RICKETS AND VITAMIN D DEFICIENCY IN CHILDREN

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OBJECTIVES

- Understand the causes and prevention of rickets and vitamin D deficiency in Alaska
- Know the diagnosis and management of rickets
- Learn about the recent vitamin D deficiency and rickets study performed in Alaska Native children
CASE

• 19 month old girl from Bethel region, seen in April by a pediatrician in Anchorage for ear recheck s/p 10 days Augmentin for recurrent otitis media
• Mother was also concerned because her legs seemed bowed
  • Mother noted bowing of legs over last 6 months
  • Breastfeeds 6-8 times per day, plus some table foods and juice (8-12oz/day)
  • No vitamin D supplementation
  • No seizures or twitching
• PMH: recurrent otitis media, otherwise negative
• FH: + for Kuskokwim syndrome, otherwise negative
Girls
Length and Weight

Name: [redacted]
Date: 4/6/2012

diagnosis
CASE

On Exam:

- White sclera
- 4 teeth upper and lower, premolars coming in on bottom
- No tetany; negative Chvostek sign
- Enlargement of sizes of wrists was noted
- Mild ankle flaring
- Bilateral genu varus
  - thigh – foot angle >20 degrees

Labs and studies were ordered...
VITAMIN D

- Synthesized in the skin using UVB photons (or absorbed from food)
- Conjugated by the liver to 25(OH)D₃
- Activated in the kidney to 1,25(OH)₂D₃
- Increases absorption of calcium (and phosphorous) from the intestines (and bone)
- With sufficient Ca and Phos, increases bone calcification

• Sources (less than 10% vit D obtained from diet):
  • Vitamin D3 (cholecalciferol) is synthesized from the skin, obtained from animals
  • Vitamin D2 (ergocalciferol) is obtained from plants
  • Vitamin D crosses the placenta
    • (but minimal in breastmilk)
• 25-hydroxyvitamin D—the conjugated form (prehormone)
  • Reflects vitamin D stores and nutritional status
• 1,25-dihydroxyvitamin D (calcitriol)—the active form (hormone)
  • Reflects renal function
  • **Increases calcium** absorption from intestines, bone, and kidney
25O H-Vitamin D receptors present in:
- Small intestines, activated T and B lymphocytes, beta islet cells of pancreas, most organs in the body including brain, heart, skin, gonads, prostate, breast, mononuclear cells

**Important effects of vitamin D:**
- Immune system:
  - Autoimmune diseases s/a T1DM, MS, RA, IBD a/w vit D deficiency
  - Vit D deficiency a/w Increased risk of recurrent respiratory infections, ear infections
- Vit D sufficiency may be assoc w/ lower risk of certain cancers (breast, prostate, colon)
- Psychiatric conditions: adequate Vit D assoc w/ decreased risk of schizophrenia and low Vit D assoc w/ SAD and mood disturbances, bipolar disorder

• Eucalcemia is important for:
  • Intercellular communication
  • Intracellular signal transduction
  • Neural transmission especially at neuromuscular junction
    \( \text{decreased extracellular Ca} \rightarrow \) neuromuscular excitability
  • Cell-cell adhesion
  • Clotting
  • Muscle contraction
  • Cardiac rhythm
  • Enzyme action
  • Synthesis and secretion of endocrine and exocrine factors
  • Cell proliferation
  • Survival
CALCIUM

- Calcium is tightly regulated by:
  - Parathyroid hormone
  - Vitamin D
    - Sufficient D, net Ca abs is 30%, up to 60-80%
    - Insufficient D, net Ca abs 10-15%
VITAMIN D DEFICIENCY

• **Nutritional deficiency:**
• Increasing in prevalence
• Risk factors—insufficient dietary intake and sun exposure:
  • Darker skin color; Use of sunscreen
    • Melanin is a natural sunscreen and absorbs UVB photons
    • Sunscreen above SPF 8 reduces capacity of skin to produce vitamin D by >95%
  • Breastfeeding exclusively without Vit D supplementation
    • Breastmilk contains inadequate vitamin D to support skeletal health
  • Northern latitudes (above 37° latitude)
    • Above 37° Latitude during Nov-Feb, ~80-100% decrease (dep on latitude) in the number of UVB photons reaching the earth’s surface
  • Anticonvulsants, antifungals, glucocorticoids
  • Limited intake of foods high in Vitamin D (very few exist naturally)

VITAMIN D DEFICIENCY

• Other causes (that is, besides nutritional)
  • Gastrointestinal
    • Decreased absorption if fat malabsorption
    • Decreased conjugation if liver disease
  • Renal disease
    • Decreased activation of 1,25(OH)2D due to decreased 1-alpha hydroxylase
  • Obesity or have had bariatric surgery
RICKETS

- First described in the 17th century
- Became endemic at the beginning of the 20th century with industrialization until it was discovered that exposure to sunlight and cod liver oil could prevent and treat rickets.

RICKETS

Game addict kids hit by ‘extinct’ bone disease

By EMMA MORTON, Health and Science Editor
Published: 13 Nov 2019

CRIPPLING bone disease rickets has made a shock comeback - because kids are staying indoors with video games instead of playing in the sunshine.

Rickets: Not a Disease of the Past

LINDA S. NIELD, M.D., West Virginia University School of Medicine, Morgantown, West Virginia
PRASHANT MAHAJAN, M.D., M.P.H., Wayne State University School of Medicine, Detroit, Michigan
APARNA JOSHI, M.D., Children’s Hospital of Michigan, Detroit, Michigan
DEEPAK KAMAT, M.D., PH.D., Wayne State University School of Medicine, Detroit, Michigan

Reemerging Nutritional Rickets

A Historical Perspective
Kunaravul Rajakumar, MD; Stephen B. Thomas, PhD

Science in medicine

Resurrection of vitamin D deficiency and rickets
Michael F. Holick
Department of Medicine, Section of Endocrinology, Nutrition, and Diabetes, and Vitamin D, Skin and Bone Research Laboratory, Boston University Medical Center, Boston, Massachusetts, USA.
RICKETS

- Failure of mineralization of growing bone and cartilage
- A state of extreme vitamin D deficiency
- Peak incidence between 3 and 18 months of age
RICKETS

- Bone mineralization requires sufficient extracellular calcium and phosphorous; AlkP essential for normal mineralization (increased with high bone turnover)
- Insufficient vitamin D →
- Insufficient calcium →
- PTH increases to maintain eucalcemia →
- In the kidney, PTH increases Ca reabsorption, Phos excretion, and increases 25OHD activation to 1,25OHD; in the bone, PTH increases Ca release into blood →
- Decreased Ca*P product in the bone →
- Decreased bone mineralization → RICKETS
- With ongoing vitamin D deficiency → ongoing insufficient Ca → HYPOCALCITEMIA
# Rickets – Biochemical Abnormalities

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ca</th>
<th>P</th>
<th>AlkP</th>
<th>1,25D</th>
<th>25D</th>
<th>PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca def</td>
<td>v. lo</td>
<td>Lo</td>
<td>v. hi</td>
<td>Hi</td>
<td>N</td>
<td>hi</td>
</tr>
<tr>
<td>P def</td>
<td>Nl, hi</td>
<td>v. lo</td>
<td>v. hi</td>
<td>Hi</td>
<td>N</td>
<td>N,lo</td>
</tr>
<tr>
<td>Mild Vit D def</td>
<td>Nl/lo</td>
<td>Nl/lo</td>
<td>Hi</td>
<td>Nl</td>
<td>Lo</td>
<td>Nl/hI</td>
</tr>
<tr>
<td>Mod vit D def</td>
<td>Nl,lo</td>
<td>Lo</td>
<td>v. hi</td>
<td>Lo, nl,</td>
<td>Lo</td>
<td>hi</td>
</tr>
<tr>
<td>Severe vit D def</td>
<td>Lo</td>
<td>Lo</td>
<td>vv. hi</td>
<td>Lo</td>
<td>v. lo</td>
<td>v. hi</td>
</tr>
<tr>
<td>LOF CYP27 (25hydroxylase)</td>
<td>lo</td>
<td>lo</td>
<td>hi</td>
<td>lo</td>
<td>lo</td>
<td>hi</td>
</tr>
<tr>
<td>LOF CYP1a (1ahydroxylase)</td>
<td>v. Lo</td>
<td>v. lo</td>
<td>v.hi</td>
<td>v. lo</td>
<td>Nl</td>
<td>v. hi</td>
</tr>
<tr>
<td>LOF VDR (vit D res)</td>
<td>lo</td>
<td>v.lo</td>
<td>v. hi</td>
<td>v. hi</td>
<td>Nl</td>
<td>v. hi</td>
</tr>
<tr>
<td>LOF PHEX (XLH)</td>
<td>Nl</td>
<td>v. lo</td>
<td>Hi</td>
<td>N, lo</td>
<td>nl</td>
<td>nl</td>
</tr>
</tbody>
</table>
RICKETS—CLINICAL PICTURE

- Symptoms and signs of bone deformity +/- bone pain
- Symptoms and signs of hypocalcemia may be associated
- 3 stages of rickets
  - First stage of rickets
    - Osteopenia, subclinical or overt hypocalcemia
  - Second stage
    - Decreased bone mineralization → bone pain
  - Third stage
    - Bone changes are more severe, hypocalcemia can be severe
RICKETS – CLINICAL PICTURE

- Irritability, pain
- Delay in gross motor development
- Widening of the wrists and ankles
- Genu varum or valgum
- Prominent costochondral junction (rachitic rosary)
- Delayed closure of fontanels
- Craniotabes
- Frontal bossing
- Delayed tooth eruption, increased risk of caries
- Poor growth
- Increased susceptibility to infections
- Severe hypocalcemia—tetany, seizures (more often infancy or adolescence with increased growth velocity)
HYPOCALCEMIA

Usually asymptomatic until serum Ca < 7.5 mg/dl

- Jitteriness, confusion
- Poor appetite/vomiting
- Seizure, apneic episodes
- Tetany, laryngospasm
- Chvostek, Trousseau signs
- Hypocalcemic cardiomyopathy
- ECG changes: long QTc, T-wave flattening and inversion, U-wave, narrow QRS, prolonged ST, reduced PR, narrow QRS
BACK TO OUR CASE

- Labs obtained:
- CBC consistent with anemia
- Thyroid studies normal; Celiac screen normal
- Renal function panel:
  - Calcium normal at 9.3 mg/dl
  - Phosphorous low at 2.8 mg/dl
  - Alkaline phosphatase high at 531 U/L
  - Intact PTH very high at 253.3 pg/mL
  - Creatinine normal at 0.2 mg/dl
  - Magnesium normal at 2.1 mg/dL
  - Albumin normal at 4.5 g/Dl
- 25-hydroxyvitamin D was less than 4
- 1,25-dihydroxyvitamin D was normal at 70
What stage of vitamin D deficiency would you say she is in?

<table>
<thead>
<tr>
<th></th>
<th>Ca</th>
<th>P</th>
<th>AlkP</th>
<th>1,25D</th>
<th>25D</th>
<th>PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Vit D def</td>
<td>NL/lo</td>
<td>NL/lo</td>
<td>Hi</td>
<td>NL</td>
<td>Lo</td>
<td>NL/hi</td>
</tr>
<tr>
<td>Mod vit D def</td>
<td>NL,lo</td>
<td>Lo</td>
<td>v. hi</td>
<td>Lo,nl,hi</td>
<td>Lo</td>
<td>hi</td>
</tr>
<tr>
<td>Severe vit D def</td>
<td>Lo</td>
<td>Lo</td>
<td>v. hi</td>
<td>Lo</td>
<td>v. lo</td>
<td>v. hi</td>
</tr>
</tbody>
</table>
DIAGNOSIS OF RICKETS

• Depends on presence of clinical features and radiologic and laboratory abnormalities

• Radiologic studies: Wrist or Knee XRays
  • Osteopenia, cortical thinning of long bones
  • Stress fractures
  • Metaphyseal widening and fraying, splaying, cupping

• Laboratory studies: Alk Phos is a good screen for rickets; 25OHD level is needed for assessment of Vitamin D status
  • Hypophosphatemia, varying degrees of hypocalcemia
  • Increased alkaline phosphatase
  • Increased PTH
  • Low 25OHD levels
DIAGNOSIS

• 25-hydroxyvitamin D—the conjugated form
  • Reflects vitamin D stores and nutritional status
  • 1/2 life is 2-3 weeks

• 1,25-dihydroxyvitamin D—the active form
  • Not a good indicator of Vit D sufficiency (1/2 life is 4 hrs, altered by subtle changes in Ca and PTH)

TABLE 5 Vitamin D Status in Relation to 25(OH)-D Levels

<table>
<thead>
<tr>
<th>Vitamin D Status</th>
<th>25(OH)-D Level, nmol/L (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe deficiency</td>
<td>≤12.5 (5)</td>
</tr>
<tr>
<td>Deficiency</td>
<td>≤37.5 (15)</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>37.5–50.0 (15–20)</td>
</tr>
<tr>
<td>Sufficiency</td>
<td>50–250 (20–100)</td>
</tr>
<tr>
<td>Excess</td>
<td>&gt;250 (100)</td>
</tr>
<tr>
<td>Intoxication</td>
<td>&gt;375 (150)</td>
</tr>
</tbody>
</table>

Ped, 122, 2, 2008
• Started 3000 IU cholecalciferol (vit D 3) daily plus 50mg/kg/day elemental Calcium divided TID
• Recommended that her breastfeeding mother begin to take 4000 IU vitamin D
• Monitored labs monthly for 3 months
  • After 1 month, her Ca was normal at 9.2, Phos was normal at 5, Alk phos was lower at 348—decreased her Ca to 30mg/kg/day divided BID
  • After 3 months, her intact PTH was normal at 38, Ca still normal at 10, Phos still normal at 4.5, Alk phos normal at 247, urine Ca/Cr was normal at 0.13, 25OHD normal at 30, 1,25OHD normal, Xrays showed improvement in bowing and metaphyseal fraying
TREATMENT

- Replace vitamin D and calcium
- Proposed treatment plans by AAP:
  - Pharmacological doses of vitamin D: 1000-10,000 IU per day for 8-12 weeks depending on age of the child, then maintain at 400-1000 IU per day
    - 1000-5000 IU/day up to age 1, >5000 IU/day after age 1
  - Stoss therapy: 100,000 – 600,000 IU vitamin D orally, over 1-5 days, then maintain at 400-1000 IU vitamin D per day or 50,000 IU vitamin D2 weekly for 8 weeks (teens and adults only)
  - Calcium: 30-75 mg/kg/day elemental Ca in 3 divided doses (start at higher dose, then wean down to lower end of the range over 2-4 weeks
  - May also need Calcitriol (1,25D) if hypocalcemic
TREATMENT

• Monitoring of therapy (proposed, by AAP)
  • At 1 month: measure Ca, Phos, Alk Phos
  • At 3 months, measure Ca, Phos, Mg, Alk Phos, iPTH, 25OHD, urine Ca/Cr and recheck X-rays
  • At 1 year and annually, measure 25OHD
### TABLE 8
Available Vitamin D, Calcium, and Phosphorus Preparations

**Vitamin D and its analogs**
- Vitamin D<sub>2</sub> (ergocalciferol): available in 3 forms
  - 200 μg/mL (8000 IU/mL) solution in propylene glycol solution
  - 1250 μg (50 000 IU) gelcaps
- 625- and 1250-μg (25 000- and 50 000-IU) tablets have been available
- Trade names: Calciferol, Drisdol, most children’s chewable multivitamins including Flintstones and Garfield, prenatal and women’s multivitamins

**Vitamin D<sub>3</sub>** (cholecalciferol): may be 3 times as potent as vitamin D<sub>2</sub>
- Trade names: Delta-D, Poly-Vi-Sol
- 1.0 μg of vitamin D = 40 IU; 1.0 mg of vitamin D = 40 000 IU

**Calcium preparations**
- Calcium gluconate: 10% injection, preservative-free solution, 100 mg/mL; elemental calcium 9 mg/mL
- Calcium chloride: 10% injection, preservative-free solution, 100 mg/mL; elemental calcium 27.2 mg/mL
- Calcium carbonate: oral suspension 1250 mg/5 mL (elemental calcium 500 mg/5 mL); chewable tablets (400 mg elemental calcium per gram of calcium carbonate); trade names: Tums, Viactiv, Caltrate, OsCal, and others
- Calcium gluconate: oral solution 1800 mg/5 mL (elemental calcium 115 mg/5 mL); trade name: Calcioate
- Tribasic calcium phosphate: caplet containing 600 mg of calcium and 280 mg of phosphorus (390 mg of elemental calcium per gram of tribasic calcium phosphate); Trade names: Posture
HYPOCALCEMIA ACUTE TREATMENT

If Symptomatic - tetany, sz, apnea, heart failure, laryngospasm

• Slow (≤1 ml/min) IV infusion 10% Ca gluconate 1 ml/kg
  • 100 mg/ml Ca Gluconate = 9 mg/ml elemental Ca
  • Cardiac monitoring (bradycardia, shortened QTc due to IV Ca); close attention to infusion site if not central IV (risk of tissue necrosis if peripheral IV infiltration)

• If Mg low, replace with 0.1-0.2 ml/kg 50% Mg Sulfate
WHEN TO REFER TO ENDO

• If no healing after 3 months of Vit D and Ca replacement
  • Concern for malabsorption, liver disease, adherence
• When considering other causes of rickets (not Vit D deficiency)
  • Rickets <6 months old or between 3 and 10 years old
  • Xrays that show periostal reaction and moth-eaten metaphysis rather than splaying, cupping, etc.
  • Normal levels of AlkP, 25OHD, very low or very high levels of 1,25OHD, high BUN and Cr
• Severe hypocalcemia
PREVENTION

• Prevention of vitamin D deficiency is crucial to preventing the complications of Vit D Deficiency, Rickets, and the complications/side effects of treatment of vitamin D deficiency
  • Risks of treatment include hypercalcemia, hypercalciuria, kidney stones
• AAP, IOM, and Endocrine Society recommendations for vitamin D intake to prevent vitamin D deficiency
2008 AAP Guidelines (Ped 2008; 122; 1142)
• Vitamin D insufficiency is 25OHD below 20ng/ml
• Vitamin D deficiency is 25OHD below 15ng/ml

2010 Institute of Medicine Guidelines
• Vitamin D deficiency is 25OHD below 20ng/ml

2011 Endocrine Society Clinical Practice Guidelines
• Vitamin D deficiency is 25OHD below 20 ng/ml;
  Vitamin D insufficiency is 25OHD 21-29 ng/ml
PREVENTION

• AAP Guidelines:
  • Any breastfed or partially breastfed infant should be supplemented with **400 IU Vitamin D** (unlikely that a breastfed infant would consume 1L of formula/day) beginning within the first few days of life
  • If formula fed infants are receiving at least 1 L of formula per day, vitamin D supplementation may not be necessary (infant formulas contain 400 IU/L vit D)
  • All nonbreastfed infants and older children who receive <1 L/day of vitamin D fortified milk/formula: should receive **400 IU Vit D** supplement
  • Older children and adolescents, supplementation with **400 IU Vit D** is warranted
  • Those with increased risk (darker skin color, decreased sun exposure, fat malabsorption, anticonvulsant medications (induce cyto p450) may require even higher doses

• Endo Society Guidelines:
  • Infants 0-1 year require at least **400 IU Vit D** daily
  • Children 1-18 years require at least **600 IU Vit D** daily
  • Maintaining 25OHD above 30 consistently may require at least **1000 IU Vit D** per day
  • Obese children or children taking antifungals, anticonvulsants, glucocorticoids, & AIDS meds require **2-3 times more** vit D for their age group

• IOM Guidelines
  • Infants 0-1 year require at least **400 IU Vit D** daily
  • Children and adults (<70 y.o) require at least **600 IU Vit D** daily

Incidentally, 400 IU is the amount of vitamin D measured in a teaspoon of cod liver oil
**PREVENTION**

- **Dietary sources of vit D**
  - Oily fish such as salmon
    - Frying fish reduces active vit D content by ~50%
  - Liver and Organ meats
  - Egg yolks
  - Foods fortified with Vit D (infant formulas, some milk and OJ)

- **Vitamin D in breastmilk**
  - Vit D content in breast milk averages ~22 IU/L in a vitamin D sufficient mother
  - Assuming average consumption of 750ml/day, exclusive breast feeding provides 11-38 IU/day Vit D
# Vitamin D Content of Foods

<table>
<thead>
<tr>
<th>Food</th>
<th>Vitamin D Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod liver oil</td>
<td>~400-1,000 IU/teaspoon vitamin D₃</td>
</tr>
<tr>
<td>Salmon, fresh wild caught</td>
<td>~600-1,000 IU/3.5 oz vitamin D₃</td>
</tr>
<tr>
<td>Salmon, fresh farmed</td>
<td>~100-250 IU/3.5 oz vitamin D₃, vitamin D₂</td>
</tr>
<tr>
<td>Salmon, canned</td>
<td>~300-600 IU/3.5 oz vitamin D₃</td>
</tr>
<tr>
<td>Sardines, canned</td>
<td>~300 IU/3.5 oz vitamin D₃</td>
</tr>
<tr>
<td>Mackerel, canned</td>
<td>~250 IU/3.5 oz vitamin D₃</td>
</tr>
<tr>
<td>Tuna, canned</td>
<td>236 IU/3.5 oz vitamin D₃</td>
</tr>
<tr>
<td>Shiitake mushrooms, fresh</td>
<td>~100 IU/3.5 oz vitamin D₂</td>
</tr>
<tr>
<td>Shiitake mushrooms, sun-dried</td>
<td>~1,600 IU/3.5 oz vitamin D₂</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>~20 IU/yolk vitamin D₃ or D₂</td>
</tr>
<tr>
<td>Sunlight/UVB radiation</td>
<td>~20,000 IU equivalent to exposure to 1 minimal erythemal dose (MED) in a bathing suit. Thus, exposure of arms and legs to 0.5 MED is equivalent to ingesting ~3,000 IU vitamin D₃.</td>
</tr>
<tr>
<td>Fortified milk</td>
<td>100 IU/8 oz, usually vitamin D₃</td>
</tr>
<tr>
<td>Fortified orange juice</td>
<td>100 IU/8 oz vitamin D₃</td>
</tr>
<tr>
<td>Infant formulas</td>
<td>100 IU/8 oz vitamin D₃</td>
</tr>
<tr>
<td>Fortified yogurts</td>
<td>100 IU/8 oz, usually vitamin D₃</td>
</tr>
<tr>
<td>Fortified butter</td>
<td>56 IU/3.5 oz, usually vitamin D₃</td>
</tr>
<tr>
<td>Fortified margarine</td>
<td>429 IU/3.5 oz, usually vitamin D₃</td>
</tr>
<tr>
<td>Fortified cheeses</td>
<td>100 IU/3 oz, usually vitamin D₃</td>
</tr>
<tr>
<td>Fortified breakfast cereals</td>
<td>~100 IU/serving, usually vitamin D₃</td>
</tr>
</tbody>
</table>
# TABLE 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Calcium Intake, mg/d (mmol/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 mo&lt;sup&gt;a&lt;/sup&gt;</td>
<td>210 (5.3)</td>
</tr>
<tr>
<td>7–12 mo&lt;sup&gt;b&lt;/sup&gt;</td>
<td>270 (6.8)</td>
</tr>
<tr>
<td>1–3 y</td>
<td>500 (12.5)</td>
</tr>
<tr>
<td>4–8 y</td>
<td>800 (20.0)</td>
</tr>
<tr>
<td>9–18 y</td>
<td>1300 (32.5)</td>
</tr>
<tr>
<td>19–50 y</td>
<td>1000 (25)</td>
</tr>
<tr>
<td>50 to &gt;70 y</td>
<td>1200 (30)</td>
</tr>
<tr>
<td>Food</td>
<td>Serving Size</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td><strong>Dairy foods</strong></td>
<td></td>
</tr>
<tr>
<td>Whole milk</td>
<td>1 cup (244 g)</td>
</tr>
<tr>
<td>Low-fat (1%) milk</td>
<td>1 cup (244 g)</td>
</tr>
<tr>
<td>Nonfat milk</td>
<td>1 cup (245 g)</td>
</tr>
<tr>
<td>Yogurt, nonfat, fruit variety</td>
<td>6 oz (170 g)</td>
</tr>
<tr>
<td>Frozen yogurt, vanilla, soft serve</td>
<td>1/2 cup (72 g)</td>
</tr>
<tr>
<td>Cheese</td>
<td>1 oz slice (28 g)</td>
</tr>
<tr>
<td>Cheese, pasteurized, processed</td>
<td>1 3/4 oz slice (21 g)</td>
</tr>
<tr>
<td>Cheese, ricotta, part skim milk</td>
<td>1/2 cup (124 g)</td>
</tr>
<tr>
<td><strong>Non-dairy foods</strong></td>
<td></td>
</tr>
<tr>
<td>Salmon, sockeye canned, drained, with bones</td>
<td>3 oz (85 g)</td>
</tr>
<tr>
<td>Tofu, firm, prepared with calcium sulfate and magnesium chloride</td>
<td>1/2 cup (126 g)</td>
</tr>
<tr>
<td>White beans, cooked, boiled</td>
<td>1 cup (179 g)</td>
</tr>
<tr>
<td>Broccoli, cooked</td>
<td>1 cup, chopped (156 g)</td>
</tr>
<tr>
<td>Collards, cooked, boiled, drained</td>
<td>1 cup, chopped (190 g)</td>
</tr>
<tr>
<td>Baked beans, canned</td>
<td>1 cup (253 g)</td>
</tr>
<tr>
<td>Tomatoes, canned, stewed</td>
<td>1 cup (255 g)</td>
</tr>
<tr>
<td><strong>Foods fortified with calcium</strong></td>
<td></td>
</tr>
<tr>
<td>Calcium-fortified orange juice</td>
<td>1 cup (240 mL)</td>
</tr>
<tr>
<td>Selected fortified breakfast cereals</td>
<td>3/4–1 cup (30 g)</td>
</tr>
<tr>
<td>Instant oatmeal, fortified, plain, prepared with water</td>
<td>1/2 cup (117 g)</td>
</tr>
<tr>
<td>English muffin, plain, enriched, with calcium propionate</td>
<td>1 muffin (57 g)</td>
</tr>
<tr>
<td>Calcium-fortified soy milk</td>
<td>1 cup (240 mL)</td>
</tr>
</tbody>
</table>
# Calcium and Vitamin D Content of Some Traditional Foods

<table>
<thead>
<tr>
<th>Food</th>
<th>Calcium (mg)</th>
<th>Vitamin D (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chum Salmon, canned with bone (3 oz)</td>
<td>212</td>
<td>328</td>
</tr>
<tr>
<td>Sockeye Salmon, canned (3 oz)</td>
<td>197</td>
<td>715</td>
</tr>
<tr>
<td>King Salmon, with skin, kippered (3 oz)</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>Blueberries (1 cup)</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Muktuk (3.5 oz)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Beluga Whale Oil</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Seal Flesh (100g)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Seal Oil (100g)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Caribou (3 oz)</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>


[www.nativeknowledge.org](http://www.nativeknowledge.org)

[Nutritiondata.self.com](http://Nutritiondata.self.com)
TAKE HOME POINTS

• Vitamin D deficiency and Rickets are much more common problems today than in recent history.
• Prevention of vitamin D deficiency is key to preventing rickets and likely other impacts of deficiency of this ubiquitous hormone.
• Infants require minimum 400 IU daily and children require minimum 600 IU daily.
• Treatment of Vit D deficiency and rickets requires replacement Vit D with 1000-10,000 IU vit D plus calcium.
• More information is needed to know the true prevalence of Vit D deficiency and Rickets in Alaska and the effects of vitamin D supplementation on preventing disease.
RICKETS AND SEVERE VITAMIN D DEFICIENCY IN ALASKA NATIVE CHILDREN

AREA IRB PROTOCOL # 2012-06-020

Authors: Rosalyn Singleton MD, MPH, Rachel Lescher MD, Bradford D. Gessner MD, Matthew Benson MD, Lisa Bulkow MS, John Rosenfeld MD, Timothy Thomas MD, Robert C. Holman MS, Dana Haberling MS, Gail Thompson RN, Michael Bruce MD, James Tiesinga MD, Thomas Hennessy MD.

Institutions: Alaska Native Tribal Health Consortium, Anchorage, AK Arctic Investigations Program, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Centers for Disease Control and Prevention (CDC), Anchorage, AK Southcentral Foundation, Anchorage, AK Division of High-Consequence Pathogens and Pathology, NCEZID, CDC, Atlanta, GA.
BACKGROUND: RICKETS IN ALASKAN CHILDREN

Rickets cases have been identified in Alaskan children, including Alaska Native children, for many years:

- 1997 article described 5 cases of rickets – 3 black and 2 Alaska Native – 11-22 months, all partly/completely breastfed.
  

- 2003 article showed 11% of WIC children with 25OH Vit D level <15 ng/ml.
  

Risk factors for developing rickets are characteristics of those living in Alaska → Alaskan children may be at higher risk.
METHODS: RETROSPECTIVE DATA ANALYSIS

We obtained IRB and tribal approval to conduct:

Retrospective analysis of hospitalizations and outpatient visit 2001-2010 with an ICD9 diagnosis of rickets/vitamin D deficiency among American Indian and Alaska Native (AI/AN) children <10 years of age from all US regions using the Indian Health Service (IHS) direct and contract health care data, and hospitalizations for the US general population <10 years of age using the Nationwide Inpatient Sample.
RESULTS: RETROSPECTIVE ANALYSIS
Rickets-associated and Vitamin D deficiency-associated hospitalization rates/100,000/year in American Indian/Alaska Native children and the general United States child population <10 years, 2001-2010.

The Rickets hospitalization rate in Alaska Native children was 2-fold higher than the U.S. rate (2.2 vs. 1.2/100,000/yr)
Rickets-associated and Vitamin D deficiency-associated outpatient visit rates/100,000/year in American Indian/Alaska Native children <10 years, 2001-2010.

The outpatient visit rate for rickets rate in Alaska Native children was 3-fold higher than any other American Indian child population (33.1 vs. 4.3-10.4/100,000/yr); however, the visit rate for vitamin D deficiency was similar.
METHODS: CASE CONTROL STUDY

- Case-control study using chart reviews in Alaska regions.
  - Rickets cases were identified as children <10 years with clinical/radiographic evidence of rickets and severe vitamin D deficiency defined as 25 OH Vitamin D level <15 ng/mL, diagnosed during 1999-2012.
  - Cases were matched to 3 controls by birthdate and region.
RESULTS: CASE-CONTROL STUDY
Rickets and Severe Vitamin D deficiency cases
Alaska Native children <10 years by year of diagnosis, 1999-2012

Number of rickets cases were similar in the early (1999-2005) and late (2006-2013) periods, while vitamin D deficient cases increased in the late period.

* Other rickets: Children with Rickets/Vitamin D deficiency secondary to hepatic disease or malabsorption.
Alaska Native Rickets and Vitamin D deficiency Cases by Month of Diagnosis
Age at diagnosis of Alaska Native children < 10 years of age with confirmed vitamin D deficiency and rickets, 1999-2012.

Among the 16 confirmed rickets cases, the mean age of diagnosis was 0.98 years, 63% (n=10) were aged <1 year. Among the 14 children with confirmed vitamin D deficiency, the mean age at diagnosis was 4.04 years.
<table>
<thead>
<tr>
<th>No.</th>
<th>Age dx (mos)</th>
<th>Sex</th>
<th>Laboratory results at Diagnosis</th>
<th>Presenting Reason</th>
<th>Radiographic findings</th>
<th>Physical exam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>25OH vit D (ng/mL)</td>
<td>Calcium (mg/dl)</td>
<td>Alkaline Phos (IU/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>M</td>
<td>5</td>
<td>6</td>
<td>927</td>
<td>Pneumonia, FTT</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>M</td>
<td>0</td>
<td>6</td>
<td>626</td>
<td>FTT, Hypocalcemic Seizure</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>M</td>
<td>4</td>
<td>6</td>
<td>1057</td>
<td>Hypocalcemic Seizure</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>F</td>
<td>6</td>
<td>9</td>
<td>1240</td>
<td>Rickets on xray</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>F</td>
<td>7</td>
<td>8</td>
<td>953</td>
<td>VSD</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>M</td>
<td>16</td>
<td>10</td>
<td>469</td>
<td>FTT, Rachitic Rosary</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>M</td>
<td>7</td>
<td>8</td>
<td>1192</td>
<td>Other</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>M</td>
<td>7</td>
<td>8</td>
<td>124</td>
<td>FTT</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>M</td>
<td>5</td>
<td>7</td>
<td>504</td>
<td>Seizure meds</td>
</tr>
<tr>
<td>10**</td>
<td>12</td>
<td>F</td>
<td>10</td>
<td>6</td>
<td>628</td>
<td>Hypocalcemic Seizure, Seizure meds</td>
</tr>
<tr>
<td>11</td>
<td>15</td>
<td>M</td>
<td>8</td>
<td>977</td>
<td></td>
<td>FTT, Leg Bowing</td>
</tr>
<tr>
<td>12</td>
<td>19</td>
<td>M</td>
<td>7</td>
<td>9</td>
<td>756</td>
<td>Leg Bowing, Hyponatreemic Seizure</td>
</tr>
<tr>
<td>13**</td>
<td>20</td>
<td>F</td>
<td>4</td>
<td>9</td>
<td>531</td>
<td>Leg Bowing</td>
</tr>
<tr>
<td>14**</td>
<td>28</td>
<td>M</td>
<td>9</td>
<td>1273</td>
<td></td>
<td>Leg Bowing</td>
</tr>
<tr>
<td>15</td>
<td>29</td>
<td>M</td>
<td>10</td>
<td>288</td>
<td></td>
<td>Leg Bowing</td>
</tr>
<tr>
<td>16</td>
<td>30</td>
<td>M</td>
<td>10</td>
<td>597</td>
<td></td>
<td>Leg Bowing</td>
</tr>
</tbody>
</table>

**Note:** No. 10, 13, and 14 have **double asterisks** indicating they were diagnosed in 2012.
Rickets annual incidence increased by latitude of residence from 0.0 in latitude 50-57 degrees (southeast Alaska), to 21.4 per 100,000 in latitude 70-73 degrees (northern Alaska; p<0.001)
Characteristics of Alaska Native children with **rickets or vitamin D deficiency** diagnosed between 1999 and 2012.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Rickets (A)</th>
<th>Vitamin D Deficiency (B)</th>
<th>Rickets with underlying cause</th>
<th>Rickets/ Vitamin D deficiency (A+B)</th>
<th>p-value A vs B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.98 yrs</td>
<td>4.04 yrs</td>
<td>5.23 yrs</td>
<td>2.41 yrs</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>10 (63%)</td>
<td>4 (25%)</td>
<td>1 (20%)</td>
<td>14 (47%)</td>
<td>0.081</td>
</tr>
<tr>
<td>Sex</td>
<td>12 (75%)</td>
<td>6 (43%)</td>
<td>2 (40%)</td>
<td>18 (60%)</td>
<td>0.135</td>
</tr>
<tr>
<td>Presenting Reason</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Sx (eg. leg bowing)</td>
<td>8 (50%)</td>
<td>2 (14%)</td>
<td>1 (20%)</td>
<td>10 (33%)</td>
<td>0.058</td>
</tr>
<tr>
<td>Failure to Thrive</td>
<td>5 (31%)</td>
<td>1 (7%)</td>
<td>2 (40%)</td>
<td>6 (20%)</td>
<td>0.175</td>
</tr>
<tr>
<td>Seizures</td>
<td>3 (19%)</td>
<td>0</td>
<td>0</td>
<td>3 (10%)</td>
<td>0.228</td>
</tr>
<tr>
<td>Underlying conditions*</td>
<td>1 (6%)</td>
<td>6 (43%)</td>
<td>1 (20%)</td>
<td>7 (23%)</td>
<td><strong>0.031</strong></td>
</tr>
<tr>
<td>One of first 3 above</td>
<td>13 (81%)</td>
<td>3 (21%)</td>
<td>2 (40%)</td>
<td>16 (53%)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Underlying conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>8 (50%)</td>
<td>6 (43%)</td>
<td>2 (40%)</td>
<td>14 (47%)</td>
<td>0.730</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1 (6%)</td>
<td>0</td>
<td>4 (80%)</td>
<td>1 (3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Prematurity</td>
<td>1 (6%)</td>
<td>1 (7%)</td>
<td>0</td>
<td>2 (7%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Seizures</td>
<td>1 (6%)</td>
<td>1 (7%)</td>
<td>0</td>
<td>2 (7%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>5 (31%)</td>
<td>1 (7%)</td>
<td>1 (20%)</td>
<td>6 (20%)</td>
<td>0.175</td>
</tr>
<tr>
<td>Radiologic findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No x-ray</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Normal/negative</td>
<td>3 (19%)</td>
<td>3 (21%)</td>
<td>0</td>
<td>6 (20%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Any evidence</td>
<td>8 (50%)</td>
<td>1 (7%)</td>
<td>0</td>
<td>9 (30%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Metaphyseal changes</td>
<td>6 (38%)</td>
<td>1 (7%)</td>
<td>0</td>
<td>7 (23%)</td>
<td>0.086</td>
</tr>
<tr>
<td>Bowing</td>
<td>4 (25%)</td>
<td>1 (7%)</td>
<td>0</td>
<td>5 (14%)</td>
<td>0.336</td>
</tr>
<tr>
<td>Fracture</td>
<td>2 (13%)</td>
<td>0</td>
<td>0</td>
<td>2 (6%)</td>
<td>0.485</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>1 (6%)</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Rachitic rosary</td>
<td>2 (13%)</td>
<td>0</td>
<td>0</td>
<td>2 (7%)</td>
<td>0.485</td>
</tr>
<tr>
<td>Exam Findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowing</td>
<td>5 (31%)</td>
<td>1 (7%)</td>
<td>1 (20%)</td>
<td>6 (20%)</td>
<td>0.175</td>
</tr>
<tr>
<td>Rachitic Rosary</td>
<td>1 (6%)</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Frontal bossing</td>
<td>1 (6%)</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Wrist flaring</td>
<td>1 (6%)</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Any of above</td>
<td>7 (44%)</td>
<td>1 (7%)</td>
<td>1 (23%)</td>
<td>8 (27%)</td>
<td>0.039</td>
</tr>
<tr>
<td>Vitamin D level -25 OH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>6.5</td>
<td>9.5</td>
<td>6.1</td>
<td>7.98</td>
<td>0.069</td>
</tr>
</tbody>
</table>

*group A (VSD), group B (hypothyroid, CAH, intestinal disaccharidease def, brain malformation, renal disease, apnea), group C (endstage liver disease)*
Case-Control Analysis and Odds Ratios
Cases of Rickets/Vitamin D deficiency compared with matched controls

<table>
<thead>
<tr>
<th></th>
<th>Case N=26</th>
<th>Control N=93</th>
<th>Unmatched OR (p-value)</th>
<th>Matched OR (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 (54%)</td>
<td>39 (42%)</td>
<td>1.62 (0.280)</td>
<td>1.69 (0.249)</td>
</tr>
<tr>
<td><strong>Underlying conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>12 (47%)</td>
<td>2 (2%)</td>
<td>39 (&lt;0.001)</td>
<td><strong>38.1 (0.001)</strong></td>
</tr>
<tr>
<td>Prematurity</td>
<td>2 (8%)</td>
<td>5 (5%)</td>
<td>147 (0.657)</td>
<td>1.62 (0.614)</td>
</tr>
<tr>
<td>Seizures</td>
<td>2 (8%)</td>
<td>1 (1%)</td>
<td>7.67 (0.057)</td>
<td>--</td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>5 (19%)</td>
<td>11 (12%)</td>
<td>1.77 (0.328)</td>
<td>1.70 (0.387)</td>
</tr>
<tr>
<td><strong>GA &lt;37 wks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4/22 (18%)</td>
<td>7/71 (10%)</td>
<td>2.03 (0.291)</td>
<td>2.06 (0.408)</td>
</tr>
<tr>
<td><strong>Ever Breast fed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15/20 (75%)</td>
<td>60/79 (76%)</td>
<td>0.95 (0.930)</td>
<td><strong>1.35 (0.655)</strong></td>
</tr>
<tr>
<td><strong>Ever Exclusively breast fed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10/15 (67%)</td>
<td>39/75 (52%)</td>
<td>1.85 (0.298)</td>
<td><strong>2.13 (0.292)</strong></td>
</tr>
<tr>
<td><strong>Vitamin D in first 6 months</strong> (among cases dx≥6 months)</td>
<td></td>
<td></td>
<td>0.22 (0.017)</td>
<td><strong>0.23 (0.030)</strong></td>
</tr>
</tbody>
</table>

Rickets/Vit D deficiency cases were *more* likely to be diagnosed with malnutrition/FTT than controls (OR 38.1); Cases were *less* likely than controls to have any documentation of vitamin D supplementation in the first 6 months of life (OR 0.23)
FINDINGS

- Rickets cases were young (mean 0.98 years) compared with Vitamin D deficiency (mean 4.4 years).
- Rickets cases presented with seizures/FTT early (first 6 months of life) or leg bowing (after 1 year).
- Malnutrition was a significant risk factor for Rickets/Vitamin D deficiency.
- Breastfeeding was common in Cases (and Controls) but breastfeeding was not a risk factor for Rickets/Vitamin D deficiency.
- Rickets and Vitamin D deficiency cases were less likely to receive infant Multivitamins than Controls.
SUMMARY OF RICKETS/VITAMIN D DEFICIENCY STUDY

• Rickets appears to be more common in Alaska Native children than in the US or in other IHS sites
  • In addition, our calculated incidence of confirmed rickets in AN children <10 years of age from the case control study (4.2/100,000) is higher than incidence estimates in Canadian children except among aboriginal children in the far north

• Rickets increases with increasing latitude
  • Above 37 degrees latitude during November – February, there is an 80-100% decrease in the number of ultraviolet B photons reaching the earth’s surface

• Multivitamin supplementation of newborn infants is important to prevent Vitamin D deficiency
  • Consistent with AAP guidelines that regardless of sunlight and food intake, all breastfed infants/children and those receiving < 1 Liter per day of infant formula receive 400 IU/day of vitamin D supplementation
LIMITATIONS

- Use of IHS/Tribal and NIS data for evaluating US and other IHS site rates
- We were unable to calculate reliable outpatient visit rates for the general U.S. population due to the low disease occurrence
- Our analysis was dependent on documentation of ICD-9-CM codes, laboratory, clinical data, feeding and vitamin D supplementation in electronic medical records and charts
- For the case/control study, some potential cases could not be confirmed because of missing data
- Our case numbers are small, limiting the generalizability of results
IMPLICATIONS AND FUTURE WORK

• Highlights the importance of latitude (ie, sunlight exposure), adequate nutrition, and vitamin D supplementation in breastfed and formula-fed infants.

• Further studies:
  • Explore the relationship between traditional marine diet and maternal Vitamin D levels
  • Assess contribution of traditional Alaska Native diet to healthy vitamin D levels
  • Evaluate methods to optimize vitamin D supplementation/intake in infants and children


CONCLUSIONS

- Vitamin D deficiency and Rickets are much more common problems today than in recent history
  - Our study in Alaska Native children indicate that rickets is more common in Alaska Native children since 2001 than in other American Indian children and than in US children as a whole
- Rickets and vitamin D deficiency are associated with increased morbidity, such as malnutrition, poor growth/weight gain, developmental delay, hypocalcemia/seizures
  - In our study group, we found increased risk of rickets in children who had malnutrition
- Increased risk of vitamin D deficiency and therefore rickets in infants/children who live at higher latitudes, have darker skin color, breastfeed exclusively, and do not receive vitamin D supplementation
  - In our study group, there was no increased risk of rickets in those who ever breastfed exclusively, but there was an increased risk in those who did not receive vitamin D supplementation
- Prevention of vitamin D deficiency is key to preventing rickets and likely other impacts of deficiency of this ubiquitous hormone
  - Infants require minimum 400 IU daily and children require minimum 600 IU daily
- Treatment of Vit D deficiency and rickets requires replacement Vit D
  - 1000-10,000 IU vit D plus calcium
QUESTIONS??

THANK YOU