Vitamin D in Allergic and Immune Disorders

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ACAAI Meet the Professor Breakfast (S3)
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Disclosure

We have no potentially relevant financial interests, conflicts of interest, or other affiliations with any corporate organizations relevant to the subject of my presentation. We do not intend to discuss off label use of medications or devices.

Disclosure

I take 1400 IU of vitamin D q.d.
Hopefully, this topic will interest you enough to read more on your own including some of the references.
The handout can serve as a framework for our discussion.
Learning Objectives

At the conclusion of this CME activity, the participant will be able to:

1. Define levels of sufficient, insufficient, and deficient vitamin D.
2. Describe associations vitamin D levels and atopic diseases.
3. Identify the potential role of vitamin D in immune modulation.

Growth of Publications:
Vitamin D and Allergy, Asthma, and Respiratory Infection

Sales of Vitamin D Supplements in the United States

Nutrition Bus J 2012
### Vitamin D Synthesis

- **Skin**
  - Sunlight (UVB)
  - 7-dehydrocholesterol
- **Liver**
  - Dietary intake
  - Supplements
- **25-hydroxyvitamin D3**
- **Kidney**
  - 1,25-dihydroxyvitamin D3 (calciferol)-active molecule

### RDA for Vitamin D

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>0-1</th>
<th>1-13</th>
<th>14-18</th>
<th>19-50</th>
<th>51-70</th>
<th>&gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>IU/d</td>
<td>400</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>800</td>
</tr>
<tr>
<td>Pregnancy and lactation</td>
<td>600</td>
<td>600</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Sources of Vitamin D

<table>
<thead>
<tr>
<th>Source</th>
<th>Serving size</th>
<th>IU per serving</th>
<th>% RDV (1-70 yrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk, fortified</td>
<td>8 oz.</td>
<td>120</td>
<td>20</td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>15 ml.</td>
<td>1360</td>
<td>227</td>
</tr>
<tr>
<td>OJ, fortified</td>
<td>8 oz.</td>
<td>137</td>
<td>23</td>
</tr>
<tr>
<td>Salmon</td>
<td>3 oz.</td>
<td>447</td>
<td>75</td>
</tr>
<tr>
<td>Egg, large</td>
<td>One</td>
<td>41</td>
<td>7</td>
</tr>
<tr>
<td>Skin</td>
<td>Up to 30’</td>
<td>20,000</td>
<td>3333</td>
</tr>
</tbody>
</table>
Food sources of Vitamin D

<table>
<thead>
<tr>
<th>Food</th>
<th>IU per serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod liver oil, 1 tablespoon</td>
<td>1,360</td>
</tr>
<tr>
<td>Salmon (sockeye), cooked, 3 ounces</td>
<td>794</td>
</tr>
<tr>
<td>Mushrooms that have been exposed to ultraviolet light to increase vitamin D, 3 ounces (not commonly available)</td>
<td>400</td>
</tr>
<tr>
<td>Mackerel, cooked, 3 ounces</td>
<td>388</td>
</tr>
<tr>
<td>Tuna fish, canned in water, drained, 3 ounces</td>
<td>154</td>
</tr>
<tr>
<td>Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup</td>
<td>115-124</td>
</tr>
<tr>
<td>Orange juice fortified with vitamin D, 1 cup [check product labels, as amount of added vitamin D varies]</td>
<td>100</td>
</tr>
<tr>
<td>Yogurt, fortified, 6 ounces</td>
<td>80</td>
</tr>
<tr>
<td>Liver, beef, cooked, 3.5 ounces</td>
<td>46</td>
</tr>
<tr>
<td>Egg, 1 whole (vitamin D is found in yolk)</td>
<td>25</td>
</tr>
</tbody>
</table>


2 Teaspoons (10 mL)
Number of Servings: 50

Vitamin D 920 IU
Vitamin A 2000 IU
DHA 1058 mg
EPA 690 mg
Lemon Flavoring

25-OH-D3 Levels and Health

<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>DEFICIENT: Associated rickets in infants and children and osteomalacia in adults.</td>
</tr>
<tr>
<td>12–19</td>
<td>30–49</td>
<td>INSUFFICIENT: Generally considered inadequate for bone and overall health in healthy individuals</td>
</tr>
<tr>
<td>≥20</td>
<td>≥50</td>
<td>SUFFICIENT: Generally considered adequate for bone and overall health in healthy individuals</td>
</tr>
<tr>
<td>20–29</td>
<td>50–75</td>
<td>INSUFFICIENT</td>
</tr>
<tr>
<td>30–50</td>
<td>75–125</td>
<td>SUFFICIENT</td>
</tr>
<tr>
<td>&gt;50</td>
<td>&gt;125</td>
<td>Emerging evidence links potential adverse effects to such high levels, particularly &gt;60 ng/mL (&gt;150 nmol/L)</td>
</tr>
</tbody>
</table>

** Conversion: 1 ng/ml=2.496 nmol/L

nei.nih.gov/NIH-PA.time/Research/Health/grant (2014-11)
Serum PTH and [25(OH)D]

Definitions of Vitamin D Status

Who is at Risk of Vitamin D Deficiency?

Dark complexion.
Older children/teenagers.
Girls.
Obesity.
More screen time.
More time indoors.
Extremes of latitude.
Low milk consumption.
Breast fed babies.
Malabsorption.

Vitamin D Deficiency is More Common than You Think

Estimates of 30-80% deficiency reported.

NHANES (2001-2004) study of 6000 1-21 year olds:
- 9% vitamin D deficient (<15 ng/ml).
- 61% vitamin D insufficient (<30 ng/ml).
- Lower in older children, female, African and Mexican Americans, drank milk <once/week, >4 hours per day in front of screens.

Adolescents (72% Black or Hispanic):
- 24% vitamin D ≤ 15 ng/ml.
- 42% vitamin D ≤ 20 ng/ml.

Infants and toddlers 8-24 months (90% Black or Hispanic):
- 12% vitamin D ≤ 20 ng/ml.
- 40% vitamin D ≤ 30 ng/ml.


Vitamin D Levels in a Random Population (NHANES 2005-06)

Frequency in survey population

25-OH vitamin D3 level (ng/ml)

Insufficient
Sufficient
Deficient

Adapted from Allergy Asthma Proc. 2011;32:438-44.

Non-Calcemic Roles of Vitamin D

Vitamin D receptor (VDR) and α-1-hydroxylase have been found on and in most cell types and tissues of the body.

Numerous conditions have been associated with vitamin D deficiency:
- Atherosclerosis.
- Cardiac contractility.
- Autoimmunity.
- Neoplasm
- Breast
- Colon
- Prostate
- Impaired insulin synthesis.
- In the PICU:
  • More critical illness
  • Longer admission.
  • Pressor need.
  • Risk of septic shock
Associations of Vitamin D Status with Things We Do for a Living

- Atopic diseases
- Total and specific IgE
- Asthma
- Atopic dermatitis
- Anaphylaxis
- Food Allergy
- Chronic urticaria?
- Infections
- Atopic dermatitis
- Influenza, resp. viruses
- Tuberculosis, HIV
- Autoimmunity
- Type 1 diabetes mellitus
- Multiple sclerosis
- Rheumatoid arthritis

An Association Does not Imply Cause and Effect. It is Merely a Place to Start Your Research.

Isomers of Vitamin D₂ & D₃

Vitamin D₃
- 7-Dehydrocholesterol
- Ergosterol
- Made in the skin by UV
- Fully active
- Made in the liver
- One 1/3 that of D₃

Vitamin D₂
- Precursor
- Full activity
Bioequivalence

• Higher affinities of D3 for:
  – Hepatic 25-hydroxylase
  – Vitamin D-BP (VDBP)
  – Vitamin D receptor (VDR)
### Vitamin D Production in the Skin Is Related to Skin Type:
(The Darker the Skin the More Sunlight Exposure Required to Make Enough Vitamin D)

<table>
<thead>
<tr>
<th>Skin Type</th>
<th>Color</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Pale, Never Tans</td>
<td>Usually burns, red and Painful</td>
</tr>
<tr>
<td>Type 2</td>
<td>Very light tan, May freckle</td>
<td>Usually burns, tans gradually</td>
</tr>
<tr>
<td>Type 3</td>
<td>Light tan, Brown, Olive</td>
<td>Usually tans, rarely burns.</td>
</tr>
<tr>
<td>Types 4–6</td>
<td>Brown, Dark Brown, Black</td>
<td>Always tans fast, almost no burns</td>
</tr>
</tbody>
</table>

### Skin Type: Melanin Content

- **Type I** skin always burns, never tans, and is extremely fair.
- **Type II** skin always burns, occasionally tans, and is considered fair.
- **Type III** skin occasionally burns, gradually tans, and is considered medium.
- **Type IV** skin rarely burns, always tans, and is considered olive.
- **Type V** skin seldom burns, always tans, and is considered medium to dark.
- **Type VI** skin never burns, always tans, and is considered dark.

### Latitude and Epinephrine Prescriptions

- **Prescriptions may vary based on geographical location.**

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*References:*

**Latitude and Epinephrine (Southern Hemisphere)**

![Graph showing the Epinephrine rate per 100,000 population against Latitude (degrees) for different age groups (0-4 years, 5-14 years, >14 years).]

*Adapted from Ann Allergy Asthma Immunol. 2009;103:488-95.*

**Vitamin D Levels and Atopy**

![Bar chart showing the prevalence of total IgE, Any ImmunoCAP, Perennial ImmunoCAP, and Pollen ImmunoCAP with different vitamin D levels (>30, 15-29, <15 ng/ml).]

*Adapted from J Allergy Clin Immunol. 2011;127:1364-262.*

**Vitamin D and Asthma Control**

- Vitamin D levels are correlated with FEV₁, FVC, asthma control, and steroid responsiveness.
- Vitamin D level is inversely correlated with asthma symptoms, bronchial hyperreactivity, asthma exacerbations, steroid requirement, and bronchial smooth muscle mass.
- Vitamin D deficiency is a risk for asthma hospitalization and airway remodeling, and is associated with steroid resistant asthma.

Asthma and Vitamin D Supplementation

- Vitamin D enhances T cell steroid responsiveness *in vitro*.
- Supplementation at 1 (cod liver oil) decreases risk of allergies and asthma at 31 years.
- In established and newly diagnosed asthma, vitamin D supplementation leads to better asthma control.


Vitamin D Levels, Lung Function, and Steroid Response in Adult Asthma


Sutherland

- 54 adult asthmatics
- **Objective**: Determine whether there is correlation between ER to asthma severity, & treatment response
- Low vit D levels were associated with increased production of pro-inflammatory protein in blood
- Subjects with higher vit D levels had:
  - Better lung function measures (↑23 ml increase in FEV₁ for every 1 ng/mL increase in serum vit D)
  - Improved AHR
  - Better response to corticosteroid in vitro

Pre-, Peri, and Neonatal Vitamin D and Risks for Atopy

• VDR polymorphisms.
• Low maternal vitamin D intake and levels and low cord levels of 25-OH-D3 are associated with increased risk of atopic dermatitis in infancy and for wheeze and/or asthma at 3, 5, and 9 years old.
• Breast fed babies at risk.

Vitamin D and Infections

• Vitamin D supplementation maintains epithelial barrier and improves control of atopic dermatitis.
• Deficiency is associated with increased risk of sinusitis and increased rate of viral respiratory illnesses.
• Supplementation decreases rate of URIs and influenza (dose dependent).
• Vitamin D enhances immunity to M. tuberculosis.

National Jewish Hospital for Consumptives

How Can We Make Sense of All That?

It’s easy.....

VDR and α-1-hydroxylase are everywhere!

They have to be there for a reason, not by accident.

VDR and α-1-hydroxylase are everywhere

• APCs (Dendritic cells, monos, macros, etc.):
  - Exposure to lipopolysaccharide up-regulates VDR and α-1-hydroxylase.
  - Vitamin D3 up-regulates toll-like receptors (TLR) for better response to microbes.
  - Vitamin D3 up-regulates antimicrobial proteins, maintains epithelial barrier integrity in AD.
  - Vitamin D3 enhances tolerance in adaptive immunity by up-regulating IL-10, IL-19, and TGF-β (enhances Treg [FoxP3+] cell development).
  - Vitamin D3 down-regulates co-stimulatory molecules CD40 and CD80/86.
VDR and α-1-hydroxylase are everywhere

- **Lymphocytes:**
  - Decreased proliferation.
  - Inhibition of Th1 and Th2 cytokines by naïve (cord) T cells with enhanced Treg phenotype.
  - Vitamin D3 enhances IL-2 production.
  - Enhances steroid responsiveness and immunosuppressive effects.
  - Decreased IL-6, decreased IL-12 induced IFN-γ synthesis.
  - Decreased CD40 and CD80/86 on B cells → Decreased T cell activation.
  - Better response to SCIT.

Other cells we think about everyday:

- **Mast Cells**
  - Inhibition of maturation.
  - Apoptosis.
- Decreased eosinophil recruitment.
- Respiratory epithelium and smooth muscle.
  - Inhibits smooth muscle proliferation.
  - Decreased RANTES (CCL5) production.
  - Decreases matrix metalloproteinase production.
  - Helps fetal lung growth (mice).

Reversing the defective induction of IL-10–secreting regulatory T cells in glucocorticoid-resistant asthma patients

Response to Glucocorticoids in SR Asthmatics?

- Human CD4⁺ Treg secrete high levels of IL-10 when stimulated in presence of dexamethasone (dexa) & vit D₃.
- Dexa does not enhance secretion of IL-10 by CD4⁺ T cells of SR asthmatics.
- Vit D₃ overcame inhibition of GC-receptor (GC-R) expression by dexa while IL-10 upregulated GC-R expression by CD4⁺ T cells.

**Conclusion:** Vit D₃ treatment may overcome poor GC responsiveness in SR asthmatics.


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**UV Radiation & Vitamin D Synthesis**

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**BMI vs Plasma Concentration**

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Indoor/Sedentary Lifestyle

Above 37 degrees North Latitude (Atlanta) little or no vit D3 can be produced between November and February.

Aging reduces 7-dehydrocholesterol in skin
- By age 70 by 75%

Sunscreen Use: absorbs UVB rays
- SPF 8 decreases synthesis by 92.5%
- SPF 15 decreases synthesis by 99%

Skin Pigment-Melanin: absorbs UVB rays by up to 99%

Causes of Vitamin D Deficiency

Vitamin D₃ vs 1α,25(OH)₂-Vitamin D₃

Are they the same or different?

Vitamin D₃ VERSUS 1α,25(OH)₂D₃

Properties:
- Biologically Inactive Itself
- Does not bind to VDR
- Nutritional Substance
- Steroid Hormone
- Acts through VDR

Two Faces of Vitamin D Function

Reverse Causation?

• Some evidence suggests that vit D might increase the risk of allergic disease.

• Reverse causation: more severe asthmatics spend less time outdoors in which case vit D deficiency is secondary to the disease. [Wijt, M. Allergy Asthma Clin Immunol. 2009;5:9].


The Case for Vitamin D

Blood Levels: 25(OH)D Recommendations

• Literature (2000-2010): 30-60 ng/mL

• IOM (November 2010): > 20 ng/mL
Institutes of Medicine Recommendations (Nov 2010+)

Dietary Reference Intakes for Calcium and Vitamin D

<table>
<thead>
<tr>
<th>Life Stage Group</th>
<th>Calcium Requirement (mg/day)</th>
<th>Calcium Upper Level Intake (mg/day)</th>
<th>Calcium Recommended Dietary Allowance (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 0-6 months</td>
<td>* * 1000 ** ** 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants 6-12 months</td>
<td>* * 1500 ** ** 1500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 years</td>
<td>500 700</td>
<td>2500</td>
<td></td>
</tr>
<tr>
<td>4-8 years</td>
<td>800 1000</td>
<td>2500</td>
<td></td>
</tr>
<tr>
<td>9-13 years</td>
<td>1100 1300</td>
<td>3000</td>
<td></td>
</tr>
<tr>
<td>14-18 years</td>
<td>1100 1300</td>
<td>3000</td>
<td></td>
</tr>
<tr>
<td>19-30 years</td>
<td>800 1000</td>
<td>3000</td>
<td></td>
</tr>
<tr>
<td>31–50 years</td>
<td>800 1000</td>
<td>4000</td>
<td></td>
</tr>
<tr>
<td>51–70 year, males</td>
<td>800 1000</td>
<td>4000</td>
<td></td>
</tr>
<tr>
<td>51–70 year, females</td>
<td>1,000 1200</td>
<td>4000</td>
<td></td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>1,000 1200</td>
<td>4000</td>
<td></td>
</tr>
<tr>
<td>14–18 years, pregnant/lactating</td>
<td>1,100 1300</td>
<td>4000</td>
<td></td>
</tr>
<tr>
<td>19–50 years, pregnant/lactating</td>
<td>800 1000</td>
<td>4000</td>
<td></td>
</tr>
</tbody>
</table>

* For infants, Adequate Intake is 200 mg/day for 0 to 6 months of age and 260 mg/day for 6 to 12 months of age.
** For infants, Adequate Intake is 400 IU/day for 0 to 6 months of age and 400 IU/day for 6 to 12 months of age.

Knowledge Gaps

• What are the differences between naïve T cell responses to vit D & mature T cell responses to vit D?

• What dose of supplemental vit D is optimal for prevention or control of asthma (allergy)?

• Can excessive vit D intake potentiate Th2 responses in asthmatics?
Knowledge Gaps

• Does the host’s vit D status modify the effect of the intestinal microbiota on the immune system?

• Does vit D deficiency affect the composition of the intestinal microbiota?

How Vitamin D Works

Complex Problem. Simple Solution?
<table>
<thead>
<tr>
<th>Selected References</th>
</tr>
</thead>
</table>