - Intermittent and occupational sun exposure has been found to reduce the risk of malignant melanoma. *Holick M. British Medical Journal 2008; 336:1318–1319*
  - A history of severe sunburn with blistering was associated with nearly 3-fold melanoma risk among poor tanners (OR = 2.9) but was protective among good tanners (OR = 0.79). *Environ Health Perspect*. 1989 May; 81: 139–151
  - **Ironically, sunscreens appear to dramatically increase the risk of melanoma, probably by increasing the amount of time one spends in the sun. Until recently, sunscreens only blocked vitamin D producing UVB and let UVA through. That is, the sunscreen-promoting dermatologists many be partially responsible for melanoma epidemic. Godar DE, Landry RJ, Lucas AD. Increased UVA exposures and decreased cutaneous Vitamin D(3) levels may be responsible for the increasing incidence of melanoma. *Med Hypotheses*. 2009 Apr;72(4):434-43.**

Vitamin D Supplementation

- **Use D3 (cholecalciferol) rather than D2 (ergocalciferol)**
- **For correcting deficiency:** Dosages should reflect physiologic requirements and natural endogenous production and should be in the range of 2,000-10,000 units per day
  - Supplementation should be continued for 3-9 months
  - Vitamin D levels do not plateau until 3-4 months.
  - Most studies of Vitamin D supplementation have been flawed due to insufficient therapeutic intervention
  - Vitamin D levels should be monitored to assess effectiveness of therapy, by measuring Vitamin D 25 hydroxy
  - Vitamin D1,25 levels do not reflect body stores of Vitamin D
  - Supplements should be used that have been tested for potency

Ergocalciferol (D2)

- **Prescriptions available in North America made exclusively with vitamin D2**
  - **D2 produced by irradiating yeast with UV light.**
  - **D2 used in the fortification of milk and other foods**
- **Vitamin D3 preferable to Vitamin D2**
  - **D2 has a shorter shelf life**
  - **D2 has a reduced affinity for Vit D binding protein**
  - **D2 increases vitamin D catabolism**
  - **D2 not measured on some lab tests**
  - **D3 is considerably more potent (3-9 times)**
  - **D3 has a longer ½ life**

- **Houghton LA, Vieth R. The case against ergocalciferol (vitamin D2) as a vitamin supplement. Am J Clin Nutr 2006;84:694-7. Armas LAG, et al. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab 2004;89:5387-91.**

Vitamin D Supplementation

- For Maintenance (Persons with adequate Vitamin D levels)
  - Adults without sun exposure should receive 2000-3000 IUs of Vitamin D daily, possibly more
  - Pregnant women without sun exposure should receive 2000-3000 IUs of Vitamin D daily, possibly more
  - Infant should receive 1000 units daily and older children 2000 units daily
  - Present recommendations of 200-600 IUs are woefully inadequate
  - Testing of Vitamin D supplements by ConsumerLabs showed accurate amounts and no contaminants.