Vitamin D: The Sunshine Vitamin and Aging

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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.
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*
Natural Sources

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

• Low in vitamin D
  Skeletal muscle, meats

• Minimal vitamin D
  Plants
Vitamin D Fortification

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

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

<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>
<tr>
<td>Fortified juice + Ca</td>
<td>100 IU/8 fl oz</td>
</tr>
</tbody>
</table>

*1μg = 40 IU
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, margarines, cereal bars, bread, etc.
Requirements

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 μg = 40 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
Synthesis of Vitamins $D_2$ & $D_3$

**Plant**
- Ergosterol (provitamin D)
- UV light
  - Ergocalciferol (vitamin $D_2$)

**Animal**
- 7-dehydrocholesterol (7-DHC) (provitamin D)
  - UV light
  - Cholecalciferol (vitamin $D_3$)
Vitamins D$_2$ & D$_3$

**Vitamin D$_2$** (Ergocalciferol)
- Found in plants
- Produced by UV irradiation of ergosterol from yeast, fungi, mushrooms
- Available as pharmaceutical
- Used to treat rickets in the past
- Available in supplements
- Equally effective for bone health

**Vitamin D$_3$** (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 D$_2$ in maintaining serum 25(OH)D levels

Vit D
Humans obtain vitamin D from 2 sources:
- Dietary
- UVB light exposure to skin

Liver:
Vitamin D is hydroxylated to 25-hydroxyvitamin D [25(OH)D]

- Serum 25(OH)D used to measure vitamin D status

Kidney:
1(OH)ase hydroxylates 25(OH)D to active compound [1,25(OH)₂D₃]

- Helps maintain Ca levels in blood by increasing Ca absorption from intestines
Assessing Vitamin D Status 2010

Assessment | Serum 25(OH)D
---|---
Deficient | <12 ng/mL (<30 nmol/L)
At Risk of Inadequacy | 12-19.5 ng/mL (30 - 49 nmol/L)
Sufficient | 20 – 50 ng/mL (50 – 125 nmol/L)
Possibly Harmful | > 50 ng/mL (125 nmol/L)

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

NOTES: 25OHD is 25-hydroxyvitamin D. To convert nmol/L to ng/mL, divide by 2.5.
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey (NHANES); data for ages 1–5 years from NHANES 2003–2006.

CDC, NCHS Data Brief, No. 59, March 2011
Do You Know Your Number?

• Measurement of 25(OH)D over 4 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>
</tbody>
</table>
### FUNCTIONS

**Vitamin D – vitamin & prohormone?**

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Prohormone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition:</strong></td>
<td></td>
</tr>
<tr>
<td>• Organic compound needed in small amounts</td>
<td></td>
</tr>
<tr>
<td>• Not oxidized to provide energy or to form structures of the body</td>
<td></td>
</tr>
<tr>
<td><strong>Vitamin characteristics:</strong></td>
<td></td>
</tr>
<tr>
<td>• May be ingested from dietary sources (fish, liver oil)</td>
<td></td>
</tr>
<tr>
<td>• Can correct vitamin D deficiency</td>
<td></td>
</tr>
<tr>
<td><strong>Definition:</strong></td>
<td></td>
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<tr>
<td>Chemical precursor of a hormone which has no hormone activity of its own</td>
<td></td>
</tr>
<tr>
<td><strong>Prohormone characteristics:</strong></td>
<td></td>
</tr>
<tr>
<td>• Synthesized in the skin by photochemical process</td>
<td></td>
</tr>
<tr>
<td>• May be converted to active hormone 1,25(OH)D</td>
<td></td>
</tr>
</tbody>
</table>
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 $1,25 (OH)_2$ D mediated process.”

Holick, MF (2002). Vitamin D: The underappreciated D-lightful hormone that is important for skeletal cellular health. *Curr Opin Endo Diabetes, 9*: 87-98.
Calcium Functions

• Structure in bones & teeth

• Regulatory roles
  • Cofactor degradative enzymes
  • Cofactor for blood clotting
  • Initiation of neurotransmitter release by nerves
  • Muscle contraction
Possible Role for Vitamin D Beyond Bone: Immune Function, Cancer, & Cardiovascular Disease Risk
Vitamin D in the News

Higher Doses of Vitamin D Required to Protect Your Bones

Researchers pooled data on 31,022 participants in 11 controlled trials. Unlike previous studies and meta-analyses, this review focused not only on how much vitamin D, with or without calcium, people were actually taking.

Vitamin D a Possible Tool in Diabetes Prevention

Tufts researchers have identified a surprising factor in diabetes risk that might help keep people with pre-diabetes from developing the disease: vitamin D. In a new study published in Diabetes Care, high-risk patients with the highest blood levels of vitamin D could help ward off diabetes by improving the workings of the pancreas, which plays a key role in the disease. In a 2011 randomized trial published in the American Journal of Clinical Nutrition, Dr. Pittas and other Tufts researchers found that daily...
Tissues Utilizing Vitamin D

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
- Keratinocytes differentiation
- Restore reproduction
Effects of the Active Vitamin D Metabolite

25(OH)D
Major circulating metabolite

1-(OH)ase

1,25(OH)₂D
Biologically active

Calcium and phosphorus homeostasis
Bone Health

Neuromuscular effects
Muscle

Immunomodulatory effects
Multiple Sclerosis
Type 1 diabetes
Psoriasis

Cardiovascular effects
Hypertension
Type 2 diabetes

Growth and regulation
Antiproliferation:
Prostate, Colon,
Breast cancers

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

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

• Insulin sensitivity *

* Relevant with aging

Summary of Vitamin D Conversions: Cancer and CVD Prevention

7-Dehydrocholesterol in the skin → Vitamin D ← Diet and supplements

25 (OH)D (Liver)

Various tissues (kidney, colon, breast, prostate, vascular smooth muscle, other)

1α-hydroxylase

1,25 (OH)₂D (circulating or binding to vitamin D receptor)

↑ P21
↑ P27
↑ EGFR
↑ TGFβ
↓ IGF-1
↓ BCL2
↑ BAK
↑ TERT

↓ VEGF
↓ IL-8
↓ MMP-2
↓ MMP-9

↓ PG
↓ COX-2
↓ CRP
↓ IL-6
↑ IL-10
↓ TNFα

↓ Ca²⁺ cellular influx
↑ Matrix
↑ Gla protein

↓ Renin
↓ RAAS
↑ Insulin sensitivity

Inhibit cell proliferation
Induce apoptosis/differentiation
Inhibit angiogenesis/metastasis
Inhibit inflammation

Inhibit vascular smooth muscle proliferation and vascular calcification
Regulate blood pressure/volume homeostasis
Regulate glucose metabolism

Cancer Prevention
CVD Prevention

(↑ = increase, ↓ = decrease expression or levels)

Fig. 1. Mechanisms by which vitamin D may lower cancer and cardiovascular risk. BAK, BCL2-antagonist/killer; BCL2, B-cell chronic lymphocytic leukemia/lymphoma 2; COX-2, cyclooxygenase-2; CRP, C-reactive protein; EGFR, epidermal growth factor receptor; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; PG, prostaglandin; RAAS, renin-angiotensin-aldosterone system; TERT, telomerase reverse transcriptase; TGFβ, transforming growth factor-β; TNFα, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

Contemp Clin Trials 2012; 33: 159-171
Factors Reducing Vitamin D$_3$ Synthesis

- Aging
- Sunscreen
- Skin pigmentation
- Decreased UVB exposure

Vit D
Factors Reducing Vitamin D$_3$ Synthesis

**Aging**

• ↓ concentration of 7-dehydrocholesterol (provitamin D$_3$) in skin with aging

• ↓ capacity of human skin to produce vitamin D$_3$ with ↑ age

• 70 yr old produces 75% less 7-dehydrocholesterol than a younger adult
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 ➔

Vitamin D Health Disparities by Gender and Race/Ethnicity

Figure 4. Age- and season-adjusted prevalence at risk of deficiency and inadequacy among persons aged 1 year and over: United States, 2001–2006

<table>
<thead>
<tr>
<th>Group</th>
<th>At risk of inadequacy (30–49 nmol/L)</th>
<th>At risk of deficiency (&lt;30 nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>White</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Black</td>
<td>241</td>
<td>32</td>
</tr>
<tr>
<td>Mexican</td>
<td>233</td>
<td>33</td>
</tr>
<tr>
<td>Pregnant or lactating (females aged 12–44 years)</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>12</td>
</tr>
</tbody>
</table>

\[^1 p < 0.05 compared with males.\]
\[^2 p < 0.05 compared with non-Hispanic white persons.\]
\[^3 p < 0.05 compared with pregnant or lactating women.\]

SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey (NHANES); data for ages 1–5 years from NHANES 2003–2006.

CDC, NCHS Data
Brief, No. 59, March 2011
Factors Reducing Vitamin D$_3$ Synthesis

**Sunscreen**

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

**Vitamin D$_3$ Synthesis Reduction:**
- Solar radiation causes cutaneous production of vitamin D$_3$; therefore sunscreen diminishes/prevents D$_3$ production in skin
Factors Reducing Vitamin D₃ Synthesis

**Clothing**

Clothing absorbs UV radiation; therefore prevents cutaneous production of vitamin D₃

![Graph showing serum vitamin D₃ levels with different clothing options](Modified from Matsuzaki, Y, Venham, J, Osterberg, M, Heikis, R, Kuk, Z, Heick, M-F. [1999]. Clothing prevents ultraviolet-B radiation-dependent photosynthesis of vitamin D. J Clin Endocrinol Metab 84:1109–1113, Copyright The Endocrine Society.)
Factors Reducing Vitamin D₃ Synthesis

Environment

Latitude - Vitamin D₃ Synthesis Reduction:

Factors Reducing Vitamin D₃ 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
Factors Reducing Vitamin D₃ Synthesis

Environment
Seasons (con’t):

Fall-Winter: ↓25(OH)D
↑PTH

Fall-Winter:
Bone Mineral Density (BMD) ↓ Hip & Spine

Stipanuk, pg 872, 2006.
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
Seniors Vitamin 25(OH)D Levels by Ethnic Group

25(OH) D
Seniors August Boston

% Seniors Vitamin D Insufficient

Fracture Risk Factors & Vitamin D

- 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
- NHANES III – up to 30% of people age 60 yr & older who reside in lower latitudes have vitamin D insufficiency in the winter
  - Up to 26% residing in higher latitudes are insufficient

Average 10 Year Hip Fracture Risk

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

Vitamin D-Related Bone Diseases

Serum 25(OH)D and Muscle Atrophy in the Elderly

- Vitamin D receptors in skeletal-muscle cells
  - Activation by 1,25-dihydroxyvitamn D
- Several studied examined effect of supplemental vitamin D on:
  - Strength
  - Balance
  - Falls
- Meta-analysis 17 trials
  - ↑ strength ≤ 25(OH)D nmol/L
NHANES III
Serum 25(OH)D$_3$ & Walk Time

![Graph showing the relationship between serum 25(OH)D$_3$ levels and walking time.](image)


Vitamin D
NHANES III
Serum 25(OH)D & Time to Stand


≥ 60 yr
40 – 94 nmol/L
better lower musculoskeletal function

Vitamin D
Forest Plot Meta-analysis: Effect of Vitamin D on Falls

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
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
  - EPA+DHA (1 gm/d); N=5000
  - Placebo N=5000
- Placebo N=10,000
  - 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)
Total (Diet + Supplement) Vitamin D Intake by Age, 2007-2010

Vitamin D Consumed (ug/d)

Age in year

Diet alone
Supplement
% Not Meeting the Estimated Average Requirement (EAR) for Vitamin D by Age, 2007-2010

EAR = 400 IU/d
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 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
- Target health messaging to:
  - Males
  - Blacks and Hispanics

The D-Lightful Vitamin D
Thank You. Questions?