“THE SUNSHINE VITAMIN”

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Vitamin vs. Prohormone

- Technically not a vitamin since it isn’t obtained solely through diet

- Synthesized by the skin when exposed to UVB radiation from sunlight
  - Other examples:
    - Vitamin A generated in body by beta carotene
    - Niacin can also be synthesized
“The explanation was given by an English medical man, Dr. T. A. Palm, in 1890. He first pointed out that rickets is prevalent wherever there is little sunlight and unknown or comparatively rare wherever sunshine is abundant”.

- Giving 1-3 tsp/d Cod-liver oil to prevent rickets was practiced until 19th Century
- Vitamin D discovered in 1922
- Vitamin D ensures that serum phosphate and calcium levels are sufficient to facilitate the mineralization of bone.
Forms

- 2 forms – have identical metabolism and function - both biologically inert
  - Vitamin D2 – Ergocalciferol (used as a supplement – occurs as ergosterol in fungi and plants)
  - Vitamin D3 – Cholecalciferol (manufactured & synthesized in skin from 7-dehydrocholesterol)
D3 travels to the liver – hydroxylated to calcidiol, or 25-hydroxyvitamin D [25(OH)D]

Calcidiol then carried to kidneys and other tissues where it is enzymatically converted to its active form – calcitriol, or 1alpha,25(OH)2D – circulates as a hormone in the blood

Conversion primarily occurs in kidneys, but can also occur in muscle tissue; the cells of the colon, prostate, pancreas, lungs, skin, breasts, brain and the immune system

Calcitriol = Activated form Vitamin D  
Calcidiol = Inactive form
7-Dehydrocholesterol

Diet → Vitamin D₃ → Solar UVB radiation

Vascular cells
- Increases smooth muscle cell proliferation
- Reduces inflammation

Parathyroid gland
- Decreases PTH synthesis and release

Heart
- Decreases LVH

Bone
- Increases bone mineralization
- Increases osteoclast differentiation

Intestine
- Increases absorption of calcium and phosphate

Pancreas
- Increases insulin secretion

Breast, colon, prostate cells
- Inhibits clonal proliferation

Macrophages Monocytes
- Increases microbicidal activity
- Induces differentiation in immune cells

Red Blood Cells
- Improves hemopoiesis

1,25(OH)₂D₃

25(OH)D₃

1-OHase
- Decreases renin expression

1-OHase
- 1-OHase
Vitamin D essential to Ca and P homeostasis and therefore, bone maintenance

- Promotes absorption of Ca & P
- Regulates how much Ca remains in blood
  - Calcitriol increases Ca and P absorption from the intestine and prevents the kidneys from excreting Ca and P
  - Calcitriol stimulates pre-osteoclasts to mature to osteoclasts, which break down bone and release Ca and P into the blood
FAQ

How does vitamin D help lower the risk of fracture?

1) Promotes Ca absorption & therefore bone mass and strength
2) Affects muscle performance, balance & risk of falling by promoting type 2 muscle fibers (rapid responder muscle fibers)
Vitamin D has many other roles in the body

- Receptors found in membranes of many cells - brain, gonads, skin, vascular smooth muscle, immune
- May directly or indirectly influence as much as 5% of genes in genome
  - Between 200 & 600 genes are primary targets of Vitamin D as they are directly involved w/Vit D receptors
Vitamin D status - Serum 25(OH)D
Can be reported as nmol/L or ng/ml

- Calcidiol is used as a primary marker of Vitamin D status
  - Reflects Vitamin D produced cutaneously and from food and supplements
  - More stable than calcitriol, it will remain in blood ~2 wks
    - Circulating half life of ~15 days
- Calcitriol isn’t a useful marker because it lasts only a few hours & closely regulated by parathyroid hormone, Ca and Phosphate
  - Circulating half life of ~15 hours
### Institute of Medicine (IOM)

**Blood Level (nmol/L)** | **Blood Level (ng/ml)** | **Health Status**
--- | --- | ---
< 20 nmol/L | < 8 ng/ml | -Deficiency
< 30 nmol/L | < 12 ng/ml | -Evidence of Osteomalacia
- Threshold for preventing hip & non-vertebral fx
< 50 nmol/L | < 20 ng/ml | -Insufficiency
80 nmol/L | 32 ng/ml | -Minimum level for general population to ensure serum levels don’t fall below 50 nmol/L (20ng/ml) in winter mos.
- Vitamin D no longer the limiting factor for Ca absorption in intestine
90-100 nmol/L | 36-40 ng/ml | -Lower extremity fx, dental health, BP, risk of fall, fx, CVD, colorectal cancer are reduced
> 125 nmol/L | > 50 ng/ml | -Increased risk of vitamin D excess
Screening

- USPSTF and Endocrine Society recommend screening only in individuals at risk for deficiency
  - “no evidence that it’s beneficial to screen in general, healthy adults”

- Endocrine Society guidelines: >30ng/ml
- National Academy of Medicine: >20ng/ml
  - Cut points have not been developed by a scientific consensus process
Factors Determining Vitamin D Synthesis

- Age
- Skin pigmentation
- UVB Intensity
  - Season
  - Time of day
  - Cloud cover/pollution
  - Latitude at which we live
  - Angle of sun in the sky
- Sunscreen use

- Rx for Vitamin D production: 10am-3pm, 10% of body exposed, long enough to absorb sun, but not be burned
  - Reliable for most regions in US, but only during summer months
  - In other seasons, the body makes little if any at latitudes above 37 degrees north in US
Hypovitaminosis D <30 nmol/L (<12 ng/mL)

- Insufficient consumption
  - Vitamin D deficient diets associated with milk allergy, lactose intolerance, ovo-vegetarianism, and veganism
- Insufficient absorption in digestive tract
- Exposure to sunlight is limited
- Kidneys cannot convert Vitamin D to active form
- Older population: greater loss of bone mass (osteoporosis) and risk of softening bones (osteomalacia) increases
- Children: may develop rickets or defective bone growth
  - Fortifying milk with Vitamin D started in 1930’s and has virtually wiped out rickets in the US
Hypervitaminosis D >150nmol/L (>60 ng/ml)

- The body limits its own vitamin D production
  - Excessive sun exposure won’t result in Vitamin D excess
- Vitamin D stored in liver and adipocytes
- Can be toxic, possibly leading problems w/heart rhythm, kidney stones or damage
  - Symptoms: Poor appetite, weakness, constipation, nausea, wt loss
Fat soluble vitamin naturally present in very few foods, added to others.

<table>
<thead>
<tr>
<th>Food</th>
<th>Vitamin D (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon, 3.5 oz.</td>
<td>400</td>
</tr>
<tr>
<td>Mackerel, 3.5 oz.</td>
<td>345</td>
</tr>
<tr>
<td>Tuna, canned, 3.5 oz.</td>
<td>200</td>
</tr>
<tr>
<td>Orange juice, fortified, 8 oz.</td>
<td>100</td>
</tr>
<tr>
<td>Milk, fortified, 8 oz.</td>
<td>100</td>
</tr>
<tr>
<td>Breakfast cereals, fortified, 1 serving</td>
<td>40-100</td>
</tr>
<tr>
<td>Sardines, 2 whole</td>
<td>45</td>
</tr>
<tr>
<td>Egg, Whole (yolk)</td>
<td>40</td>
</tr>
</tbody>
</table>
Recommended Dietary Allowances (RDA)*

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>Pregnancy</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12 mos.</td>
<td>400 IU</td>
<td>400 IU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-13 yrs.</td>
<td>600 IU</td>
<td>600 IU</td>
<td></td>
<td></td>
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<tr>
<td>14-18 yrs.</td>
<td>600 IU</td>
<td>600 IU</td>
<td>600 IU</td>
<td>600 IU</td>
</tr>
<tr>
<td>19-50 yrs.</td>
<td>600 IU</td>
<td>600 IU</td>
<td>600 IU</td>
<td>600 IU</td>
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<tr>
<td>51-70 yrs.</td>
<td>600 IU</td>
<td>600 IU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 70 yrs.</td>
<td>800 IU</td>
<td>800 IU</td>
<td></td>
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</tbody>
</table>

*For bone health only – may be different for other disease states?
Individualize intake recommendations using RDA as guideline

Consider lifestyle, environmental factors, malabsorption issues, medication use and other health conditions that can increase or decrease skin synthesis, metabolism and usability of Vitamin D

IOM

- An intake of 600 IU’s per day will result in an average serum 25 (OH)D of 63 nmol/L (25ng/ml) for adults and children of all ages in northern latitudes during the winter (sun exposure lowest).

Endocrine Society

- Individuals may need as much as 1,500 IU’s per day to ensure levels higher than 30nmol/L (12ng/ml)
- People of normal weight need 100 IU/d to raise serum 25 (OH)D by 1 ng/ml
Consider

- Only 66% of adults can achieve a serum 25 (OH) D = 50nmol/L (20ng/ml) when following the IOM’s Estimated Average Requirement for Vitamin D.

- When healthy adults consumed 1,800-4,000 IU/d for at least 42 days, they maintained a serum 25 (OH)D = 75-100 nmol/L (30-44 ng/ml).

Interactions with Medications

- Corticosteroids such as prednisone
  - Reduce Ca absorption and impair Vitamin D metabolism
- Orlistat and cholestyramine
  - Reduce absorption of Vitamin D and other fat soluble vitamins
- Phenobarbital and phenytoin
  - Increase hepatic metabolism of Vitamin D to inactive compounds
  - Reduce Ca absorption
Available evidence shows Vitamin D linked to bone health

- Studies currently exploring the links to Vitamin D’s potential role in preventing:
  - Cancer
  - CVD
  - Autoimmune Conditions
  - Diabetes
  - Immunity
  - Muscular function

- Evidence currently insufficient to offer guidance
Began in 2010
25,874 healthy older men (>50 y.o.) and women (>55 y.o.)
Daily 2000 IU/d Vitamin D or Omega-3 fa {1 g Fish Oil (Omacor)} for an average of 5 years
To see if either can lower risk of: cancer, heart disease and stroke
Also: HTN, DM, memory loss, depression, a-fib, bone health, fx, falls, knee pain, asthma, RA, thyroid disease, lupus
Arthritis and Vitamin D

- Australian researchers
  - 400 subjects with knee arthritis and low levels of serum Vitamin D (5-24ng/ml)
  - Age 50-79
  - Given either high dose of Vitamin D (50,000 IU 1x/mo) or placebo

- After 2 years: Vitamin D takers had no less pain and lost no less knee cartilage than placebo takers.

- Vitamin D takers did rate their knee function higher than placebo takers
  - JAMA 315: 1005, 2016
A meta analysis of randomized controlled trials found that taking 700-1000 IU Vitamin D per day lowered the risk of falls by 19%, but taking 200-600 IU per day did not offer any such protection.

People with low Vitamin D levels in their blood have an increased risk of DMT2.

Norwegian researchers:
- 500 subjects with prediabetes (most did not have low serum Vitamin D levels at outset)
- Received either a high dose of Vitamin D (20,000 IU/wk) or a placebo

After 5 yrs, ~40% of participants in both groups were diagnosed with DM.

May protect the pancreas from DM in people who are high risk because glucose levels are above normal

- 92 adults w/pre-DM
- 2000 IU/d or 400mg Ca/d, both or a placebo
- Measured how well beta cells in pancreas secreted insulin

After 4 mos, beta-cell function improved by 26% in those who received Vitamin D. In those who received no vitamin D, beta-cell function worsened by 14%

- Ca had no impact on beta-cell function

Am J Clin Nutr doi:10.3945/ajcn.111.011684
Researchers in New Zealand
- 5100 subjects
- Age 50-84
- Given initial dose (200,000 IU) followed by monthly dose (100,000 IU)

After 3 yrs, the vitamin D takers had no lower risk of a heart attack, stroke, or other cardiovascular event.

It didn’t matter if people entered the study w/low serum Vitamin D or not (<20ng/ml)

JAMA Cardiol. 2017. 10.1001
Scientists reviewed nine research trials testing vitamin D against placebo – the trials lasted anywhere from 4-12 mos.

- ~1100 children and adults with mild to moderate asthma & continued to take asthma medication

- Vitamin D supplements reduced the risk of severe asthma attacks requiring hospital admission or visit from 6% to 3%; however, there was no impact on lung function or day-to-day symptoms

  - Lead Author, Adrian Martineau of Queen Mary University of London: “It is not yet clear whether vitamin D supplements can reduce risk of severe asthma attacks in all patients, or whether this effect is just seen in those who have low vitamin D levels to start with. More trials are needed to find out if vitamin D can help people with severe asthma.”

  - Cochrane Database Syst. Rev. 9:CD011511, 2016
Cancer & Vitamin D

- 2300 postmenopausal women
  - 2000 IU/d + 1500mg Ca or placebo

- After 4 yrs., supplement takers did not have significantly lower risk of cancer than placebo takers

- JAMA 317: 1217, 1234, 2017