Vitamin D, Infection, and Allergy

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Disclosure

Nothing to disclose

Objectives

At the conclusion of this session, the participant should be able to:

- To identify main sources, clinical measurement, and general health effects of vitamin D
- To describe key studies on the association between vitamin D, infection, and allergy
- To discuss implications of recent vitamin D findings for allergy/immunology patients

Overview of Presentation

1. Vitamin D
2. Respiratory infections / wheezing
3. Asthma
   - Incident asthma
   - Exacerbations
4. Winter-related atopic dermatitis
5. Food allergy

Vitamin D Synthesis & Metabolism

Sun → 7-dehydro cholesterol → Skin

Liver → 25-hydroxylase (CYP27A1) → Vitamin D

Kidney → 1α-hydroxylase (CYP27B1) → 25(OH)D

Kidney → 24-hydroxylase → 1,25(OH)2D

Severe Vitamin D Deficiency → Rickets
Vitamin D Receptor (VDR)

- VDR present in most tissues and cells of body
- Growing recognition that many different cells have the enzymatic machinery to convert 25(OH)D to the active hormone, 1,25(OH)₂D
- >2,700 binding sites for VDR along genome
- Significant effects on activity of 229 genes

A. Norman, 2006; Ramagopalan, Genom Res 2010

Non-Calcemic Functions of Vitamin D

- Cancer
- CVD
- Autoimmune

Holick, J Clin Invest 2006

Risk Factors for Vitamin D Insufficiency

- Winter at higher latitudes
- Darker skin
- Lifestyle-related ↓ UVB exposure
  - Newborns with exclusive breastfeeding
  - Age 50+ (more indoors + ↓ skin conversion)
  - Sunscreen use
- Obesity (fat storage +)

Bischoff-Ferrari, Osteopor Int 2010; Canadian Paediatric Society 2007; Wagner, Pediatrics 2008; Institute of Medicine 2011

Serum 25(OH)D (cut-points vary by author)

- Conversion factor: 1 ng/ml = 2.496 nmol/L
- Looking across multiple conditions, optimal level probably is ~40 ng/ml = ~100 nmol/L
  Note: Some recommend 40-60 ng/ml
- Insufficiency: 10 – 29 ng/ml
- Deficiency: <10 ng/ml

2008 AAP: Defic <20 ng/ml
2011 IOM: Goal ≥20 ng/ml

Figure 1. Global climatology (1979-1992) of mean daily erythemal (i.e., “sunburning”) UV dose (from the NCAR website http://www.oes.ucar.edu/TUV/).

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**Institute of Medicine (IOM)**

<table>
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<tr>
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<th>1997 AI</th>
<th>Tol. UIL</th>
<th>RDA</th>
<th>ULI</th>
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<tr>
<td>Birth to 12 months</td>
<td>200</td>
<td>1000</td>
<td>~400</td>
<td>&lt;8m: 1000</td>
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<td>51-70: 400</td>
<td>600</td>
<td>1-3: 2500</td>
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<tr>
<td>Age 71+ years</td>
<td>600</td>
<td></td>
<td>800</td>
<td></td>
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<tr>
<td>Pregnant / lactating</td>
<td>200</td>
<td></td>
<td>600</td>
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* Assumes minimal sunlight and target 25(OH)D ≥20 ng/ml

IOM 1997; IOM 2011

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**Low 25(OH)D Levels in US Children**

- 0-5 months: <30 ng/ml
- 6-11 months: <20 ng/ml
- 12 months: <10 ng/ml

Mansbach, Pediatrics 2009

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**Dietary Vitamin D → Serum 25(OH)D**

- Dietary intake has modest effect on 25(OH)D:
  - Glass of fortified milk (100 IU) = ↑ 1 ng/ml
  - 5 µg (200 IU) per day = ↑ 2 ng/ml
  - 10 µg (400 IU) per day = ↑ 4 ng/ml
  - 25 µg (1000 IU) per day = ↑ 10 ng/ml

- Typical MVI (200-600 IU)

- Cod liver oil: variable (400 - 1300 IU per tbsp)

- Skin can create many thousands of IUs after only 15-20 minutes of direct UVB exposure

Multiple sources

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**Niels Finsen and Heliotherapy**

Finsen, Br Med J 1903

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**1903 Nobel Prize – UVR and Lupus Vulgaris**

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**Heliotherapy for TB**

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Vitamin D and Epidemic Influenza

“The nature of the seasonal stimulus remains undiscovered” (1981)

Hope-Simpson, J Hygiene 1981; Cannell, Epidemiol Infect 2006

Cathelicidin Antimicrobial Peptide (CAMP)

Human CAMP gene is direct target of VDR and strongly up-regulated in myeloid cells by 1,25(OH)₂D₃

Gombart, FASEB 2005

Maternal Vitamin D and Risk of Child Wheezing

Camargo, Am J Clin Nutr 2007

Immunologic Effects of Vitamin D


Project Viva

- Based in Boston (northeastern USA)
- Prospective cohort study of ~2,000 pregnant women and their offspring (pre-birth cohort)
- Objective: To study pre- and peri-natal influences on outcomes of infancy, childhood, adulthood
- Data collection includes:
  - In-person visits (during pregnancy & childhood), with multiple interviews & questionnaires
  - Blood samples (frozen for future testing)

Published Cohort Studies (as of Dec 2010)

<table>
<thead>
<tr>
<th>Study</th>
<th>Maternal intakes</th>
<th>Age</th>
<th>Risk of Child Wheezing</th>
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<tbody>
<tr>
<td>Camargo, 2007 USA</td>
<td>Maternal intake ... 3y</td>
<td>↓</td>
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<tr>
<td>Devereux, 2007 Scotland</td>
<td>Maternal intake ... 5y</td>
<td>↓</td>
<td>ns</td>
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<tr>
<td>Erkkola, 2009 Finland</td>
<td>Maternal intake ... 5y</td>
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<td>Miyake, 2010 Japan</td>
<td>Maternal intake ... 2y</td>
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<td>Hypponen, 2004 Finland</td>
<td>Infant supplement ... 31y</td>
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<td>↑</td>
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<td>Gale, 2008 England</td>
<td>Maternal 25(OH)D ... 9m, 9y</td>
<td>(↑)</td>
<td>(↑)</td>
</tr>
<tr>
<td>Bäck, 2009 Sweden</td>
<td>Infant supplement ... 6y</td>
<td>composite</td>
<td>↑</td>
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</tbody>
</table>
NZ Asthma & Allergy Cohort Study

• Based in New Zealand (PI: Julian Crane)
• Prospective cohort study of ~1,000 pregnant women and their offspring (birth cohort)
• **Objective**: To study peri-natal influences on asthma, allergies, and eczema
  - Cord blood 25(OH)D = median 18 ng/ml
  - Respiratory infection by age 3 months
  - Wheezing by age 5 years
  - Doctor-diagnosed asthma at age 5 years

Camargo, *Br J Nutr* 2010

Respiratory Infection By Age 3 Months

• Season-adjusted odds ratio (OR) was higher among those with low 25(OH)D:
  - 30+ ng/ml: 1.00
  - 10-29: 1.39 (95% CI, 0.98-1.99)
  - <10: 2.16 (95% CI, 1.35-3.46)

• This inverse association was not materially changed by adjustment for 14 other factors

Camargo, *Pediatrics* 2011

Cord Blood 25(OH)D, Wheeze, and Asthma

Camargo, *Pediatrics* 2011

Curvilinear Association with IgE?

- **UK** (Hypnøen, *Allergy* 2009):
  - Cross-sectional study, n=9377 adults, age 45y
  - Low & high 25(OH)D associated with higher levels of total IgE

- **Arizona** (Rothers, *JACI* 2011):
  - Birth cohort study, n=219 newborns → age 5 years
  - Low & high 25(OH)D associated with higher risk of aeroallergen sensitization

Randomized Trials on Respiratory Infection

• Post hoc analyses of bone RCTs suggest benefit
• First published RCTs (2009-2010):
  - New York (Li-Ng, *Epidemiol Inf* 2009):
    n=162 adults, 2000 IU/day x 3 mo: NS
    n=430 children, 1200 IU/day x 4 mo: P<0.05
  - Finland (Laakso, *J Inf Dis* 2010):
    n=164 adults, 400 IU/day x 6 mo: P~0.05
  - Afghanistan (Manaseki-Holland, *Trop Med Int Health* 2010):
    n=224 children with pneumonia, 100k IU bolus: P<0.05
• Several ongoing RCTs of likely relevance, including studies of pregnancy/infancy and in all age groups

Ginde, *Arch Intern Med* 2009

Vitamin D and Recent URI

ACAAI Annual Meeting
Nov. 3 - 8 2011, Boston
Asthma Exacerbations

- Prospective cohort data suggest benefit
  - Childhood wheezing studies
    - USA (Brehm, J Allergy Clin Immunol 2010)
      n=1024 children, baseline 25(OH)D, 4 years: P<0.01
  - First published RCTs (2010-2011)
    - Japan (Urashima, Am J Clin Nutr 2010): n=430 children, 1200 IU/day x 4 mo: P<0.05
    - Poland (Majak, J Allergy Clin Immunol 2011) n=48 children, 500 IU/day x 6 mo: P<0.01
  - Several ongoing RCTs, including studies of COPD

Asthma Severity & CS Response

- 54 adults + 100 children with asthma:
  - cross-sectional analyses + in vitro testing
- Mean 25(OH)D = 28 ± 31 ng/ml
- Higher serum 25(OH)D levels were associated with:
  - Better lung function (both)
  - Reduced airway hyper-responsiveness (adults)
  - Less corticosteroid use & fewer positive SPTs (children)
  - Improved in vitro response to corticosteroids (both)
- Vitamin D supplementation may improve multiple parameters of asthma severity & treatment response.

Sutherland, AJRCCM 2010; Searing, JACI 2010

Skin – Norwegian RCT of Heliotherapy

- Health Ministry – “Health Travels” program
- Children with severe atopic dermatitis (AD) were randomly assigned to:
  - Visit Gran Canary Island for 4 weeks
  - Stay at home in Norway
- Improvement in all AD outcomes, including:
  - ↓ AD severity score
  - ↓ skin colonization by S. aureus
- No mention of vitamin D

Byremo, Allergy 2006

Randomized Trials on Winter-related AD

- Boston (Sidbury, Br J Dermatol 2008)
  - Pilot RCT of vitamin D supplement (1000 IU x 1 mo) vs. placebo; n=11 children
  - Vitamin D appeared to improve AD severity
- Mongolia (presented at 2009 WCPD, Bangkok)
  - clinicaltrials.gov NCT00879424
  - RCT of vitamin D supplement (1000 IU x 1 mo) vs. placebo; n=107 children
  - Vitamin D improved AD severity (p<0.05)
- Mediated by ↓ bacterial colonization of skin (?)
Potential mechanisms for the hypothesized link between sunshine, vitamin D, and food allergy in children

Vassallo & Camargo, JACI 2010

Population-based RCTs (as of Sept 2011)

• VIDA (Scragg & Camargo)
  – 5,100 men + women, age 50-84
  – Vit D3 100,000 IU/month (equals ~3,300 IU/day)
  – Primary outcomes: CVD, infection, fractures ...
  – Enrollment started 2011 → results in 2017

• VITAL (Manson)
  – 20,000 subjects (men age 50+, women age 55+)
  – 2x2 factorial: 2000 IU/d Vit D3 + 1 g/d EPA+DPA
  – Primary outcomes: cancer, CVD ...
  – Enrollment started 2011 → results in 2017

Summary & Clinical Implications

• Low 25(OH)D levels are associated with:
  – ↑ respiratory infections = ↑ wheezing & asthma exacerbations
  – Possible ↑ corticosteroid responsiveness
  – No association with incident childhood asthma
  – Winter-related atopic dermatitis
  – Possible ↑ risk of incident food allergy

• Emerging data from RCTs support benefit for infection

• Safety of high doses in pregnancy & infancy uncertain (possible ↑ allergy risk ... then traditional concerns re: ↑ calcium)

• Further research is needed, especially RCTs

• My best guess? Aim for serum 25(OH)D ~40 ng/ml

Mullins, Ann Allergy Asthma Immunol 2009