Vitamin D Deficiency: What’s the Big Deal?

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Faculty Disclosure
Dr. Akiyode has no actual or potential conflicts of interest related to this program.

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Objectives

- Describe the increasing prevalence of vitamin D deficiency in the US population
- Describe the association of vitamin D deficiency with non-skeletal medical conditions
- Review the treatment options for vitamin D deficiency

What is the big deal?

Greater than ~50% of the global population at risk?

In US, 60% of nursing home residents; 57% of hospitalized patients are deficient

In a study of healthy young adults in Boston, ~2/3 had insufficient vitamin D level at winter end.


Vitamin D Deficiency: What’s the Big Deal?

What is vitamin D?

- Fat soluble vitamin
- Two main forms:
  - Ergocalciferol (vitamin D2): made by plants
  - Cholecalciferol (vitamin D3): made by humans via sunlight

Sources of Vitamin D

- Sun
  - 10 minutes exposure to UVB rays from sunlight
- Foods
  - Fish, eggs, fortified milk, cod liver oil
- Dietary supplement

Role of Vitamin D

- Maintain calcium and phosphorus levels in blood
- Promotes absorption of calcium, thus contribute to bone health
- Decreases parathyroid hormone
- Others: osteoporosis, diabetes, hypertension, cancer, autoimmune diseases

Activation of Vitamin D

Vitamin D

25-hydroxyvitamin D[25(OH)D] **

1,25-dihydroxyvitamin D [1,25(OH)2D]

**serum level marker
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**IOM Report: Vitamin D Dietary Reference Intakes**

<table>
<thead>
<tr>
<th>Age</th>
<th>Intake (international units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 12 months</td>
<td>400</td>
</tr>
<tr>
<td>Children 1-13 years</td>
<td>600</td>
</tr>
<tr>
<td>Teens 14-18 years</td>
<td>600</td>
</tr>
<tr>
<td>Adults 19-70 years</td>
<td>600</td>
</tr>
<tr>
<td>Adults 71 and older</td>
<td>800</td>
</tr>
<tr>
<td>Pregnant/breastfeeding</td>
<td>600</td>
</tr>
</tbody>
</table>

* upper safety limit: 4000 IU/day for ≥9 yo

Source: Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC, November 2010.

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**Vitamin D recommendation in general population:**

**National Osteoporosis Foundation (NOF)**

<table>
<thead>
<tr>
<th>Age</th>
<th>Intake (international units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults 19-49 years</td>
<td>400-800</td>
</tr>
<tr>
<td>Adults 50 and older</td>
<td>800-1000</td>
</tr>
</tbody>
</table>


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**Vitamin D Deficiency in History**

- First described in the mid 1600s
- Commonly referred as rickets in children and osteomalacia in adults
- Fortification of milk with vitamin D

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Complication of Vitamin D Deficiency

Vitamin D serum levels and Diagnosis of vitamin D Deficiency

<table>
<thead>
<tr>
<th>ng/ml</th>
<th>nmol/L</th>
<th>Health status</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12</td>
<td>&lt;30</td>
<td>Vitamin D deficiency</td>
</tr>
<tr>
<td>12-20</td>
<td>30-50</td>
<td>Vitamin D insufficiency</td>
</tr>
<tr>
<td>≥20</td>
<td>≥50</td>
<td>Adequate Vitamin D</td>
</tr>
<tr>
<td>&gt;60</td>
<td>&gt;150</td>
<td>Potentially toxic</td>
</tr>
</tbody>
</table>

**controversial

Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D, Washington, DC, 2010.

The state of Vitamin D Level in the US

- A study of National Health and Nutrition Examination Survey 2005-2006 data; N =4,495; Vitamin D deficiency ≤20ng/ml
- Prevalence of vitamin deficiency was 41.6%
  - Blacks at 82.1%
  - Hispanics 69.2%
- Higher prevalence also noted in people:
  - With no college education
  - Who are obese
  - With poor health status
  - With hypertension
  - With Low HDL cholesterol
  - Not consuming milk daily

Figure 1: Age-and-season-adjusted prevalence at risk of deficiency and inadequacy among persons aged 12 years and over United States, 1988-1994 through 2005-2006
Vitamin D Deficiency: What’s the Big Deal?

Using data from the National Health and Nutrition Examination Survey III

Breastfed infants
Older adults
Limited sun exposure
Dark skin
Fat malabsorption condition
Obese/gastric bypass surgery

Prevalence of Vitamin D Deficiency

Prevalence Estimates (95 percent confidence intervals) of serum 25-hydroxyvitamin D among US persons 60 years and older by race/ethnicity

Risk factors for Vitamin D deficiency (1 of 2)

Risk factors for vitamin D deficiency (2 of 2)

NIH office of Dietary Supplements, Dietary Supplement Fact Sheet: Vitamin D
Randomized clinical trials
- A study of 1,200 health postmenopausal women on daily calcium of 1400mg-1500mg and vitamin D of 1,100 IU vs placebo for 4 years
  - Result: 60% lower overall incidence of cancer in the treatment group


Observational studies
- Colorectal cancer
- Breast cancer
- Prostate, pancreatic, other rare cancers
  - Outcome: inconsistent results
    - Due to potential inaccuracies with questionnaires, diet records, interviews used in study methods

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Association with type 1 diabetes
- Epidemiological studies signal connection between vitamin D deficiency in early stage of life and the later development of type 1 diabetes


Association with type 2 diabetes
- In humans and animal models, vitamin D deficiency was noted to affect insulin synthesis and secretion

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Retrospective, observational study (data over almost 6 years period)
- Study participants from cardiovascular practice
- 10,899 patients, mean age 58±15 years, average BMI 30±8 kg/m²
- 3,294 (29.7%) had serum vitamin D level ≥30 ng/ml
- 7,665 (70.3%) had serum vitamin D level <30 ng/ml
  - Outcome
    - Vitamin D deficiency was associated with hypertension (p<0.05)
    - Vitamin D supplementation yielded improved survival, especially in patients with documented deficiency

**Vitamin D Deficiency in Multiple Sclerosis**

- Stein et. al studied twenty-three (23) subjects on the role of high dose vs. low dose vitamin D supplementation on multiple sclerosis severity over 6 months
- Outcome
  - Higher dose group had more multiple sclerosis relapses and severe disability compared to the low dose group by study end.

*Solomon AJ. Multiple sclerosis and vitamin D. Neurology. 77:99-100, 2011.*

**Vitamin D’s role in Mortality?**

- Meta-analysis of 18 randomized controlled trials studied role of vitamin D supplementation on all-cause mortality
- Outcome: 7% relative risk reduction for death


**Vitamin D2 vs. Vitamin D3**

- Chemically different (side chain)
- Vitamin D3 may increase vitamin D levels more
- High dose vitamin D2 available with prescription
- Many OTC products contain vitamin D3


**Ergocalciferol (vitamin D2)**

- Calciferol
  - Oral liquid
- Drisdol
  - Oral capsule, liquid filled
  - Oral liquid
- Ergocalciferol (generic)
  - Oral capsule, liquid filled
  - Oral tablet

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Cholecalciferol (vitamin D3)
- D3-50
  - Oral capsule
- D3-5
  - Oral capsule
- D3
  - Oral capsule
- Cholecalciferol (generic)
  - oral capsule, liquid filled
  - Oral capsule, tablet, powder, solution

Sources of Vitamin D (1 of 3)

<table>
<thead>
<tr>
<th>Natural Sources</th>
<th>Fortified Foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon (3.5oz): 600-1000 IU vitamin D3: (wild)</td>
<td>Fortified milk: 100 IU/8oz vitamin D3</td>
</tr>
<tr>
<td>Cod liver oil (1 tsp): 400-1000 IU vitamin D3</td>
<td>Fortified orange juice: 100 IU/8oz vitamin D3</td>
</tr>
<tr>
<td>Canned sardines (3.5oz): 300 IU vitamin D3</td>
<td>Infant formulas: 100 IU/8oz vitamin D3</td>
</tr>
<tr>
<td>Shiitake mushrooms</td>
<td>Breakfast cereals: 100 IU/serving; vitamin D3</td>
</tr>
<tr>
<td>Sun-dried (3.5oz): 1600 IU vitamin D2</td>
<td>Egg yolk: 20 IU Vit D3 or D2</td>
</tr>
</tbody>
</table>

Sources of Vitamin D (2 of 3)

- Dietary supplements
  - Over the counter:
    - Vitamin D3: 400 IU, 800 IU, 1000 IU, 2000 IU
- Prescription
  - Vitamin D2: 50,000 IU/capsule
  - Vitamin D2: 8000 IU/ml
- Drug interactions
- Caution with OTC products

Sources of Vitamin D (3 of 3)

- Sunlight exposure
  - Ultraviolet B radiation
    - average of 5 to 10 minutes of exposure of legs and arms to sunlight; based on time of day, season, latitude, skin sensitivity.
    - ~3000 IU of vitamin D3
Pharmacological Treatment Options: In prevention of Vitamin D Deficiency

- Children
  - Breastfeeding
    - 400 IU vitamin D3/day + sensible sun exposure
  - Inadequate skin exposure or dark skin
    - 400-1000 IU vitamin D3/day + sensible sun exposure


Adults

- Inadequate skin exposure or dark skin
  - 800-1000 IU vitamin D3/day + sensible sun exposure
  - 50,000 IU vitamin D3/month + sensible sun exposure
- Malabsorption syndromes-50,000 IU vitamin D2 every week
- With drugs that increase vitamin D metabolism
  - 50,000 IU vitamin D2 every 1, 2, or 4 weeks


Vitamin D Screening

“At the present time, there is not sufficient evidence to recommend screening individuals who are not at risk for deficiency or to prescribe vitamin D to attain the non-calcemic benefit for cardiovascular protection”

--Michael F. Holick, PhD, MD
Pharmacological Treatment options:
In Treatment of Vitamin D Deficiency

- Children
  - Breastfeeding without vitamin D supplementation
    - Vitamin D2/D3, 1000-2000 IU/day with calcium supplementation
  - Inadequate sun exposure or dark skin
    - 50,000 IU vitamin D2 every week for 6 weeks

- Adults
  - Inadequate sun exposure or if aging
    - 50,000 IU vitamin D2 every week for 8 weeks, maintenance therapy of 1500-2000 IU/day
  - Malabsorption syndromes
    - 6000-10,000 IU/day, maintenance dose of 3000-6000 IU/day
  - With drugs that increase vitamin D metabolism
    - 6000-10,000 IU/day, maintenance dose of 3000-6000 IU/day


Vitamin D Supplementation Doses

100 IU/day of vitamin D

= Increase serum 25(OH)D by ~1 ng/ml


Challenges of IOM’s Report

- Vitamin D blood levels cut-points
- Most Americans have adequate vitamin D; deficiency overstated
- Vitamin D Recommended Dietary Allowance
- Vitamin D only beneficial in bone health

Summary

- There appears to be an association between vitamin D deficiency in cancer, diabetes, hypertension, and multiple sclerosis conditions.
- Studies are inconclusive on the supplementation of vitamin D on non-skeletal related conditions.
- Considering the ease, safety, cost of vitamin D supplements, all efforts should be made to avoid vitamin D deficient state.