Vitamin D and Immunity
NASPghan Annual Meeting
October 12, 2013

James E. Heubi, M.D.
Associate Dean for Clinical and Translational Research
University of Cincinnati College of Medicine

Financial Disclosures
In the past 12 months, I have the financial relationships with the following
• Equity interest in Asklepion Pharma, LLC.
• Funding: NCATS, NIDDK, NICHD, and CFF
• Consultant to Nordmark
None of these relationships will be discussed in the presentation

Definition of an Expert
• Travels more than 50 miles
• Has no more knowledge of the subject than members of the audience
• Has a PowerPoint® Presentation
Objectives

- IOM recommendations re: vitamin D/Ca
- IOM findings re: vitamin D and immunity
- Role of vitamin D in immunity associated with infectious diseases and immune-mediated disease
- How current recommendations re: vitamin D and its impact on immune function might influence practice

Outline of Presentation

- Function of vitamin D
- Vitamin D status in IBD patients
- Institute of Medicine (IOM) Report
- Role of Vitamin D
  - Immune function
  - Autoimmune/infectious disease
  - IBD
- Summary /Conclusions

Vitamin D Publications per Year
Vitamin D - Overview

• Sources:
  - Sunlight/UVB irradiation
    • 10-15 minutes total body exposure to peak summer sun => 20,000 IU D3
  - Diet/supplements
    • Naturally occurring: Fatty fish, fish liver oil, egg yolk
    • Fortified food: milk, plant-based beverages
  - Assessment
    • 25 OHD (20 g/ml=50nmol/l)
    • Not 1,25(OH)2D

Vitamin D Metabolism/Actions
Vitamin D Paracrine System

Institute of Medicine Report on Vitamin D and Ca

- 2010 IOM report
  - 1016 page document with hundreds of references
  - Summarized in 4 page Report Brief
  - Task: Review evidence and update the Dietary Reference Intakes
  - Conclusions
    - Vitamin D/Ca play key role in bone health
    - Monitor with serum 25 OHD
    - Current evidence not sufficient for other benefits

Institute of Medicine
Endocrine Society Recommendations

- Screen:
  - Non-specific symptoms: poor growth, gross motor delays, unusual irritability
  - Dark-skinned infants at higher latitudes in the winter and spring
  - Children on anticonvulsants and chronic glucocorticoids
  - Children with chronic diseases associated with malabsorption

- Possibly screen:
  - Kids with frequent fractures and low BMD

Misra M. Pediatr 2008; 122:398-417

IBD and Vitamin D Status - 2 Studies

- 150 IBD: 94 CD, 36 UC
  - Age 15 ± 3 yrs
  - 92% white
  - Mean 25 OHD 20.9 ± 10.7 ng/ml
  - 35% 25 OHD ≤ 15 ng/ml: 38% CD, 25% UC
  - Vitamin D supplement: 77%
    - Reduced 25 OHD related to Season, serum albumin

- 448 IBD: 288 CD, 143 UC
  - Age 15.7 ± 3.2 yrs
  - 83.3% white
  - Mean 25 OHD 31 ± 12
  - 58.5% <32 ng/ml; 14.3% <20 ng/ml
  - Vitamin D supplement: 57.1%
    - Serum 25 OHD related to Season, serum albumin, race/ethnicity, supplements, ESR
  - Pappa H et al. JPGN 2011; 53:11-25
Tutorial: Relation to Vitamin D/GI and Immune System
- Maintenance of epithelial barrier
- Innate immune response
- Adaptive T-cell response

Vitamin D in Autoimmune-Infectious Disease
- Multiple Sclerosis
- Type 1 DM
- Respiratory Conditions
- Influenza A
- Tuberculosis

Serum 25 OHD and MS
Vitamin D Supplementation and DM

Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study

-Risk of Type 1 DM reduced by ~80% with regular* Vitamin D supplementation during the first year of life

* Regular supplementation – based on mothers report
Cord Blood 25 OHD and risk of wheeze/asthma

- Cord-blood 25-OH Vitamin D levels inversely correlated with risk of wheezing
- No correlation with asthma


Vitamin D Supplementation-Influenza A

<table>
<thead>
<tr>
<th>Subjects with influenza A</th>
<th>Vitamin D3</th>
<th>Placebo</th>
<th>Relative risk</th>
<th>P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza A</td>
<td>18/167 (10.8)</td>
<td>31/167 (18.6)</td>
<td>0.58</td>
<td>0.04, 0.99</td>
<td>0.06</td>
</tr>
<tr>
<td>Additional vitamin D</td>
<td>8/140 (6.0)</td>
<td>22/140 (16.5)</td>
<td>0.36</td>
<td>0.17, 0.79</td>
<td>0.09</td>
</tr>
<tr>
<td>All doses given per week</td>
<td>10/34 (29.4)</td>
<td>9/34 (26.5)</td>
<td>1.11</td>
<td>0.52, 2.39</td>
<td>0.79</td>
</tr>
<tr>
<td>Starting age of nursery school</td>
<td>0.04</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


SUCCINT Trial in TB

Salahadin

8
Vitamin D in IBD models

- DSS model with vitamin D deficiency
- Protective effect of 1,25 (OH)₂D on epithelial barrier function and cytokine production in DSS model
- Cytokine production by non-diseased and Crohn’s disease patient T-cells

Vitamin D Effect in Murine Model of Colitis

1,25(OH)₂D and Epithelial Barrier
1,25 (OH)₂D Effect on IL-10/IFN-γ Production in CD

Bartels LE. International Immunopharm 2007; 7:1755-1764

Vitamin D Treatment Effects on Cytokines in CD

Bendix-Struve M. Aliment Pharmacol Ther 2010; 32:1364-1372

Effect of Vitamin D on CD

- Predicted vitamin D status and risk of CD
- Serum 25 OHD and QI efforts in CD
- Serum 25OH D and surgery risk in CD
- Clinical Trials of vitamin D in CD
  - Animal Models
  - Human
Summary/Conclusions

• Biologic plausibility for vitamin D role in pathogenesis of immune mediated diseases such as IBD
• No clear evidence of direct relationship between vitamin D status and CD course
• Current recommendation: Monitor vitamin D status with serum 25 OHD and maintain level ≥ 20 ng/ml or 50 nmol/l.

Questions?