VITAMIN D DEFICIENCY
RICKETS IN ALASKA NATIVE AND CANADIAN CHILDREN

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Rachel K. Lescher, MD, FAAP
Pediatric Endocrinology and Diabetes
Alaska Native Medical Center
Anchorage, Alaska, USA
Disclosures

• Rachel Lescher, MD has no relevant financial relationships with the manufacturers of commercial services discussed in this CME activity.

• Rachel Lescher, MD does not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Objectives

• Understand the epidemiology of vitamin D deficiency and rickets in children
• Identify risk factors for vitamin D deficiency and rickets in children
• Use this knowledge to determine best practices for treatment and prevention of rickets and vitamin D deficiency in children
Vitamin D

- Synthesized in the skin using UVB photons (or absorbed from food)
- Conjugated by the liver to 25(OH)D_{3}
- Activated in the kidney to 1,25(OH)_{2}D_{3}
- Increases absorption of calcium (and phosphorous) from the intestines (and bone)
- With sufficient Ca and Phos, increases bone calcification

Nutritional Vitamin D Deficiency

• Risk factors—insufficient sun exposure and dietary intake
  • Darker skin color
  • Use of sunscreen
  • Latitudes above 37° Lat in Northern hemispheres; below 37° Lat Southern hemispheres

• Limited intake of foods high in Vitamin D
  • Oily fish such as salmon; liver and organ meats; sundried shiitake mushrooms; foods fortified with Vit D (infant formulas, some milk)

• Breastfeeding without Vitamin D supplementation
  • Vit D content in breast milk averages ~16-33 IU/L in a vitamin D sufficient mother

• Medications: anticonvulsants, antifungals, glucocorticoids
Definition of Vitamin D Deficiency

2014 AAP Guidelines (Ped 2014;134:e1229)

• Vitamin D deficiency is 25OHD below 20 ng/ml (50 nmol/L)
  • Also Institute of Medicine (2010), Pediatric Endocrine Society, and the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition

2011 Endocrine Society Clinical Practice Guidelines (JCEM 2011;96(7):1911)

• Vitamin D deficiency is 25OHD below 20 ng/ml (50 nmol/L)
• Vitamin D insufficiency is 25OHD 21-29 ng/ml (50-75 nmol/L)
Vitamin D Deficient Rickets

- Failure of mineralization of growing bone and cartilage; a disorder of the growth plate
- A state of extreme vitamin D deficiency
  - Insufficient vitamin D $\rightarrow$ insufficient calcium absorption $\rightarrow$ PTH increases to maintain eucalcemia $\rightarrow$ Increased calcium release from bone into blood $\rightarrow$ decreased bone mineralization $\rightarrow$ RICKETS
- Peak incidence between 3-18 months old
  - BUT Congenital Rickets has also been described
- Diagnosis: bone pain/deformity, radiologic abnormalities, biochemical abnormalities
Rickets

- Limb deformities
- Thoracic cage deformities
- Permanent skeletal deformity
- Tooth enamel defects, dental caries

- Poor growth and weight gain
- Delayed motor development

Time of diagnosis of rickets in an 18 mo girl

- Widening of growth plates
- Irregular metaphyseal border
- Epiphyseal cupping
- Bowing of long bones

Credit: Wellcome Library, London
Vitamin D Deficient Rickets in Alaska and Canada

• 3 studies
  • Singleton R, Lescher R, et al. JPEM 2015
• Background and methods
  • Reports of vitamin D deficient rickets despite prevention guidelines led researchers in Ontario to conduct a study collecting data from Canadian Paediatric Surveillance Program to calculate incidence rates over a 2 year period and identify geographical distribution clinical characteristics of children with vitamin D deficient rickets

**Institutions:**
• University of Ottawa, Ottawa, Ont.
• McMaster University, Hamilton, Ont.
• University of Toronto, Toronto, Ont.
• The Hospital for Sick Children, Toronto, Ont.
Incidence of vitamin D deficiency rickets in Canadian children

- 104 cases over 2 years
- Overall annual incidence rate: 2.9 cases per 100,000
- For children >1 year old, highest incidence in northern regions
  - Yukon territory
  - Northwest territories
  - Nunavut

Clinical presentation of children diagnosed with vitamin D deficiency rickets in Canada from 2002-2004

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt; 1 n = 34</th>
<th>1-2 n = 56</th>
<th>&gt; 2-7 n = 14</th>
<th>Total n = 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean (SD)</td>
<td>0.6 (0.3)</td>
<td>1.4 (0.3)</td>
<td>3.2 (1.3)</td>
<td>1.4 (1)</td>
</tr>
<tr>
<td>Male</td>
<td>22 (65)</td>
<td>28 (50)</td>
<td>4 (29)</td>
<td>54 (52)</td>
</tr>
<tr>
<td>Skeletal deformity</td>
<td>8 (24)</td>
<td>26 (46)</td>
<td>10 (71)</td>
<td>44 (42)</td>
</tr>
<tr>
<td>Hypocalcemic seizures</td>
<td>16 (47)</td>
<td>4 (7)</td>
<td>0</td>
<td>20 (19)</td>
</tr>
<tr>
<td>Delayed developmental milestones</td>
<td>1 (3)</td>
<td>10 (18)</td>
<td>1 (7)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Fractures</td>
<td>3 (9)</td>
<td>6 (11)</td>
<td>2 (14)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Incidental finding of rickets</td>
<td>3 (9)</td>
<td>3 (5)</td>
<td>1 (7)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>2 (6)</td>
<td>3 (5)</td>
<td>0</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Irritability</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Limp</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Weakness</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
Background and Methods:

- Increasing reports of vitamin D deficiency and rickets in Alaska Native children led ANTHC providers to conduct an epidemiologic study with two components:
  - Data analysis of rickets hospitalizations in Alaska Native children and US child population
  - Case control study of Alaska Native children with rickets/vitamin D deficiency and matched controls

Institutions:
- Alaska Native Tribal Health Consortium
- Arctic Investigations Program – CDC
Incidence rates of Rickets in AN children, 2001-2010

- Hospitalization rates in AN children – 2.2/100,000/yr
- Outpatient visit rates in AN children – 33.1/100,000/yr
- Calculated incidence of confirmed rickets in AN children <10 y.o. from the case-control portion of the study – 4.2/100,000/yr
Rickets Incidence by Latitude, Alaska Native children <10 years, 1999-2012

Latitude

- 70-73.9: 21.36
- 66-69.9: 17.89
- 62-65.9: 2.8
- 58-61.9: 2.65
- 54-57.9: 0
- 50-53.9: 0

Annual Incidence/100,000 < 10 yrs

Case-Control Study:

- Cases of rickets/vitamin D deficiency were more likely to be diagnosed with malnutrition/failure to thrive than controls (OR 38.1)
- Cases were less likely than control to have any documentation of vitamin D supplementation in the first 6 months of life (OR 0.23)
- Similar proportions of cases and controls were breastfed or exclusively breastfed
Serologic Survey of Biomarkers for Traditional Marine Diet and Vitamin D Levels in YK Delta Childbearing-aged Women

Objective:
• Explore how intake of traditional marine foods and serum Vitamin D levels have changed from 1960s through the present

Method:
• Test representative Alaska Area Specimen Bank serum samples of YK Delta women 20-29 years old at points in time from 1960s to 1990s, for biomarkers of traditional marine diet ($\delta^{15}$N) and 25-OH vitamin D levels

• Diane O’Brien PhD, University of Fairbanks, Center for Alaska Native Health Research (CANHR)
• Rosalyn Singleton MD, ANTHC
• Ken Thummel PhD, U Wash, Pharmacy, CANHR
• Bert Boyer PhD, U of Fairbanks, CANHR
• Lisa Bulkow MS, AIP-CDC
• Joseph Klejka MD, YKHC
Vitamin D content of some traditional foods

- Chum Salmon, canned with bone (3 oz)
  - 328 IU Vit D
- Sockeye Salmon, canned (3 oz)
  - 715 IU Vit D
- King Salmon, with skin, kippered (3oz)
  - 44 IU Vit D
- Beluga Whale Oil
  - 51 IU Vit D
- Seal Oil (100g)
  - 30 IU Vit D

Salmon has one of the highest vitamin D contents of any food.

A Biomarker of Traditional Marine Food Intake – $\delta^{15}\text{N}$

- Fish and marine mammals are naturally enriched in the heavy stable isotope of nitrogen
- As fish and marine mammal intake increases, so does the nitrogen isotope ratio ($\delta^{15}\text{N}$) in blood and hair
- A person with no marine diet intake would have a $\delta^{15}\text{N}$ of ~8 ‰
- Each increase of 1‰ (unit of relative enrichment) corresponds to an increase in traditional food intake of ~7% of total energy

Validated by Diane O’Brien’s group at UAF (CANHR)
Correlation of Serum Vitamin D and $\delta^{15}\text{N}$

Pearson correlation 0.596 (p<0.001)
Summary: Vitamin D and $\delta^{15}N$

- Vitamin D levels and intake of traditional marine foods decreased in YK child-bearing aged women during 1960s-1990s.

- Vitamin D levels highly correlated with traditional marine food intake.

- Marine dietary intake by women of child-bearing age was very high in the 1960s – similar to that of current Yup’ik elders - but has dropped to low levels.

- Decreased marine food intake and vitamin D levels in pregnant women could put their infants at risk for vitamin D deficiency rickets.
Prevention of Rickets

- Prevention of vitamin D deficiency is crucial to preventing the complications of Vitamin D Deficiency, Rickets, and the complications/side effects from treatment of rickets.

- Organization recommendations for vitamin D intake to prevent vitamin D deficiency and rickets:
  - American Academy of Pediatrics (AAP)
  - Canadian Pediatric Society (CPS)
  - Endocrine Society
  - European Society for Pediatric Endocrinology (ESPE)
  - Pediatric Endocrine Society (PES)
Vitamin D Supplementation Guidelines

  • Any breastfed or partially breastfed infant: **400 IU Vit D/day**
  • Non-breastfed infants who take <1 L/day of vitamin D fortified milk/formula: **400 IU Vit D/day**
  • Infant consuming >1 L/day fortified infant formula or vitamin-D fortified milk: **no supplementation** (?)
  • Older children and adolescents: if dietary intake is inadequate: **600 IU Vit D/day**

  • Breastfed infants: **400 IU Vit D/day** until infant diet includes at least 400 IU per day from other sources
  • Northern Native communities during winter: **800 IU Vit D/day**

  • Infants and children 0-1 year: at least **400 IU Vit D/day**
  • Children 1 year and older: at least **600 IU Vit D/day**
  • Whether this is sufficient to provide all the health benefits of vitamin D is not currently known
Conclusions

• Vitamin D deficient rickets has reemerged as an important public health problem, associated with limited sun exposure and limited intake of foods high in Vitamin D

• There is an increased risk of vitamin D deficiency and therefore vitamin D deficient rickets in infants/children who live at higher latitudes, have darker skin color, breastfeed and do not receive vitamin D supplementation

• Vitamin D deficient rickets is associated with increased morbidity and mortality such as poor growth, poor weight gain, developmental delay, hypocalcemia, seizures

• Prevention of vitamin D deficiency is the key to eradicating rickets