Vitamin D Deficiency \textit{Rickets}: Prevention and Treatment

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Disclosures

• Leanne Ward has no relevant financial relationships with the manufacturers of commercial services discussed in this CME activity

• Leanne Ward does not intend to discuss an unapproved/investigative use of a commercial product in this presentation
Vitamin D
“Insufficiency”

RICKETS
Guiding Principles

• Our focus has been diluted in recent years by the debate over vitamin D levels in relationship to myriad health outcomes

• As pediatric health care providers and policy makers, our focus should be on the global eradication of *RICKETS*
  – Technically a radiological diagnosis and not to be confused with asymptomatic, low vitamin D status
Objectives

• To review the evidence from well-designed trials on vitamin D supplementation in infants and children
• To discuss how these trials highlight key concepts that can inform our approach to: prevention of vitamin D deficiency rickets in at-risk children
• To discuss treatment of vitamin D deficiency rickets among those who escape effective prevention
Rickets: Eradication through Prevention is the Goal

The most effective prevention strategy is to target *mother-infant dyads*
The Importance of the Peri-Natal Milieu

- Mother’s 25(OH)D status during pregnancy determines the infant’s status at birth
- Congenital vitamin D deficient rickets has been described
- Even optimal vitamin stores in mother have a half-life of only 20 to 30 days
- Post-natal dietary source is essential
  - Endogenous production (sun exposure) is not recommended
  - Breast-milk contains 33 IU/L vitamin D

Reeve, 1992
Rickets Prevention Among High Risk Infants at Different Latitudes

Specker, J Peds, 1992

56% had vitamin D deficiency pre-treatment

% with Serum 25OHD < 11 ng/ml

27.5 nmol/L

None had rickets before or after treatment

North

South

40 - 47° N

22 - 30° N
Vitamin D Deficiency
Rickets Prevention

Vitamin D 400 IU/day as a supplement was sufficient to prevent radiological signs of rickets at 6 months, even in infants with severe vitamin D deficiency at birth.

Specker, J Peds, 1992
The efficacy and safety of vitamin D 400 to 1600 IU/day among infants born with vitamin D sufficiency

No differences at 12 months in BMD at the spine, total body, femur

Gallo JAMA 2013
Vitamin D 400 IU/day maintains 25OHD levels among infants who are sufficient at birth

• Safety:
  – A few cases of hypercaleemia or hypercalciuria were suspected in all but the 400 IU/day group
    • Without short-term clinical consequences
  – 800 and even 1200 IU/day was not excessive
  – 1600 IU/day led to unnecessarily high 25(OH)D levels

Gallo JAMA 2013
Supplementation Practices

- 2004 Canadian Community Health Survey (Millar, 2005)
  - 17% of moms exclusively breastfed up to 6 months
  - 50% gave their infant supplemental vitamin D
Single or intermittent dosing for the prevention of rickets
Higher dose prevention therapy

• 4 studies
  – 189 children (infants to 15 years)
  – Entry 25(OH)D levels: < 25 nmol/L or < 50 nmoL/L

  – 100,000 to 600,000 IU D$_3$ every 3 mo for 9 mo

• Gordon *JCEM* 2008
  – 50,000 IU D$_3$ weekly compared to 2,000 IU daily for 6 weeks

• Emel *J Ped Endocrinol Metab* 2012
  – 150,000 IU D$_3$ as a single dose, evaluated after 6 weeks
Higher dose prevention therapy

- Results:
  - Rickets not assessed except in Duhamel 2000 study
  - No episodes of hypercalcemia
  - Hypercalciuria not assessed except in one study
  - Generally effective in achieving levels $>50$ nmol/L
  - 600,000 IU D$_3$ 3 monthly – unnecessarily high 25(OH)D levels
High dose prevention therapy

• Attractive approach
  – Obviates the need for compliance
  – Should target individuals with low vitamin D levels

• Concern on a population basis:
  – Assumes low 25(OH)D levels in at-risk individuals

• Is this approach likely to be efficacious for rickets prevention in at-risk populations? Yes

• Has the safety as a public health policy in at-risk populations been fully studied? No
Case Reports of Infants With Severe Vitamin D Deficiency on Standard Infant Formula

- Ward 2007; Sellers 2006, Gross 2013
- The European Society of Pediatric Endocrinology 2014 Consensus statement (in preparation)
  - Vitamin D 400 IU/day to all infants, both breast and bottle-fed
  - Supported by the Gallo 2013 observation that:
    - 400 to 800 IU/day are not excessive even in infants born with vitamin D sufficiency
<table>
<thead>
<tr>
<th>Age</th>
<th>Daily Dose for 90 Days (IU)</th>
<th>Single Dose</th>
<th>Maintenance Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 months</td>
<td>2,000</td>
<td>N/A</td>
<td>400</td>
</tr>
<tr>
<td>3 months – 1 year</td>
<td>2,000</td>
<td>50,000</td>
<td>400</td>
</tr>
<tr>
<td>1 – 12 years</td>
<td>3,000 – 6,000</td>
<td>150,000</td>
<td>400</td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td>6,000</td>
<td>300,000</td>
<td>400</td>
</tr>
</tbody>
</table>

Ensure adequate intake of calcium
Other Treatment Principles

• Oral therapy is preferred to intra-muscular
  – More rapid restoration of 25OHD levels with oral treatment
    Cipriani JCEM 2013
    Zabihiyeganeh Clin Endocrinol 2013
  – May have no choice in patients with severe malabsorption of fat soluble vitamins

• Bioequivalencies of vitamin D₂ and D₃
  – Yes: for daily oral therapy
  – No: for intermittent, higher dose therapy
Single oral dose of 50,000 IU
Summary and Conclusions

• The most effective way to prevent vitamin D deficiency rickets is to target mother-infant dyads
  • Mothers: 1,000 to 2,000 IU/day
  • All infants: 400 to 800 IU/day
  • Intermittent or single-dose therapy among infants is attractive in high-risk areas
    – Vitamin D₃ is best
    – Efficacy for rickets prevention: likely
    – Safety on a population health basis has not been fully studied
Conclusions

• The abysmal failure to eradicate vitamin D deficiency rickets is:
  – Less about dosing recommendations
  – More about failure to implement guidelines and ensure compliance

• Urgently needed are studies evaluating the impact of strategies that:
  – Obviate the need for compliance (observed, high dose therapy)
  – Focus on implementation (educating the public, health care providers)