Update on Vitamin D: The Sunshine Vitamin and Aging

Carolyn Moore, PhD, RD
April 2015
**History of Vitamin D**

**Glisson (1651):** recognized that many children living in crowded, polluted cities in Europe developed a bone deforming disease. Pregnant women often had deformed pelvis leading to death.

**Mellanby (1918):** reported he could produce rickets in dogs by feeding oat meal. Cured with cod liver oil.

**McCollum (1922):** identified vitamin D separately from vitamin A in cod liver oil.

**Steenbock and colleagues (1940’s):** showed exposure of food and variety of substances to UV light produced anti-rachitic properties.
### Vitamin D:
#### A Vitamin or Prohormone?

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Prohormone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition:</strong></td>
<td><strong>Definition:</strong> Chemical precursor of a hormone which has no hormone activity of its own</td>
</tr>
<tr>
<td>• Organic compound needed in small amounts</td>
<td></td>
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<tr>
<td>• Not oxidized to provide energy or to form structures of the body</td>
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<tr>
<td></td>
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<tr>
<td><strong>Vitamin characteristics:</strong></td>
<td><strong>Prohormone characteristics:</strong></td>
</tr>
<tr>
<td>• May be ingested from dietary sources (fish, liver oil)</td>
<td>• Synthesized in the skin by photochemical process</td>
</tr>
<tr>
<td>• Can correct vitamin D deficiency</td>
<td>• May be converted to active hormone 1,25(OH)D</td>
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</table>
Deficiency

Vitamin D & Bone Health

• Osteomalacia
  – Classic vitamin D deficiency
  – Associated with painful bone disease & muscle weakness in adults & children

• Rickets
  – Associated with bony deformities & short stature in children
  – May also be due to inadequate calcium intake

Rickets caused by vitamin D deficiency
Vitamin D Metabolism

- Statins do not reduce synthesis
- Serum 25(OH)D used to measure vitamin D status

Diagram showing the steps in Vitamin D metabolism:

1. UVB photons convert 7-dehydrocholesterol to Vitamin D3.
2. Vitamin D3 is converted to 25-hydroxyvitamin D (25(OH)D) by 25-hydroxylase.
3. 25(OH)D has a 2-week blood half-life.
4. 25(OH)D is further converted to 1,25-dihydroxyvitamin D (1,25(OH)2D) by 1α-hydroxylase, encoded by CYP27B1.
5. 1,25(OH)2D has a 5-8 hour blood half-life.
6. 1,25(OH)2D mediates its effects through VDR (Vitamin D Receptor), leading to systemic and local effects.
SOURCES

Natural Sources

• Rich in vitamin D3
  – Major source of vitamin D is sunlight for most individuals
  – Oily fish, cod liver oil, egg yolk

• Low in vitamin D3
  Skeletal muscle, meats

• Minimal vitamin D2
  Plants
Vitamin D Fortification

• US Fortification Practices in 2000:
  – Breakfast cereals
  – Grain products and pasta
  – Milk
  – Milk products
  – Infant formula
  – Margarine

<table>
<thead>
<tr>
<th>Food</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod liver oil</td>
<td>38 μg/Tbsp</td>
</tr>
<tr>
<td>Unfortified milk</td>
<td>&lt;0.25 μg/c, or 1μg/qt</td>
</tr>
<tr>
<td>Fortified milk</td>
<td>2.5 μg/c, or 10μg/qt</td>
</tr>
<tr>
<td>Fortified cereal</td>
<td>1-5 μg/oz</td>
</tr>
</tbody>
</table>

*1μg = 40 IU

• Fortification of juices was not allowed under regulations set in 2000
Vitamin D Fortification

Vitamin D Addition to Calcium Fortified Juice Beverages

• Permitted vitamin D fortification level:
  – Up to 2.5 µg (100 IU) per serving -- *amount permitted in milk*

• Calcium fortification criteria for vitamin D inclusion in juice beverages:
  – Juices:  33 - 35% DV per serving – 350 mg calcium
  – Juice Drinks:  10% DV per serving – 100 mg calcium
Vitamin D Fortification

Vitamin D Addition to Calcium Fortified Juice Beverages

In 2003, allowable uses of vitamin D expanded to calcium-fortified juice and juice drinks

2.5 μg (100 IU) per 240 ml (8 fl oz.)

Other Foods Now Fortified:
Yogurt, soy milk, cereal bars, bread, etc.
METABOLISM

Synthesis of Vitamins D<sub>2</sub> & D<sub>3</sub>

**Plant**

Ergosterol
(provitamin D)

UV light

Ergocalciferol
(vitamin D<sub>2</sub>)

**Animal**

7-dehydrocholesterol (7-DHC)
(provitamin D)

UV light

Cholecalciferol
(vitamin D<sub>3</sub>)
Vitamins D₂ & D₃

**Vitamin D₂ (Ergocalciferol)**
- Found in plants
- Produced by UV irradiation of ergosterol from yeast, fungi, mushrooms
- Available as pharmaceutical
- Used to treat rickets in the past
- Undergo metabolism in:
  - Liver – forms 25(OH)D
  - Kidney – forms 1,25(OH)D
- Available in supplements
- Equally effective for bone health

**Vitamin D₃ (Cholecalciferol)**
- Produced in the skin
- Found in cod liver oil & oily fish (salmon)
- Produced by UVB irradiation of 7-DHC
- Not available as pharmaceutical
- More effective than D₂ in maintaining serum 25(OH)D levels
- Available in supplements
- Equally effective for bone health

Vitamins D₂ & D₃

Vitamin D₂

Vitamin D₃
Vitamin D Requirements

• **RDA**
  Insufficient data to establish in 1998 (was Adequate Intakes [AI])

• **Recommended Dietary Allowances (2010):**
  Dependent on age group:
  - Infants 0-6: 10μg/d \((1 \mu g = 40 \text{ IU})\)
  - Children 6mo-12 mo.: 10μg/d (400 IU)
  - 1 y - 70 y: 15μg/d (600 IU)
  - > 70 y: 20 μg/d (800 IU)

• **Tolerable Upper Intake (ULs):**
  - 9 y and older: 100 μg/d (4000 IU)
Percent of population ages 2+ with usual intakes below EAR

- vitamin D
- vitamin E
- magnesium
- calcium
- vitamin A
- vitamin C
- zinc
- vitamin B6
- folate
- iron
- thiamin
- copper
- phosphorus
- selenium
- vitamin B12
- niacin
- riboflavin

Percent of population

What We Eat in America, NHANES 2007-10

Food and Nutrient Intakes, and Health: Current Status and Trends
Total (Diet + Supplement) Vitamin D Intake by Age, 2007-2010

Factors Reducing Vitamin D₃ Synthesis

- Aging
- Sunscreen
- Decreased UVB exposure
- Skin pigmentation
- Location & Latitude
Factors Reducing Vitamin D₃ Synthesis

Aging

• ↓ concentration of 7-dehydrocholesterol (provitamin D₃)
  • – 70 yr produces 75% less 7-dehydrocholesterol than younger adult
• ↓ capacity of human skin to produce vitamin D₃ with ↑ age
  • reduced more than 50% at 70 yr compared to 20 yr
• Aging does not affect intestinal absorption of vitamin D
• Hydroxylation at C-25 position in the liver not affected by aging
  • Hydroxylation at C-1 position reduced by age-related limitations of the kidney
  • Less responsive to parathyroid hormone of 1,25-OHase
• ↓ thickness of skin
Factors Reducing Vitamin D₃ Synthesis

Skin Pigmentation

Function:
• Melanin absorbs UV radiation from sunlight

Vitamin D₃ Synthesis Reduction:
• Melanin competes with provitamin D₃ in the skin for UVB photons
• ↑ skin pigmentation; ↓ provitamin D₃ production in skin

Increasing Pigmentation →

Factors Reducing Vitamin D₃ Synthesis

Sunscreen

Function:
• Prevents high energy photons (UVA/UVB) from having adverse effects on skin
• Acts like melanin

Vitamin D₃ Synthesis Reduction:
• Solar radiation causes cutaneous production of vitamin D₃; therefore sunscreen diminishes/prevents D₃ production in skin
Factors Reducing Vitamin D₃ Synthesis

**Clothing**

Clothing absorbs UV radiation; therefore prevents cutaneous production of vitamin D₃
Factors Reducing Vitamin D₃ Synthesis

Environment

Latitude - Vitamin D₃ Synthesis Reduction:

Factors Reducing Vitamin D$_3$ Synthesis

**Environment**

**Seasons:**
- **Winter:** UVB photons pass through ozone at an oblique angle; absorbed by ozone
- **Spring, Summer, Fall:** sun is overhead, more penetration of ozone by UVB photons
How is Vitamin D Status Assessed?

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Serum 25(OH)D</th>
<th>Clinical Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficient</td>
<td>&lt;12 ng/mL (&lt;30 nmol/L)</td>
<td>&lt; 20 ng/mL</td>
</tr>
<tr>
<td>At Risk of Inadequacy</td>
<td>12-19.5ng/mL (30 - 49nmol/L)</td>
<td>20 – 29 ng/mL</td>
</tr>
<tr>
<td>Sufficient</td>
<td>20 – 50ng/mL (50 – 125nmol/L)</td>
<td>&gt; 30 ng/mL</td>
</tr>
<tr>
<td>Possibly Harmful</td>
<td>&gt; 50 ng/mL (125nmol/L)</td>
<td></td>
</tr>
</tbody>
</table>

*Figure 1. Serum 25OHD status of persons aged 1 year and over: United States, 2001–2006*

*CDC, NCHS Data Brief, No. 59, March 2011*

- IOM > 20 ng/mL bone health
- US Endocrine Society 2012: Prevalence of vitamin D deficiency is 1/3 of US population
### Do You Know Your Number?

- **Measurement of 25(OH)D over 7 years…..**

<table>
<thead>
<tr>
<th>Year</th>
<th>25(OH)D ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008 – 400 IU + 600 mg Calcium</td>
<td>22.6 – “Low” vs. “Sufficient” by IOM definition</td>
</tr>
<tr>
<td>2009 – 1000 IU/day + 400 IU = 1400 IU</td>
<td>44 – “Sufficient”</td>
</tr>
<tr>
<td>2009 – 1000 IU/day + 400 IU = 1400 IU</td>
<td>41 – “Sufficient”</td>
</tr>
<tr>
<td>2010 – 1000 IU/day + 400 IU = 1400 IU</td>
<td>53 – “Possibly Harmful”</td>
</tr>
<tr>
<td>2011 – 1000 IU ~ 3 times per wk + 400 IU = 850 IU/day</td>
<td>43 – “Sufficient”</td>
</tr>
<tr>
<td>2012 - 1000 IU ~ 3 times per wk + 400 IU = 850 IU/day</td>
<td>43 – “Sufficient”</td>
</tr>
<tr>
<td>2013- returned to 1000 IU/ day + 400 IU = 1400 IU/day</td>
<td>38 – “Sufficient” but “Low Normal personal MD”</td>
</tr>
</tbody>
</table>
Who is at Risk for a Vitamin D Deficiency?

Populations at Risk:
• Patients with malabsorption of fat
• Patients with renal disease
• Patients with cirrhosis of liver
• Individuals lacking exposure to sun: Elderly especially in nursing homes or home-bound
• Obese
• The Elderly
Bone Health

Major biological function is to maintain calcium homeostasis:
- $1,25(OH)_2D$ increases efficiency of intestinal Ca & P absorption
- Both vitamin D & Ca are needed for normal bones

“In a vitamin D deficient state, no more than 10 to 15% of dietary Ca is absorbed…However, with adequate vitamin D adults absorb approximately 30% of dietary Ca by a $1,25(OH)_2D$ mediated process.”

Calcium Functions

• Structure in bones & teeth
  • 99% in bone and teeth

• Regulatory roles
  • Cofactor degradative enzymes
  • Cofactor for blood clotting
  • Initiation of neurotransmitter release by nerves
  • Muscle contraction
Current Research in Vitamin D

Possible Role for Vitamin D Beyond Bone: Immune Function, Cognition, Cancer, & Cardiovascular Disease Risk
Effects of the Active Vitamin D Metabolite

25(OH)D
Major Circulating Metabolite

Keratinocytes

Kidney

Macrophages

Colon
Prostate
Breast etc.

1,25(OH)₂D
Biologically Active

Calcium and Phosphorus Homeostasis
Bone Health

Growth and Regulation
Antiproliferation
Prodifferentiation
Apoptotic
Anti-angiogenic
Prostate, Colon, Breast Cancers etc.

Immunomodulatory Effects
Multiple Sclerosis
Type I Diabetes (via β-islet cell destruction)
Psoriasis
Rheumatoid Arthritis
Inflammatory Bowel Disease
Periodontal Disease

Cardiovascular Effects
Renin-Angiotensin Regulation
Decreased Risk for:
Hypertension
Type II Diabetes (via stimulation of pancreatic insulin production)
Heart Failure

Neuromuscular Effects
Muscle Mass
Muscle Strength
Better Balance

Steroid Receptors

Vitamin D Receptor (VDR)

Tissues Utilizing Vitamin D: Vitamin D Receptors (VDR) & 1 α-Hydroxylase

1,25-(OH)$_2$D$_3$ found in:

- Intestinal enterocytes
- Distal renal tubules
- Bone osteoblasts
- Parathyroid glands
- Pancreas islet cells
- Skin keratinocytes
- Mammary epithelium
- Ovarian tissue
- Stomach endocrine cells
- Certain brain cells
- All malignant cell lines & freshly explanted cancerous tissues

Effect:

- Calbindin D (Ca homeostasis)
- Osteocalcin (inhibits bone mineralization)
- Suppress PTH secretion
- Restore insulin secretion
- Keratinocyte differentiation
- Restore reproduction
Fracture Risk Factors & Vitamin D

• Osteoporosis – 1 in 2 women; 1 in 4 men after age 50
  – Hip, spine, wrist

• Neuromuscular function
  – Muscle weakness, aches, & falls

• Declining bone mass, muscle mass, muscle strength with aging

• By age 65yr, 1 in 3 person fall each year; by age 80, 1 in 2 falls each year

Hip & Non-vertebral Fractures

- Meta analysis
- Mean age 76 y
- 31,000, 91% women
- 10% ↓ risk of hip fracture
- 7% non-vertebral fractures
- Intake by quartiles: 800 IU/d ↓risk

Effects of the Active Vitamin D Metabolite *

Vitamin D Roles (beyond bone health)

• Neuromuscular effects
  – Muscle weakness, aches, & falls

• Immunomodulatory effects
  – Multiple sclerosis
  – Diabetes Type 1
  – Pneumonia

• Antiproliferation effects
  – Cancers such as prostate, colon, & breast

• Diabetes and cardiovascular disease

• Cognition

* Relevant with aging
Serum 25(OH)D and Muscle Atrophy in the Elderly

- Vitamin D receptors in skeletal-muscle cells
  - Activation by 1,25-dihydroxyvitamin D
- Several studies examined effect of supplemental vitamin D on:
  - Strength (+/-)
  - Balance
  - Falls
- Recent meta-analysis 17 trials
  - ↑ strength ≤ 25(OH)D nmol/L
Forest Plot Meta-analysis: Effect of Vitamin D on Falls

<table>
<thead>
<tr>
<th>Source</th>
<th>Odds Ratio (95% CI)</th>
<th>Favors Vitamin D</th>
<th>Favors Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfeifer et al,11 2000</td>
<td>0.47 (0.20-1.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bischoff et al,12 2003</td>
<td>0.68 (0.30-1.54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallagher et al,17 2001</td>
<td>0.53 (0.32-0.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dukas et al,18 2004</td>
<td>0.69 (0.41-1.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graafmans et al,19 1996</td>
<td>0.91 (0.59-1.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled (Uncorrected)</td>
<td>0.69 (0.53-0.88)</td>
<td></td>
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</tbody>
</table>

Vitamin D reduced the relative risk of falling by 22% compared to calcium or placebo.


Calicium – 1200 mg/d
Vit D – 800 -1000 IU/d
Vitamin D and Immunity

• Autoimmune diseases
  – ↑ risk of M.S. and diabetes type 1 with low vitamin D
    • Trials vitamin D supplementation largely null
  – Macrophages, dendritic cells, T & B lymphocytes can 25(OH)D → 1,25(OH)D
    – In vitro 1,25(OH)D significant effects on immune cells; in vivo?
• Plausible pathways vitamin D deficiency → Immune suppression with poorer resistance to infection
• May influence bacterial flora
  – Cathelicidins target gram-positive and gram-negative bacteria, viruses and fungi
  – Transcription of the gene for cathelicidin is regulated by Vitamin D receptor (VDR)
  – Mycobacterium T.B. + vitamin D not successful; benefits control viral/fungal infections lower respiratory

Lucas RM et al. F1000Prime Reports 2014, 6: 118
Vitamin D and Immunity

Figure 2. A proposed network of interactions between vitamin D and the microbiome that may sway the development of immune tolerance or tissue inflammation.
Vitamin D & Blood Pressure

• Studies demonstrate lower 25(OH)D associated higher BP and ↑ hypertension

• Plausible mechanism
  – Vit D improves endothelial function, reduce proinflammatory cytokins, reduce activity of the rennin-angiotension-aldosterone system, and ↓ PTH

• Intervention studies have been conflicting

• Last month meta-analysis concluded evidence did not support use of vitamin D as individual patient treatment for hypertension or population basis
  – Did not report ethnic benefit

*Beveridge LA, et al. JAMA on line March 12, 2015.*
Vitamin D and BP: Critique

• “High” versus “low” dosages (what level?)
  – Note that clinically relevant reduction of BP was unlikely based on the dosages of vitamin D in the analysis
  – Dosing could be daily, weekly, monthly

• Note that levels to reach 30 ng/mL optimum health may range from 1600 to 5000 IU/d
  – Most dosages studies in the review were at the lower or below this range

JAMA on line March 12, 2015.
TWU & Houston Methodist Study: African American Women - 2,000 IU D/d for 10 weeks

Measurement of 25(OH)D, endothelial function, body composition, nutrient intake
VDR in the Brain

• VDR expressed and 1-OHase widespread
  – hippocampus, prefrontal cortex, cingulate gyrus, basal forebrain, thalamus, substantia nigra, cerebellum

• VDR polymorphisms associated with cognitive decline, Alzheimer's Disease (AD), Parkinson’s disease and multiple sclerosis

• Meta-analysis \(^1\) suggested more than double risk of cognitive impairment with low 25(OH)D vs. normal

• In 2012 - Do-Health: 70 y; 2,152 receiving 2,000 IU vit D and 1 gm omega-3s, exercise

\(^1\) Etgen T et al., Dement Geriatr Cogn Disorder 2012
Limitations of Systematic Reviews and Meta-Analyses

• Cross-sectional studies cannot answer the question of vitamin D deficiency leads to cognitive decline
  – Or whether people with cognitive disorder have lower exposure to sunlight or low vitamin D intake
  – Or do they reflection seasonal fluctuations

• Different cut off points status

• Different diagnostic criteria for mild cognitive decline

_Schlog and Holick. Clinical Interventions in Aging. 2014_
The Vitamin D Omega-3 Trial (VITAL)

J.E. Manson et al. / Contemporary Clinical Trials 33 (2012) 159-171

20,000 Initially Healthy Men and Women
(Men ≥ 50 yrs; Women ≥ 55 yrs)

Vitamin D₃
(2000 IU/d); N=10,000

Placebo
N=10,000

EPA+DHA
(1 gm/d); N=5000

Placebo
N=5000

EPA+DHA
(1 gm/d); N=5000

Placebo
N=5000

Mean Treatment Period = 5.0 years
Blood collection in ~16,000, follow-up bloods in ~6000
Primary Outcomes: Cancer (total) and CVD (MI, stroke, CVD death)
Health Statements

2000 NIH Consensus Statement

“Adequate calcium and vitamin D are crucial to develop optimal peak bone mass and to preserve bone mass throughout life”


The 2010 and 2015 Dietary Guidelines for Americans

Identified low vitamin D intake as a public health concern

Public Health Efforts ...

- Choose foods that provide good sources of vitamin D
- Allow food manufactures to increase levels of vitamin D supplementation
- Increase number of foods fortified with Vitamin D
- Encourage supplements – especially for older adults
- Target health messaging to:
  - Males
  - Blacks and Hispanics