The Sunshine Vitamin: Vitamin D and CV Disease
Hype or New Hope?

Jeffrey L Anderson, MD

Hormone: derived from cholesterol
1. Requires ≥ 2 tissues/organs to be activated
2. Works systemically on multiple tissues/organs
3. Changes gene expression
4. Vit D receptors in multiple organs

Vitamin D:
* Skin, Liver, Kidney
* Muscles, Bones, Heart, Brain, Vessels, Kidneys, etc
> 2,000 genes
**Selected Nonskeletal Functions of Vitamin D**

**25(OH)D**:
- Metabolic storage form of Vit D
- Principal circulating form of Vit D
- Generally accepted as best measure of total body Vit D stores
- Commonly measured in serum or plasma to assess Vit D status

**1,25(OH)2D**:
- Active form of Vit D
- Activated from 25(OH)D in the kidney
- Regulates parathyroid hormone
Defining Vitamin D Deficiency

- ≤ 10 ng/ml: Severely Deficient
- 10 to 20 ng/ml: Moderately Deficient
- 20 to 30 ng/ml: Mildly Deficient? Adequate?
- ≥ 30 ng/ml: Sufficient
- 40 to 60 ng/ml: Ideal (?)
- > 150 ng/ml: Toxic

Parathyroid hormone begins to rise at Vit D levels < 20-25 ng/ml
Vitamin D Deficiency Epidemic

Adolescents 24% Arch Ped Adol Med 2004; 158:531
Young Adults 32% Am J Med 2002; 112:659
IM Residents 51% Calcf Tissues Int 2005; 76(1):11
NHANES Survey 25-57% Bone 2002; 30:771
Hospital Pts 57% NEJM 1998; 338:777
IMC Patients 63% Am J Cardiol 2010; 106:963
Critically ill 93% NEJM 2009; 360:1912
Nursing Home Pts 90%
Worldwide 25-90%: >1-2 billion people

Reasons for Increased Risk of Vitamin D Deficiency

- INDOOR LIFESTYLE & SUN AVOIDANCE
- SUN PROTECTION (SUNSCREEN, CLOTHING)
- DARKER SKIN AND HIGH LATITUDES
  - AGING POPULATION
- DECREASED MILK CONSUMPTION
- OBESITY AND DIABETES

Vitamin D Disease Associations

- Bone/muscle: Osteoporosis, myalgias
- Cancers
  - Colorectal
  - Breast
  - Prostate
- Chronic kidney disease
- Types 1 and 2 Diabetes
- Hypertension
- Obesity
- Rheumatoid arthritis
- Multiple sclerosis
- Depression, cognitive impairment
- Cardiovascular disease risk
Proposed CV Risk Mechanisms

Vitamin D Deficiency
- Insulin Resistance
- Pancreatic Beta Cell Dysfunction
- Inflammation
- PAAS
- Diabetic and Metabolic Syndrome
- Atherosclerosis
- Advanced Cardiovascular Events
- Hyperension and Hypertrophy

25D Deficiency Increased Mortality in Dialysis Patients

90-Day Mortality by 25D Levels

<table>
<thead>
<tr>
<th>25-hydroxyvitamin D (ng/mL)</th>
<th>All-Cause</th>
<th>CV Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>A</td>
<td>R</td>
</tr>
<tr>
<td>10-20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05 vs no active vitamin D therapy; Reference group: n=634.
25-Hydroxyvitamin D and Risk of Myocardial Infarction in Men
A Prospective Study

Edward Giovannucci, MD, ScD, Yan Lu, MS, Bruce W. Holub, MD, PhD, Eric B. Rimm, ScD

Arch Intern Med. 2008;168(11):1174-1180

Background: In cross-sectional studies, low serum levels of 25-hydroxyvitamin D are associated with higher prevalence of cardiovascular risk factors and outcomes. This study aimed to determine whether prospective, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels are related to all-cause and cardiovascular mortality.

Methods: Prospective cohort study of 3228 consecutive male and female volunteers, mean age 42±11 years, scheduled for coronary angiography at a single tertiary center. We measured serum levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels within each month of blood drawings. The main outcome measures were all-cause and cardiovascular deaths.

Results: During a median follow-up period of 7.7 years, 377 patients (11%) died, including 196 deaths from cardiovascular causes. Multivariate-adjusted hazards ratios (HRs) for patients in the lowest tertile of 25-hydroxyvitamin D tertile and 1,25-dihydroxyvitamin D tertile were 1.37 (95% confidence interval [CI], 1.06-1.77) and 1.21 (95% CI, 1.00-1.46) for all-cause mortality and 1.36 (95% CI, 1.06-1.75) and 1.26 (95% CI, 1.03-1.54) for cardiovascular mortality (HRs, 2.09, 95% CI, 1.60-1.70, and HR, 1.36, 95% CI, 1.03-1.80, respectively) and for cardiovascular mortality (HR, 2.22, 95% CI, 1.57-3.13, and HR, 1.40, 95% CI, 1.27-1.59, respectively) compared with patients in the highest tertile of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels.

Conclusions: Low 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels are independently associated with all-cause and cardiovascular mortality. A causal relationship has yet to be proven by interventional studies.
Kaplan-Meier Plots Of All-cause and Cardiovascular Mortality In the 25-Hydroxyvitamin D Quartiles

IHC Vitamin D Observational Study

- Prospective analysis of patient data within Intermountain Healthcare
- Included 41,497 patients in whom at least one serum vitamin D level was obtained
- Vit D levels were drawn at the providers’ discretion for the usual indications (osteoporosis etc.)
- Vit D >30 in 36%; 16-30 in 47%; <=15 in 17%

Anderson J. Am J Cardiol 2010; 106:963
Vitamin D and CV Risk Factor Prevalence at Baseline

Vitamin D Levels
- >30 ng/ml
- 16-30 ng/ml
- <=15 ng/ml

Percent

*P-trend <0.0001

Vitamin D and Risk for Incidence (New Development) Of CV Risk Factors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Very Low (&lt;=15) vs Normal</th>
<th>Low (16-30) vs Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>HR*=1.62, p&lt;0.0001</td>
<td>HR=1.18, p=0.005</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>HR=1.27, p=0.003</td>
<td>HR=1.10, p=0.12</td>
</tr>
<tr>
<td>Diabetes</td>
<td>HR=1.89, p&lt;0.0001</td>
<td>HR=1.32, p=0.001</td>
</tr>
<tr>
<td>PVD</td>
<td>HR=1.40, p=0.04</td>
<td>HR=1.01, p=0.93</td>
</tr>
</tbody>
</table>

*HR=adjusted hazard ratios.

Anderson J. Am J Cardiol 2010; 106:963
Vit D and Risk for Incident CV Outcomes

<table>
<thead>
<tr>
<th>Outcomes (pts &gt;50 yrs)</th>
<th>≤15 vs. &gt;30 (ref)</th>
<th>16-30 vs. &gt;30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (n=27,686)</td>
<td>HR=1.77, p&lt;0.0001</td>
<td>HR=1.20, p=0.009</td>
</tr>
<tr>
<td>CAD/MI (n=21,853)</td>
<td>HR=1.45, p&lt;0.0001</td>
<td>HR=1.15, p=0.09</td>
</tr>
<tr>
<td>CHF (n=23,793)</td>
<td>HR=2.01, p&lt;0.0001</td>
<td>HR=1.31, p=0.005</td>
</tr>
<tr>
<td>CVA (n=26,025)</td>
<td>HR=1.78, p=0.004</td>
<td>HR=1.31, p=0.11</td>
</tr>
<tr>
<td>AFib (n=24,565)</td>
<td>HR=1.02, p=0.87</td>
<td>HR=0.95, p=0.61</td>
</tr>
</tbody>
</table>

*insufficient events for analysis

Intermountain Healthcare Cohort: Vitamin D and Risk of Mortality

Vitamin D and CVD Risk in NHANES

Prevalence of Hypovitaminosis D in Cardiovascular Diseases (from the National Health and Nutrition Examination Survey 2001 to 2004)

Doe Hyun Kim, MD, MPH\textsuperscript{a}, Saimik Sabour, MD, PhD\textsuperscript{a}, Upal N. Seng, MD\textsuperscript{b}, Suzanne Adams, RN, MPH\textsuperscript{a} and David J. Whelton, MD, MHS\textsuperscript{a, b}

This cross-sectional study examined the burden of cardiovascular diseases (CVDs) using serum 25-hydroxyvitamin D (25(OH)D) and prevalence of hypovitaminosis D in adults with CVDs using data from NHANES 2001 to 2004. Serum 25(OH)D levels were divided into 3 categories (<20, 20 to 29, and ≥30 ng/mL), and hypovitaminosis D was defined as vitamin D <20 ng/mL. Of 8,351 adults who had 25(OH)D measured, mean 25(OH)D was 24.4 ng/mL, and the prevalence of hypovitaminosis D was 14%. The burden of CVDs increased with lower 25(OH)D categories, with 5.3%, 6.5%, and 9.3% coronary heart disease; 1.5%, 2.0%, and 3.5% heart failure; 2.9%, 3.8%, and 5.2% stroke; and 3.4%, 3.6%, and 7.7% peripheral arterial disease. Across all CVDs, hypovitaminosis D was more common in blacks than Hispanics or whites. Compared with persons at low risk for CVDs (68%), it was more prevalent in those at high risk (75%): odds ratio (OR) 1.32, 95% confidence interval (CI) 1.05 to 1.67, with coronary heart disease (OR 1.48, 95% CI 1.14 to 1.91), and both coronary heart disease and heart failure (OR 1.52, 95% CI 1.06 to 2.16) after controlling for age, race, and gender. In conclusion, hypovitaminosis D was highly prevalent in US adults with CVDs, particularly those with both coronary heart disease and heart failure. © 2009 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;102:2049–2054)

Vit D Deficiency is Associated with Incident CVD in Framingham Offspring Study

Lower 25-OH Vitamin D Levels Associated With Higher Risk for CV Events

![Graph showing cumulative probability of CVD with lower 25(OH)D levels in hypertensive patients and normal blood pressure groups.](image-url)
Can Vitamin D Supplementation Reduce Cardiovascular Risk?

Why Vitamin D if Not A, B, C, or E*?

- Axiom of Essential Nutrients
  - Repleting a deficiency predictably confers benefits
  - Supplementing a normal level to supra-physiologic range results in neutral to harmful effects

*Or Folic Acid, or Hormone Replacement Therapy?
Vitamin D Therapy Associated With a Survival Advantage in Dialysis Patients

**Data From the Fresenius Dialysis Database**

- **2-Year Mortality Per 100 Person-Years**
  - IV vitamin D: 28.6
  - No IV vitamin D: 13.8
  - p<0.001

**Design**
- Historical cohort study
- n=37,173 patients treated with intravenous (IV) vitamin D compounds
- n=13,864 patients received no IV vitamin D

**Results**
- Adjusted 2-year survival advantage of 20% observed for IV vitamin D use
- Benefits observed even in patients with low PTH and elevated phosphorus and calcium

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Intake of Vitamin D Associated With Decreased Total Mortality

**Meta-Analysis of All Cause Mortality in 9 Randomized Controlled Clinical Trials in Which Patients Received Vitamin D or Control**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Deaths</th>
<th>No. of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention Group</td>
<td></td>
<td>Control Group</td>
</tr>
<tr>
<td>Chapuy, et al. (1992)</td>
<td>250/1134</td>
<td>216/1061</td>
</tr>
<tr>
<td>Lysniak, et al. (1994)</td>
<td>223/1294</td>
<td>218/1297</td>
</tr>
<tr>
<td>Chapuy, et al. (2005)</td>
<td>71/703</td>
<td>45/100</td>
</tr>
<tr>
<td>Moure, et al. (2002)</td>
<td>491/567</td>
<td>163/31</td>
</tr>
<tr>
<td>Freed, et al. (2003)</td>
<td>244/1345</td>
<td>244/1341</td>
</tr>
<tr>
<td>Portales, et al. (2005)</td>
<td>57/1321</td>
<td>58/1003</td>
</tr>
<tr>
<td>Grant, et al. (2005)</td>
<td>443/2940</td>
<td>443/2943</td>
</tr>
<tr>
<td>Pickard, et al. (2004)</td>
<td>753/12</td>
<td>353/83</td>
</tr>
<tr>
<td>Jackson, et al. (2005)</td>
<td>744/1070</td>
<td>507/1010</td>
</tr>
</tbody>
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Summary Relative Risk (95% CI)

Summary relative risk: 0.67 (0.56-0.80); CI: confidence interval.

Vitamin D Therapy and CV Risk:
Intermountain Healthcare Study

- 7,515 patients (>18 yrs) with a low (<30) initial Vitamin D level
  - Follow-up vitamin D level obtained at least 1 year prior to the censor date (3/25/2010)
  - The last follow-up level used was either the first level where the vitamin D level was normalized (>30) or the last level obtained.
- Patients stratified by follow-up Vitamin D level
  - Vitamin D ≥ 30 ng/mL
  - Vitamin D <30 ng/mL
- Patients followed long-term (av 2.5 years, max 5.5 years)
- Cox regression adjusted for death, new diagnosis of coronary artery disease (CAD), myocardial infarction (MI), heart failure (HF), stroke, and renal failure.

Bair T, Muhlestein JB,…Anderson JL. JACC 2010; 55:A59
Effect of Normalizing Vitamin D on Composite Endpoint

Effect of Normalizing Vitamin D on Renal Failure

P<0.0001
VITAL: A Randomized Intervention Trial

- A Vitamin D and Omega-3 Trial
- 20,000 participants, launched Jan 2010
  - Males ≥60 years
  - Females ≥65 years
  - No history of heart disease or cancer
  - Not taking major vitamin D (>800 U/d) or calcium (>1,200 mg/d) supplements

- Doses:
  - Vitamin D: 2000 U/d vs placebo
  - Omega-3 fatty acid: 1 g/d vs placebo

- Coordinating Center: Harvard/BWH
- Funding: NIH

Pending Prospective Trials, Empiric Therapy?
OR
Screen, Supplement to Target?
Recent Institute of Medicine Recommendations

Doses recommended to achieve adequate 25-OH Vitamin D Blood Levels:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 IU Daily</td>
<td>≤ 70 years old</td>
</tr>
<tr>
<td>800 IU Daily</td>
<td>&gt; 70 years old</td>
</tr>
</tbody>
</table>


Vitamin D: Who Should be Screened?

?Everyone except lifeguards who don’t wear sunscreen?

Courtesy of J O’Keefe
Groups Susceptible to Vit D Deficiency That May be Considered for Screening

- Darker Skin
- Over age 50 with other indications
- Bone, muscle disease/complaints; statin myalgias, fibromyalgia, etc.
- Hypertension, CV disease, heart failure
- Hospital, other health care settings
- Infections, autoimmune diseases
- Obesity, diabetes
- Indoor lifestyle, sun avoidance
- Neuro-degenerative diseases
- Kidney disease

Cost of 25-OH Vitamin D Assay

- Most commonly ordered “esoteric test”
- Typical outpatient lab charge = $50 to $150
- Medicare reimbursement = $43—but now limited to classical indications (not CV risk)
- On-line order (e.g. LEF.com) = $35
- Mayo Clinic wholesale = $22
### Medicare ICD-9 Diagnosis Codes that Cover Vitamin D Blood Test

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ICD-9 Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgias (unspecified)</td>
<td>729.1</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>593.9</td>
</tr>
<tr>
<td>Vitamin D Deficiency</td>
<td>268.9</td>
</tr>
<tr>
<td>Osteoporosis (unspecified)</td>
<td>733.00</td>
</tr>
<tr>
<td>Disorder of Bone and Cartilage (unspecified)</td>
<td>733.90</td>
</tr>
</tbody>
</table>

Fasting is not required.

### Supplementing Vitamin D

- **Goal:** 25(OH)D level of >20 – 30 (up to 50?) ng/ml
- **Available Supplements**
  - Vitamin D2 (ergocalciferol) – Plant based form
  - Vitamin D3 (cholecalciferol) – Animal based form
    - Generally preferred form
- **Current IOM Recommended Daily Allowance**
  - 600 IU/day for age <=70
  - 800 IU/day for age >70
- **Treatment of Deficiency**
  - Vitamin D3: 5,000 IU daily for 8-16 weeks
- **Maintenance After Repletion**
  - Vitamin D3: begin with 1,000-2,000 IU daily
What is Ideal Range and Can Too Much Vitamin D Be Harmful?

- IOM review suggests that >20 ng/ml (rather than >30) may be adequate for bone (and other) health.
- “U” shaped concentration-response curve suggested for some cancers (e.g., pancreatic) with upswing beginning as low as >50 ng/ml.
- Evidence of pro-inflammatory response as evidenced by increases in C-reactive protein at high (>50 ng/ml) as well as low (<20 ng/ml) levels suggested in recent research.
- In our database, suggestion of increased risk of atrial fibrillation at high concentrations (>100 mg/ml).

Conclusions

- Vitamin D is a hormone that acts on receptors in multiple tissues and organs.
- Vit D originates primarily by synthesis in the skin in response to sun exposure, and deficiency is a common consequence of our modern lifestyle in the general population and in CV patients.
- Growing evidence associates Vit D deficiency with CV risk factors and incident CV disease.
- Observational evidence supports the use of Vit D supplementation in deficient patients to reduce CV risk, but randomized trials are needed.
- Currently, either an empiric approach to lifestyle and supplementation or selected screening and treatment to target may be considered.
So, Vit-D Hope or Hype?

Probably some of each!
Stay tuned.
Final answers pending.