Vitamin D & Cardiovascular Disease
Disclosures

None
Objectives:

- Discuss the basics of vitamin D metabolism
- Discuss the role of vitamin D deficiency in the development of coronary disease
- Review how repletion of vitamin D may improve CV health and prognosis
- Provide recommendations for vitamin D replacement
Vitamin D

- Traditionally associated with bone health
- Rickets in children
- Osteomalacia/osteoporosis in adults
- New data confirms its importance for optimal function of the CV system
Vitamin D Basics (Two forms)

- Vitamin D$_2$ (ergocalciferol)
- D$_2$ found in plants & in fortified foods
- Vitamin D$_3$ (cholecalciferol)
- D$_3$ synthesized in human epidermis or consumed in oily fish or fortified foods
Vitamin D Basics

- Vitamin D converted in the liver to 25 (OH) D
- 25 (OH) D: major circulating metabolite
- 25 (OH) D: serum levels reflect intake & endogenous production
- 25 (OH) D: should be measured to clinically assess vitamin D status
Vitamin D Basics

- 25 (OH) D: Converted to 1, 25 (OH)$_2$ D in the kidney
- 1, 25 (OH)$_2$ D: active form of the vitamin
- 1, 25 (OH)$_2$ D: plays vital role in maintaining bone & muscle health by regulating Ca++ metabolism
- Serum level 1,25 (OH)$_2$ D: does not correlate with overall vitamin D status, generally not clinically useful
What Do You Lack? Probably Vitamin D

By JANE E. BRIDY
Published: July 26, 2010

Vitamin D promises to be the most talked-about and written-about supplement of the decade. While studies continue to refine optimal blood levels and recommended dietary amounts, the fact remains that a huge part of the population — from robust newborns to the frail elderly, and many others in between — are deficient in this essential nutrient.

If the findings of existing clinical trials hold up in future research, the potential consequences of this deficiency are likely to go far beyond inadequate bone development and excessive bone loss that can result in falls and fractures. Every tissue in the body, including the brain, heart, muscles and immune system, has receptors for vitamin D, meaning that this nutrient is needed at proper levels for these tissues to function well.

Studies indicate that the effects of a vitamin D deficiency include an elevated risk of developing (and dying from) cancers of the colon, breast and prostate; high blood pressure and cardiovascular disease; osteoarthritis; and immune system conditions that cause multiple infections.
<table>
<thead>
<tr>
<th>Serum 25-Hydroxyvitamin D (ng/ml)</th>
<th>Vitamin D Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10</td>
<td>Severe deficiency</td>
</tr>
<tr>
<td>10-20</td>
<td>Deficiency</td>
</tr>
<tr>
<td>21-29</td>
<td>Insufficiency</td>
</tr>
<tr>
<td>≥30</td>
<td>Sufficiency</td>
</tr>
<tr>
<td>&gt;150</td>
<td>Toxicity</td>
</tr>
</tbody>
</table>
Vitamin D deficiency

Prevalence

- Much more prevalent than previously recognized
- 50% of young adults & apparently healthy children
- NHANES III: 25% to 57% of US adults
- Increases in proportion to distance from the equator (Atlanta, 40° latitude)
Risk Factors for Vitamin D Deficiency

- Elderly
- Darkly pigmented skin
- Cover-up clothing and/or sunscreen
- Institutional or homebound
- Obese
- Increased distance from equator
- Winter season
- Air pollution
- Smoking
- Malabsorption
- Renal disease
- Liver disease
- Medications: anticonvulsants, glucocorticoids, antirejection and HIV medications
Specific at Risk Populations

Elderly
Decreased cutaneous synthesis
70 y/o produces 75% < D$_3$ than 20 y/o with same sun exposure

Darkly pigmented skin

Require proportionally higher sun exposure to synthesize
Equivalent amounts of vitamin D secondary to the UV blocking mechanisms of melanin
Average vitamin D level African Americans: 18-22 ng/mL
(Caucasians: 13-15 ng/mL)
Specific at Risk Populations

Cover up clothing and/or sunscreen
SPF 15 or >blocks 99% of cutaneous vitamin D production

Obese
Decreased bioavailability of vitamin D sequestered in adipose tissue
Equivalent exposure to UVB results in 50% lower blood levels of vitamin D c/w non-obese
Vitamin D

1, 25 (OH)2 D regulates over 200 genes

- Renin production in the kidney
- Insulin production in the pancreas
- Release of cytokines from lymphocytes
- Production of cathelicidin in macrophages
- Growth & proliferation of vascular smooth muscle cells and cardiac myocytes
Vitamin D Receptors (VDRs)

Present on a large variety of cell types

- Myocytes
- Cardiac myocytes
- Pancreatic beta-cells
- Vascular endothelial cells
- Neurons
- Immune cells
- Osteoblasts
Chronic Vitamin D deficiency

Causes secondary hyperparathyroidism

- Threshold for elevation of parathyroid hormone <30 ng/mL
- Further decreases → proportionally higher PTH levels to maintain serum and total body Ca++ levels
Chronic Vitamin D deficiency

- Reduces intestinal Ca++ absorption by ≥ 50%
- Attendant decrease in serum Ca++ triggers PTH release
Chronic Elevation in PTH

Leads to:

- Increase in blood pressure
- Increase in myocardial contractility
- Hypertrophy, apoptosis & fibrosis of the left ventricle
- Hypertrophy of the vascular medial smooth muscle
Vitamin D deficiency and/or Increased PTH

Predisposes to:

- Calcification of the heart valves
- Mitral annular calcification
- Myocardial calcification
Vitamin D deficiency in the genesis of coronary risk factors

Predisposes to:

- Hypertension
- Diabetes & metabolic syndrome
- Left ventricular hypertrophy
- Congestive heart failure
- Chronic vascular inflammation
Vitamin D deficiency & CV Risk

NHANES III - 15,088 subjects

25 (OH) D levels inversely associated with:

- Hypertension
- Diabetes mellitus
- Hypertriglyceridemia
- Obesity
Type I Diabetes Mellitus

“The rising incidence of Type I diabetes mellitus may in part be due to the current practice of protecting the young from sun exposure.”

Dr. Michael Holick
Boston University
“The Vitamin D Solution”
Type II diabetes mellitus & vitamin D deficiency

- Small randomized trial
- Low baseline vitamin D levels
- Single dose of 100,000 u vitamin D$_2$
- Decreased systolic B/P by 14 mmHg
- Improved endothelial function as measured by forearm blood flow

Sugden et al
Vitamin D deficiency

- Increases the risk of major CV events
- Male health professionals: 2 fold increased risk of CV death, if in the lowest quartile for vitamin D levels

Giovannucci et al.
Arch Intern Med 2008: 168:1174-80
Adverse CV events

- 3.258 German adults
- Undergoing elective cardiac catheterization
- Follow up: 7.7 years
- Two fold increased risk of death, if in the lowest quartile for vitamin D levels

Dobrig et al
Arch Intern Med 2008; 168:1340-9
Vitamin D deficiency & CV disease

Framingham offspring study – 1,739 subjects

- Free of CV disease at baseline
- 25 (OH) D levels at baseline
- Mean follow up 5.4 years
- Composite CV endpoint (MI, ischemia, stroke, HF) 53% to 80% higher in subjects with low vitamin D levels
- Rate magnified in cohort with hypertension

Wong et al
Circulation 2008; 117:503-11
Hazard ratio for cardiovascular disease by vitamin D levels:

- ≥ 15 ng/mL: 1 (Referent)
- 10 - < 15 ng/mL: 1.53 (1.05 - 3.08)
- < 10 ng/mL: 1.80 (1.00 - 2.36)

25 (OH) D Level
Vitamin D is a Prognostic Marker in Heart Failure
European Society of Cardiology 2010 Stockholm

- Large cohort patients hospitalized for heart failure
- Higher risk of rehospitalization if vitamin D deficient
- Higher risk of death if vitamin D deficient

University Medical Center
Groningen, Netherlands
Sept. 5, 2010
Vitamin D Deficiency & Myopathy

- Myalgias: first manifestation of vitamin D deficiency
- Severe vitamin D deficiency with ↑PTH reported
  - 88% males with muscle pain & weakness
- Meta analysis of 5 studies: vitamin D supplementation reduced fall risk
- Myalgias: most common complaints of patients on statins
- Anecdotal data showing repletion improves or resolves statin related myalgias
Supplementing Vitamin D

- Traditionally 95% vitamin D requirements come from the sun
- Remainder ingested from dietary sources
- Average daily consumption 230 IU
## Selected Food Sources of Vitamin D

<table>
<thead>
<tr>
<th>Food</th>
<th>IU per Serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod liver oil, 1 tablespoon</td>
<td>1,360</td>
</tr>
<tr>
<td>Wild-caught salmon, 3 oz</td>
<td>600-1,000</td>
</tr>
<tr>
<td>Farmed salmon, 3 oz</td>
<td>100-250</td>
</tr>
<tr>
<td>Mackerel, cooked, 3 oz</td>
<td>345</td>
</tr>
<tr>
<td>Tuna fish, canned in oil, 3 oz</td>
<td>200</td>
</tr>
<tr>
<td>Sardines (with bones), canned in oil,</td>
<td>250</td>
</tr>
<tr>
<td>drained, 1 oz</td>
<td></td>
</tr>
<tr>
<td>Milk, nonfat, reduced fat, and whole,</td>
<td>98</td>
</tr>
<tr>
<td>vitamin D-fortified, 1 cup</td>
<td></td>
</tr>
</tbody>
</table>
Current Recommendations for Supplementation

- 200 IU daily: <50
- 400 IU daily: 50-70 y/o
- 600 IU daily: >70 y/o
- Suspected that 1,000-2,000 IU daily is necessary for most people
Vitamin D Deficiency
25(OH)D < 20 ng/mL

50,000 IU/wk D$_2$ or D$_3$
for 8 Weeks

Maintenance Therapy
(3 Choices)

50,000 IU D$_2$ every 2 weeks
1,000 to 2,000 IU D$_3$ daily
Sunlight exposure

Recheck 25(OH)D in 3 to 6 months
Vitamin D

- Excessive sunlight exposure cannot cause vitamin D toxicity
- UVB converts excess vitamin D₃ to biologically inert isomers
- Excessive oral vitamin D can cause toxicity at high doses
Sun Exposure

- Impossible to establish universal public health recommendation
- 3000 IU D3: 5-10 min. of mid day sun, 2 to 3 x’s/wk adequate for Caucasians
- With arms and legs exposed; face always protected
- With appropriate sun exposure in summer, its possible to meet body’s year long needs

Dr. Michael Holick
Symptoms of Vitamin D toxicity

- Nausea and vomiting
- Decreased appetite and weight loss
- Constipation
- Weakness
- Increased amounts of Ca++ leading to kidney stones
- Confusion
- Abnormal heart rhythms
Vitamin D Assay Testing

- Screening for vitamin D deficiency is not covered
- Monitoring therapeutic replacement would not be expected to exceed 2 assays per year. Once therapeutic range has been reached, testing would not be expected to exceed one (1) assay per year
- 585.3-5 Chronic Kidney Disease
- 733.90 Disorder of Bone
- 733.00 Osteoporosis
- If not covered: Cost $235
Vitamin D Deficiency
An Important, Common, and Easily Treatable Cardiovascular Risk Factor?

John H. Lee, MD,* James H. O’Keefe, MD,* David Bell, MD,† Donald D. Hensrud, MD, MPH,‡ Michael F. Holick, MD, PhD§

Kansas City, Missouri; Birmingham, Alabama; Rochester, Minnesota; and Boston, Massachusetts

Vitamin D deficiency is a highly prevalent condition, present in approximately 30% to 50% of the general population. A growing body of data suggests that low 25-hydroxyvitamin D levels may adversely affect cardiovascular health. Vitamin D deficiency activates the renin-angiotensin-aldosterone system and can predispose to hypertension and left ventricular hypertrophy. Additionally, vitamin D deficiency causes an increase in parathyroid hormone, which increases insulin resistance and is associated with diabetes, hypertension, inflammation, and increased cardiovascular risk. Epidemiologic studies have associated low 25-hydroxyvitamin D levels with coronary risk factors and adverse cardiovascular outcomes. Vitamin D supplementation is simple, safe, and inexpensive. Large randomized controlled trials are needed to firmly establish the relevance of vitamin D status to cardiovascular health. In the meanwhile, monitoring serum 25-hydroxyvitamin D levels and correction of vitamin D deficiency is indicated for optimization of musculoskeletal and general health. (J Am Coll Cardiol 2008;52: 1949–56) © 2008 by the American College of Cardiology Foundation