Vitamin D

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Vitamin D3

• Steroid hormone
• Derivative of cholesterol
• Acquired by sunlight exposure or diet
• Dietary Sources: Supplements, fortified foods, fatty fish, cod liver oil

Classical Vitamin D3 Pathway

Cholesterol (skin) Diet

Vitamin D3

Liver

25(OH)D3

Target Tissues

1,25(OH)2D3

DBP

CYP27B1

Kidney

25(OH)D3

DBP

1,25(OH)2D3

DBP

25(OH)2D3

DBP
Proposed Physiological Roles of Vitamin D₃

- Calcium and phosphorus homeostasis (proven)
- Insulin secretion and sensitivity
- Immunity
- Cancer prevention: Regulation of cell growth, differentiation, and apoptosis
- Cardiovascular health

Updated View of Vitamin D₃ Pathway
Endocytosis of 25(OH)D$_3$-DBP in Kidney-not proven elsewhere

Mechanism of Vitamin D$_3$ Actions in Target Cells

Vitamin D$_3$ metabolism and actions

Reasoning Behind Current Vitamin D Recommendations

• **Intake**
  – enough to ensure adequate serum 1,25(OH)2D3 levels for bone health
  • Based on no UVB exposure

• **Upper limits** are conservative estimates
  – Cautious of soft tissue calcification

• Lack of clinical trials that demonstrate vitamin D prevents chronic disease

<table>
<thead>
<tr>
<th>Life Stage Group</th>
<th>1997 IOM Adequate Intake (AI)</th>
<th>1997 IOM Tolerable Upper Intake Level (UL)</th>
<th>2011 IOM Recommended Dietary Allowance (RDA)</th>
<th>2011 IOM Tolerable Upper Intake Level (UL)</th>
<th>2011 Endocrine Society Daily Requirement for patients at risk for vitamin D deficiency</th>
<th>2011 Endocrine Society Tolerable Upper Intake Level for patients at risk for vitamin D deficiency</th>
<th>Adequate Intake Values for Australia and New Zealand (AI)</th>
<th>Upper Level of Intake Values for Australia and New Zealand (UL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 through 6 months</td>
<td>200</td>
<td>1,000</td>
<td>400</td>
<td>(AI)</td>
<td>1,000</td>
<td>400–1,000</td>
<td>2,000</td>
<td>200</td>
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<tr>
<td>7 through 12 months</td>
<td>200</td>
<td>1,000</td>
<td>400</td>
<td>(AI)</td>
<td>1,500</td>
<td>400–1,000</td>
<td>2,000</td>
<td>200</td>
</tr>
<tr>
<td>1 through 3 years</td>
<td>200</td>
<td>2,000</td>
<td>600</td>
<td>2,500</td>
<td>600–1,000</td>
<td>4,000</td>
<td>200</td>
<td>3,200</td>
</tr>
<tr>
<td>4 through 8 years</td>
<td>200</td>
<td>2,000</td>
<td>600</td>
<td>3,000</td>
<td>600–1,000</td>
<td>4,000</td>
<td>200</td>
<td>3,200</td>
</tr>
<tr>
<td>9 through 18 years</td>
<td>200</td>
<td>2,000</td>
<td>600</td>
<td>4,000</td>
<td>600–1,000</td>
<td>4,000</td>
<td>200</td>
<td>3,200</td>
</tr>
<tr>
<td>19 through 50 years</td>
<td>200</td>
<td>2,000</td>
<td>600</td>
<td>4,000</td>
<td>1,500–2,000</td>
<td>10,000</td>
<td>200</td>
<td>3,200</td>
</tr>
<tr>
<td>51 through 70 years</td>
<td>400</td>
<td>2,000</td>
<td>600</td>
<td>4,000</td>
<td>1,500–2,000</td>
<td>10,000</td>
<td>400</td>
<td>3,200</td>
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<tr>
<td>&gt; 70 years</td>
<td>600</td>
<td>2,000</td>
<td>800</td>
<td>4,000</td>
<td>1,500–2,000</td>
<td>10,000</td>
<td>600</td>
<td>3,200</td>
</tr>
<tr>
<td>Pregnancy ≤ 18 years</td>
<td>200</td>
<td>2,000</td>
<td>600</td>
<td>4,000</td>
<td>600–1,000</td>
<td>4,000</td>
<td>200</td>
<td>3,200</td>
</tr>
<tr>
<td>19 through 50 years</td>
<td>200</td>
<td>2,000</td>
<td>600</td>
<td>4,000</td>
<td>1,500–2,000</td>
<td>10,000</td>
<td>200</td>
<td>3,200</td>
</tr>
</tbody>
</table>

Factors influencing vitamin D3 synthesis and bioavailability

• **20 minutes in the sun:** equivalent to taking 10,000-25,000 IU (25-60 vitamin D3 supplement pills, 400 IU).

• Factors influencing vitamin D3 synthesis and bioavailability: Age, melanin pigmentation, latitude, clothing, obesity.
Serum levels of vitamin D₃ metabolites

- **1,25(OH)₂D₃**
  - Serum 1,25(OH)₂D₃ synthesized only in kidney
  - Very tightly regulated
  - Only drops when individuals are severely vitamin D deficient!!!

- **25(OH)D₃**
  - Not regulated
  - Reflects vitamin D intake and sun exposure.

Recommendations for serum 25D concentrations

<table>
<thead>
<tr>
<th>Definition of vitamin D status based on 25(OH)D concentrations</th>
<th>Institute of Medicine</th>
<th>Endocrine Society</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficient</td>
<td>&lt;30 nmol/l</td>
<td>&lt;12 ng/ml</td>
</tr>
<tr>
<td>Insufficient</td>
<td>30–50 nmol/l</td>
<td>12–20 ng/ml</td>
</tr>
<tr>
<td>Sufficient</td>
<td>&gt;50 nmol/l</td>
<td>&gt;20 ng/ml</td>
</tr>
<tr>
<td>Potential adverse effects</td>
<td>&gt;125 nmol/l</td>
<td>&gt;50 ng/ml</td>
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</tbody>
</table>


Vitamin D₃ Dose Response

Each 100 IU of vitamin D intake increases serum 25(OH)D by 1 ng/ml

When should vitamin D recommendations be adjusted?

- Renal insufficiency
  - Cannot reabsorb 25D₃
  - Increased urinary loss of 25D₃ and 1,25D₃
- Uncontrolled diabetics-poor renal function
- Children
- Northern Latitudes
- Lactating women

Obesity and Serum 25(OH)D₃

Endocytosis of 25(OH)D₃-DBP in Kidney During Renal Failure
Vitamin D Status in Diabetes Mellitus-induced Chronic Renal Failure


<table>
<thead>
<tr>
<th>Nutrient</th>
<th>DM CRF</th>
<th>DM CRF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>38 ± 12</td>
<td>38 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>84±10</td>
<td>83±10</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>24±3</td>
<td>25±3</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>132±18</td>
<td>132±18</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80±10</td>
<td>80±10</td>
<td>NS</td>
</tr>
<tr>
<td>Intemat C (mg/dL)</td>
<td>213±19</td>
<td>214±18</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.2±0.3</td>
<td>1.1±0.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>42±10</td>
<td>43±10</td>
<td>NS</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>5.7±0.3</td>
<td>5.7±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>25(OH)D (ng/mL)</td>
<td>22.2±8.6</td>
<td>11.4±5.8</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Total circulating 25(OH)D concentration (nmol/L) by treatment (400 IU vs 6400 IU) groups of breastfeeding mothers: A, through V4; B, through V7; and of breastfeeding infants: C, through V4; D, through V7.

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Vitamin D and maternal and child health: Overview and implications for dietary requirements

Mothers

Infants
Extrarenal activation of 25(OH)D$_3$?

- Extra renal tissues express CYP27B1 and can make 1,25(OH)$_2$D$_3$
  - Big question: Is it accessible???
  - The more serum 25(OH)D$_3$, the more tissue 1,25(OH)$_2$D$_3$?

Extra-renal Tissues that express CYP27B1 (1α-hydroxylase)

- Mammary
- Colon
- T cells
- Prostate
- Skin
- Ovary
- Placenta, adrenal medulla, brain, and pancreas

Vitamin D$_3$ and Breast Cancer

**Vitamin D₃ and Colon Cancer**


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**Sunlight Exposure and Prostate Cancer Mortality**

Hanchette, C.L. and Schwartz, G.G., 1992 Cancer, 70: 2861-2869

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**Vitamin D₃ deficiency and autoimmunity**

Vitamin D₃ and Multiple Sclerosis


Issue with studies such as these...

- Not controlled clinical trials.
- Only associations have been made.
- Cause vs. effect?
- Variation in vitamin D status over time.
- Several trials completed or underway
  - http://www.vitamindandms.org/clinicaltrials/
  - http://jama.jamanetwork.com/article.aspx?articleid=2165869#jvp150014t1

What needs to happen to change recommendations?

- More mechanistic evidence for why vitamin D may prevent or treat illness.
- Long-term (length is debatable), well-controlled vitamin D clinical trials.
- Studies that demonstrate early life exposure to vitamin D is beneficial to long-term outcomes.
  - No small feat.
  - Feasibility is quite low.
**Table Title:** Risk vs. Reward???

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Insufficiency</th>
<th>Optimal</th>
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</thead>
<tbody>
<tr>
<td>SHORT LATENCY DISEASES:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rickets</td>
<td>• Osteomalacia</td>
<td></td>
</tr>
<tr>
<td>LONG LATENCY DISEASES:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Loss of Caloricic Effects</td>
<td>• Osteoporosis</td>
<td>• Muscle pain and fatigue</td>
</tr>
<tr>
<td>• Hypothetical Cardiovascular Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Loss of Antiproinflammatory Effects</td>
<td>• Cancer (breast, colon, prostate)</td>
<td></td>
</tr>
<tr>
<td>• Loss of Immunomodulatory Effects</td>
<td>• Diabetes</td>
<td>• Multiple Sclerosis *</td>
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<tr>
<td></td>
<td></td>
<td>• Lupus</td>
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</tbody>
</table>


**Continuum of Vitamin D3 Status in Relation to Disease**

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Insufficiency</th>
<th>Optimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Serum 25(OH)D nmol/L</td>
<td></td>
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</table>

Time Course 25(OH)D$_3$ Response


Serum Calcium Levels


How Much is Safe??

Can Dietary Vitamin D Suffice?

- Vitamin D3 in Food
  - Cod liver oil (1 tbsp): ~1400 IU vit. D
  - Catfish (3 oz): ~400 IU vit. D
  - Salmon (3 oz): ~400 IU vit. D
  - Fortified Milk (8 oz): ~100 IU vit. D
  - Fortified Cereal (8 oz): ~75 IU vit. D.


Achieving optimal serum 25(OH)D₃ through the Diet.

- Not practical without supplemental vitamin D or sun exposure.
- Not practical in elderly or individuals with darker skin pigmentation.

Putting Dietary Vitamin D into Perspective

- Achieving adequate 25(OH)D₃ through dietary means (2000 IU vitamin D/day)
  - 2 tablespoons cod liver oil/day-vit A toxicity?
  - 5 servings salmon or catfish/day
  - 20 servings milk/day
  - 25 bowls of fortified cereal/day