Why All The Hype About Vitamin D?
Micah Olson, MD
8-26-2010

“Vitamin D, miracle drug: Is it science, or just talk?”
-New York Times, February 1, 2010

Outline
1. Vitamin D physiology.
2. What is a normal vitamin D level?
3. The relationship between vitamin D and nonskeletal disorders.
4. AAP’s recommendations regarding vitamin D intake.

History
Industrial Revolution: late 1700’s/early 1800’s
Vitamin D Physiology

- The term vitamin D refers collectively to two prehormones:
  - Vitamin D₂ or ergocalciferol (synthesized by yeast)
  - Vitamin D₃ or cholecalciferol (synthesized by mammals)
- Vitamin D₃ is formed in the skin when solar ultraviolet B (UV-B) rays converts 7-dehydrocholesterol into previtamin D₃.

Vitamin D Receptor

- 1,25-OHD binds to the nuclear vitamin D receptor (VDR).

Classic Actions of Vitamin D

- Maintains calcium and phosphate concentrations in blood at levels sufficient to sustain bone mineralization.
- Stimulates calcium and phosphate absorption in the intestines.
- Stimulates calcium and phosphate reabsorption in the kidneys.
- Promotes bone formation by osteoblast and osteoclast differentiation.

VDRs are found in many tissues:

- Immune system
- Muscle
- Brain
- Liver
- Breast
- Endothelium
- Skin
- Pancreatic islet cells
- Parathyroid gland
- Adrenal gland
- Thyroid
- Ovary
- Testis

There are three sources of Vitamin D:

- Sunlight
- Supplements
- Diet
Dose-response

• Serum 25(OH)D typically increases by 6-8 ng/mL for every 1000 IU of daily vitamin D ingested.

Sources of Vitamin D: Diet

• Fish liver oils, such as cod liver oil, 15 mL provides 1,360 IU
• Salmon cooked, 100 g (3.5 oz) provides 360 IU
• Tuna canned in oil, 85 g (3 oz), 200 IU
• A whole egg provides 20 IU
• Beef liver, cooked, 100 g (3.5 oz), provides 15 IU

Sources of Vitamin D: Supplements

• Milk is typically fortified with 100 IU per 8 oz.
• Some cereals are fortified.
• Most daily multivitamins provide 400 IU.

Sources of Vitamin D: Sun

• Exposure of the back of a white adult to mid-day sun in mid-July for 10-12 minutes generates about 10,000 to 20,000 IU of vitamin D₃.
• Darker skin pigments require 5-10 times as much exposure for comparable effects.

Synthesis of Vitamin D₃ from exposure to sunlight (UVB) is influenced by:

• Time of day (10 am – 3 pm)
• Latitude
• Season of the year
• Air pollution and cloud cover
• Sun screen
• Skin pigmentation
• Age
Definition of Vitamin D Deficiency

• There is no consensus on the definition of vitamin D deficiency.
• Traditional definition of deficiency in adults: 25(OH)D < 20 ng/mL.

• Parathyroid hormone levels begin to increase when 25(OH)D falls below 30 ng/mL.
• Intestinal calcium transport is optimized when 25(OH)D levels are > 30 ng/mL.
• Multiple health outcomes (bone mineral density, fracture risk, etc) are optimized when 25(OH)D levels are > 30 ng/mL.

Vitamin D Sufficient: > 30 ng/mL
Vitamin D Insufficient: 20-30 ng/mL
Vitamin D Deficient: < 20 ng/mL

Prevalence of Vitamin D Deficiency

• NHANES III (1988-1994): 2639 subjects aged 12 to 19 years old
• Prevalence with 25(OH)D level < 20 ng/mL:
  ◦ Overall: 14%
  ◦ Non-Hispanic white: 5%
  ◦ Mexican-American: 18%
  ◦ Non-Hispanic black: 50%

• Cross-sectional study of 637 adults in southern Arizona:
  ◦ Mean serum 25(OH)D: 26.1 ng/mL
  ◦ 25% < 20 ng/mL
  ◦ 22% > 30 ng/mL

Jacobs E et al. J Nutr 2008
Risk Factors For Vitamin D Deficiency

- Increased skin pigmentation
- Northern latitude
- Decreased sun exposure
- Chronic diseases characterized by fat malabsorption (cystic fibrosis, Crohn’s disease)
- Antiseizure medications
- Elderly
- Obesity

Vitamin D Deficiency

- Among 498 children in Dallas, TX:
  - Mean serum 25(OH)D
    - Obese: 19.6 ng/mL
    - Non-overweight 27.0 ng/mL
  - 92% of obese children had a 25(OH)D level < 30 ng/mL, 50% had a level < 20 ng/mL.
  - The odds ratio for vitamin D deficiency (< 20 ng/mL) in obese children compared with non-overweight children was 4.0 (95% CI: 2.3-6.9).

Olson M et al.

Vitamin D and Tuberculosis

- “The pure fresh oil from the liver of the cod is more beneficial in the treatment of pulmonary consumption than any agent, medicinal, dietetic, or regiminal, that has yet been employed”
  - Williams, 1849, after treating 234 TB patients with cod liver oil.
- 1903 Nobel Prize in Medicine awarded to Niels Finsen
  - Successfully treated patients with lupus vulgaris (cutaneous TB) with light from an electric lamp.

Vitamin D and Type 1 Diabetes

- Birth cohort study: All pregnant women (n = 12,055) in two cities in northern Finland who gave birth in 1966.
- 10,821 children were followed up at age 1 year, at which time data was obtained.
- Frequency of vitamin D supplementation in the first year of life was recorded as regular, irregular, or none.
- Daily dose was calculated to be < 2000 IU daily, at 2000 IU daily, or > 2000 IU daily.
- A follow-up survey was done in 1997-98 (31 years).

Hypponen E et al. Lancet 2001

Vitamin D and Autoimmune Disorders

- Observational studies have shown an association between decreased sun exposure and decreased vitamin D levels with various autoimmune disorders, including multiple sclerosis, rheumatoid arthritis, and type 1 diabetes.
- 1,25-OHD promotes tolerance and anergy.
**Vitamin D and Type 1 Diabetes**

<table>
<thead>
<tr>
<th>Use of Vitamin D Supplement</th>
<th>Adjusted Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Irregular</td>
<td>0.16 (0.04 – 0.74)</td>
</tr>
<tr>
<td>Regular</td>
<td>0.12 (0.03 – 0.51)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose of Vitamin D</th>
<th>Adjusted Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Recommended (2000 IU)</td>
<td>0.22 (0.05 – 0.89)</td>
</tr>
<tr>
<td>High</td>
<td>0.14 (0.02 – 1.01)</td>
</tr>
</tbody>
</table>

**Vitamin D and Cancer**

- 1,25-OHD modulates hyperproliferative conditions by regulating cellular proliferation, differentiation, apoptosis, and angiogenesis.
- Observational studies show that levels of 25(OH)D below 20 ng/mL are associated with increased risk of colon, prostate, and breast cancer, as well as higher mortality from the cancers.

**Vitamin D and Cardiovascular Disease**

- 18,225 men aged 40 to 75 years
- Men deficient in serum 25(OH)D were at increased risk for myocardial infarction compared with men with sufficient serum 25(OH)D
- Adjusted Relative risk: 2.42
  

- 2001-2004 NHANES
- 3577 subjects aged 12-19
- Those in the lowest vitamin D quartile had a higher risk of high blood pressure compared to the highest vitamin D quartile.
- Adjusted odds ratio: 2.36
  
  Reis JP et al. Pediatrics 2009

**Vitamin D and Type 2 Diabetes**

- 2001-2004 NHANES
- 3577 subjects aged 12-19
- Those in the lowest vitamin D quartile had a higher risk of fasting glucose > 100 compared to the highest vitamin D quartile.
- Adjusted odds ratio: 2.54 (1.01-6.40)
  
  Reis JP et al. Pediatrics 2009

**Vitamin D and Pregnancy**

- 500 women at least 12 weeks pregnant were randomized to vitamin D 200 IU, 2000 IU, or 4000 IU.
- The women who took 4,000 IU were least likely to go into labor early, give birth prematurely, or develop infections.
AAP Recommendations

• In 2003, AAP recommended a daily intake of 200 IU/day of vitamin D for all infants, children, and adolescents.

• In 2008, AAP increased the recommended daily intake of vitamin D to 400 IU/day for all infants, children, and adolescents.
  Wagner et al. Pediatrics 2009

• All formula-fed infants, as well as older children and adolescents who are ingesting < 1 L/day of vitamin D–fortified formula or milk, should receive a vitamin D supplement of 400 IU/day.

AAP Recommendations

• Vitamin D content in breast milk ranges from 15-50 IU/L in vitamin D sufficient mothers.
• Infant formulas typically have at least 400 IU/L of vitamin D$_3$.
• “Infants <6 months should be kept out of direct sunlight.”
  — AAP Policy Statement 1999

AAP Recommendations

• A recent study found:
  — 16% of predominantly breastfed infants were given vitamin D supplementation.
  — 36% of pediatricians recommend vitamin D supplementation for all breastfed infants.
• In this study, the most common parental reason for not giving vitamin D supplementation was that vitamins are unnecessary because breast milk has all needed nutrition.
  Taylor IA et al. Pediatrics 2010

Conclusions

• Vitamin D deficiency is common, even in Arizona.
• Vitamin D may have important effects even beyond skeletal health, but more interventional studies are needed.
• The AAP recommends vitamin D 400 IU/day for all infants, children, and adolescents.
Dr. Micah Olson

Phoenix Children’s Hospital
Endocrinology Dept
P: (602) 546-0611
www.phoenixchildrens.com

The Emily Center
www.theemilycenter.com