Biochemical Rickets: What Does Low Vitamin D Mean in Infants?

Imaging of Child Abuse Conference
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Ingrid A. Holm, MD, MPH
Divisions of Genetics and Endocrinology
Children’s Hospital Boston
Harvard Medical School
Overview

• Bone and mineral metabolism
• Skeletal mineralization in the fetus and neonate
• Rickets
• Congenital rickets
Bone

- Mineralized osseous tissue
- Bone marrow
- Endosteum
- Periosteum
- Nerves
- Blood vessels
- Cartilage
Bone is primarily Bone Matrix

- Inorganic portion
  - Laid down as unmineralized osteoid
  - Mineralization - osteoblasts vesicles containing alkaline phosphatase
  - Calcium and phosphate deposition as hydroxyapatite crystals
- Organic portion
  - mainly Type I collagen
  - various growth factors
Bone remodeling

- **Resorption**
- **Reversal**
- **Resting**
- **Formation**
Regulation of bone mineralization
Vitamin D Metabolism

- Inactive precursor
- Reflects vitamin D status
- Marker of vitamin D deficiency

- Active form
- Normal range 15-75 pg/ml
- Concentrations 1000-fold < 25-D
- Higher in infants & adolescents
- No variation with seasons
1,25D responsible for active intestinal calcium transport

- Active, transcellular intestinal calcium transport
  - duodenum
  - when calcium intake is low
  - Facilitated by the carrier protein calbindin –

- Passive, paracellular intestinal calcium transport
  - jejunum and ileum
  - when dietary calcium levels are moderate or high, this pathway responsible for the bulk of calcium absorption
# Categories of Vitamin D deficiency

<table>
<thead>
<tr>
<th>Categories</th>
<th>25D levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient</td>
<td>&gt; 30 ng/ml</td>
</tr>
<tr>
<td>Insufficient</td>
<td>20-30 ng/ml</td>
</tr>
<tr>
<td>Deficient</td>
<td>&lt;20 ng/ml</td>
</tr>
<tr>
<td>Mild</td>
<td>10-20 ng/ml</td>
</tr>
<tr>
<td>Moderate</td>
<td>5-10 ng/ml</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 5 ng/ml</td>
</tr>
</tbody>
</table>

- Institutes of Medicine (IOM): >20 ng/ml is adequate for bone health
Parathyroid Hormone (PTH)

Low concentration of calcium in blood

Release of parathyroid hormone

Efflux of calcium from bone

Decreased loss of calcium in urine

Enhanced absorption of calcium from intestine

Increased concentration of calcium in blood
Regulation of calcium:
Hypocalcemia

- Serum Calcium decreases
  - PTH increases
    - Calcium reabsorbed from kidney
      - Increases 1,25 (OH)_2 D
    - Calcium & phosphorus released from bone
      - Increases calcium absorption
- Major hormones
  - 1,25-dihydroxyvitamin D
  - Parathyroid hormone (PTH)

(c) 2005, Elizabeth Krall, Ph.D.
Mineral metabolism and skeletal physiology in the fetus and neonate
Fetal accretion of calcium with age

Fetus accrues 30g of calcium, 99% in the bones
Maternal-Fetal Calcium Gradient

- Large amounts of calcium and phosphorus are transferred against a concentration gradient from the mother to the fetus
- Calcium and phosphorus levels in the fetus are higher than maternal levels
- Calcium levels maintained despite maternal hypocalcemia
Placental Parathyroid Related Protein (PTHrP)

- Up-regulates active placental calcium transfer
- Chondrocyte differentiation & skeletal development
Sources of fetal calcium

- PTHrP – primary source
- Fetal PTH
  - Controls fetal bone mineralization
  - Responds to maternal hypocalcemia
- Absence of PTH or PTHRP → hypocalcemia
- Intestines
  - Passive absorption of calcium
  - Trivial source since is only amniotic fluid
  - Vitamin D and VDR not important
- Kidney: Calcium excreted into amniotic fluid
Vitamin D is not required for fetal skeletal development or mineralization

- **25D**
  - Crosses the placenta
  - Reflects maternal vitamin D status
- **1,25D (calcitriol)**
  - Levels are low
  - Does not cross the placenta
  - Is produced in the placenta and fetal kidneys
  - Not important for fetal calcium and bone homeostasis
The Neonate

- **At birth:** calcium higher than mother
- **24-36 hrs:** Calcium decreases
  - Switch to dependence on PTH and 1,25D
    - intestinal calcium absorption
    - skeletal calcium stores
    - renal calcium reabsorption
  - Early ↓ ionized calcium → ↑ PTH to adult ranges by 24-48 hours
    - ↑ calcium
    - ↑ 1,25(OH)2D
    - ↓ phosphate
- **3-7 days:** Calcium increases to childhood level
Neonate is dependent on intestinal absorption of calcium

- Initial intestinal absorption of calcium is *passive* – Not dependent on vitamin D
  - Lactose in milk increases calcium diffusion
- As neonate matures
  - Passive absorption of calcium declines
  - Up-regulate vitamin D receptor (VDR) and calcium transporting genes and proteins
- Transition to active transport by weaning
- Explains why preterm babies do not respond to calcitriol (1,25D)
Absence of vitamin D or vitamin D receptor does not affect fetal blood calcium or phosphorus levels or mineralization.
Animal Studies

- Vitamin D deficient rats, mice and pigs: offspring have normal fetal blood calcium, phosphorus, PTH, normal weight, skeletal mineral and calcium content
- Fetuses with no Vitamin D receptor (Vdr) : normal calcium homeostasis and bone mineralization. No difference in morphology, growth plates, and periosteal thickness
Children with genetic disorders of vitamin D do not have rickets at birth

- 25(OH)D-1α-hydroxylase deficiency
  - Unable to convert 25D to 1,25D → Low 1,25D levels
- Hereditary 1,25D resistant rickets
  - Vitamin D receptor defect
  - End-organ resistance to 1,25D → Very high 1,25D levels
- Normal at birth
- Hypocalcemia, hypophosphatemia, and rickets develop late in the 1st year of life or 2nd year of life
Vitamin D deficiency in the mother does not appear to affect the neonate

- No difference in total calcium content in newborns who died of obstetrical accident was the same in neonates born of normal mothers compared to mothers who had extreme vitamin D deficiency.
- Bone mineral content does not differ at any site in babies within 15 days of life in vitamin D sufficient vs. deficient mothers. (Weiler HA 2008)
- Randomized trials of vitamin D supplementation during pregnancy find no effect on cord blood calcium or phosphorus, anthropometric measurement, or radiologic evidence of rickets.
Randomized controlled trial of 1000 IU D vs. no supplement in 126 Asian mothers (Brooke, et. al, Brit Med J 1980)

- Cord blood 25D
  - 10 nmol/l (4 ng/ml) in control group
  - 138 nmol/L (55 ng/ml) in treated group
- No difference in serum calcium between treated and control group
- Craniotabes in 6 infants in control group and 2 in treated group
- No rickets in the 5 infants in control group with hypocalcemia

| TABLE II—Maternal and cord plasma biochemical results in two groups of pregnant Asian women and their infants. Results given as means±SEM |
|---|---|---|---|---|---|
| 25-hydroxy vitamin D (nmol/l) | At allocation (28 weeks, n = 126) | Control group (n = 67) | Treatment group (n = 59) |
| 25-hydroxy vitamin D (nmol/l) | 20.1 ± 0.9 | 16.2 ± 0.9 | 19.3 ± 0.9 | 16.0 ± 2.0 | 13.9 ± 2.0 |
| Calcium (mmol/l) | 1.24 ± 0.03 | 1.24 ± 0.03 | 1.25 ± 0.03 | 1.25 ± 0.02 | 1.25 ± 0.02 |
| Phosphatase (nmol/l) | 0.98 ± 0.02 | 1.72 ± 0.06 | 1.54 ± 0.09 | 2.58 ± 0.02 | 2.71 ± 0.02 |
| Albumin (g/l) | 32.5 ± 0.18 | 29.1 ± 0.4 | 35.5 ± 0.6 | 29.4 ± 0.5 | 34.8 ± 0.7 |
| Total alkaline phosphatase activity (IU/l) | 83.1 ± 1.6 | 117.8 ± 15.9 | 114.3 ± 15.9 | 108.1 ± 15.9 |
| Heat-labile (placental) alkaline phosphatase activity (IU/l) | 77.8 ± 0.6 | 117.0 ± 15.1 | 114.5 ± 15.9 | 110.1 ± 15.9 |
| Vitamin D binding globulin (g/l) | 46.8 ± 1.1 | 36.0 ± 1.8 | 24.0 ± 1.8 | 36.5 ± 1.8 | 23.9 ± 1.2 |

Difference between means (control group v treatment group) significant at: *p < 0.01, †p < 0.05, ‡p < 0.001.

Conversion: SI to traditional units—Plasma 25-hydroxy vitamin D: 1 nmol/l = 0.4 ng/ml. Plasma calcium: 1 mmol/l = 4 mg/100 ml. Plasma phosphate: 1 mmol/l = 3.4 mg/100 ml. Plasma albumin: 1 g/l = 0.1 g/100 ml.
Trial of vitamin D supplementation during pregnancy (400, 2000 or 4000 IU per day) in 350 women (Hollis, et. al., JBMR 2011)

- Neonatal 25(OH)D was significantly correlated with maternal 25(OH)D and was significantly different by treatment group:
  - 18.2 ng/mL, control
  - 22.8 ng/mL, 2000-IU group
  - 26.5 ng/mL, 4000-IU group; p<0.0001

- No difference in clinical status of the newborns
Rickets
History of Rickets

- First described in 1650
- Industrial Revolution 19th century
  - Lack of sunlight, poor diet & poor working conditions of children & mothers
  - Cod liver oil described but not used
- Vitamin D identified in 1920s
  - Lead to treatment & prevention of nutritional rickets
- “Vitamin D refractory” or “vitamin D-resistant rickets”
  - A heterogenous group of disorders of various pathogenesis

- Sir Edward Mellanby, 1939 – Rickets in Vienna in the 1920s
Diagnosis of Rickets

• Usually presents during first 2 years of life & in puberty
• Presenting complaints
  ▫ Decreased growth rate
  ▫ Skeletal deformities – genu varum or valgum
  ▫ Delayed standing or walking
  ▫ Symptoms of hypocalcemia: Muscle weakness, lethargy, recurrent respiratory infections, stridor, irritability, tetany, seizures
Physical Findings in Rickets

• Swelling around growth plates
  ▫ wrists, ankle, costrochondral junction (rachitic rosary)
• Skeletal deformities - mechanical stresses on undermineralized bone
  ▫ Chest deformities: Harrison’s grooves
  ▫ Spine: scoliosis, kyphosis, lordosis
  ▫ Long bones - once children walk
    • Genu varum, genu valgum,
    • Waddling gait
• Craniotabes & frontal bossing

Harrison’s grooves

Rachitic rosary

Craniotabes
Vitamin D Deficiency Rickets (Nutritional Rickets)

- Peak incidence 6-18 months
  - Even in regions where severe vitamin D deficiency during pregnancy is endemic
- The maturation of intestinal calcium absorption to a vitamin D-dependent process likely explains why vitamin D deficient rickets does not usually develop until later
- Typical scenario
  - Unsupplemented breast-fed infants > 6 months of age
    - Breast milk is low in vitamin D (50 IU/L)
  - Darkly pigmented children
  - Limited exposure to the sun
Effect of vitamin D deficiency

- Low Vit D
  - Decreased 1-25 Vitamin D
  - Increased Renal Calcium resorption
  - Increased PTH
  - Increased Intestinal Calcium Absorption
  - Se Calcium Normal or low

- Urine calcium Low

Vitamin D Deficient Rickets

- Stage 1 – Decreased 25(OH)-D $\rightarrow$ decreased 1,25D $\rightarrow$ hypocalcemia
- Stage 2 – secondary hyperparathyroidism $\rightarrow$ normocalcemia
  - Increased conversion of 25(OH)-D to 1,25(OH)2-D
  - Hypophosphatemia
  - Radiographic & clinical manifestations of rickets
- Stage 3 - Further increase in PTH without effect $\rightarrow$ hypocalcemia
  - Severe manifestations of rickets

<table>
<thead>
<tr>
<th></th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>PTH</td>
<td>Normal</td>
<td>High</td>
<td>high</td>
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<tr>
<td>Alkaline phosphatase</td>
<td>High</td>
<td>Higher</td>
<td>Highest</td>
</tr>
<tr>
<td>1,25D</td>
<td>Normal-low</td>
<td>High</td>
<td>Normal-low</td>
</tr>
</tbody>
</table>
Treatment of Nutritional Rickets

- **Vitamin D**
  - 200,000 - 500,000 IU vitamin D in 1 oral dose
    - Lasts about 3 months
  - 5000 IU vitamin D daily for 1-2 months

- **Calcium**
  - 500-1000 mg/d Ca
  - To avoid “hungry bone” syndrome

- **Prevention**
  - 400-800 IU vitamin D

**Recommendations**
- Vitamin D supplements for all breast-fed children over 6 months
So if vitamin D is not involved in fetal bone mineralization, then what is “congenital rickets” and how can it occur?
Congenital rickets

- Very rare – Study of 337.68 million in India (1963-2005): 3 newborns were identified with congenital rickets (Teotia and Teotia, Indian J Med Res. 2008)
- Usually in developing countries when women are covered and vitamin D intake is low
- Results when maternal vitamin D and calcium are low and mothers have osteomalcia
### Table 1: Properties of mothers

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>21</td>
<td>19</td>
<td>27</td>
<td>31</td>
<td>28</td>
<td>26</td>
<td>18</td>
<td>28</td>
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<td>Number of pregnancies</td>
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<td>1</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Time after last pregnancy (y)</td>
<td>—</td>
<td>—</td>
<td>2.5</td>
<td>3</td>
<td>7</td>
<td>1.5</td>
<td>—</td>
<td>4</td>
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<td>Economic class</td>
<td>MEC**</td>
<td>LEC*</td>
<td>LEC*</td>
<td>LEC*</td>
<td>LEC*</td>
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<td>Calcium (mmol/L)</td>
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<td>2.22</td>
<td>2.4</td>
<td>2.27</td>
<td>2.1</td>
<td>2.22</td>
<td>2.37</td>
<td>2.27</td>
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<td>Phosphorus (mmol/L)</td>
<td>1.29</td>
<td>1.35</td>
<td>1.45</td>
<td>1.51</td>
<td>1.29</td>
<td>1.22</td>
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<td>Alkaline phosphatase (IU/L)</td>
<td>227</td>
<td>317</td>
<td>286</td>
<td>304</td>
<td>347</td>
<td>199</td>
<td>461</td>
<td>251</td>
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<td>Parathyroid hormone (micromol/L)</td>
<td>356</td>
<td>405</td>
<td>352</td>
<td>483</td>
<td>517</td>
<td>585</td>
<td>735</td>
<td>491</td>
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<tr>
<td>25-OH-vitamin D (micromol/L)</td>
<td>6.9</td>
<td>—</td>
<td>16.2</td>
<td>—</td>
<td>18.6</td>
<td>13.9</td>
<td>11.6</td>
<td>11.6</td>
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</tbody>
</table>

* LEC: lower economic class, ** MEC: moderate economic class

- Normal ranges:
  - Calcium 2.12–2.62 mmol/L
  - Phosphorus 1.44–1.76 mmol/L
  - alkaline phosphatase 105–210 IU for baby, 30–90 IU for mother
  - PTH 45–270 micromol/L
  - 25-hydroxyvitamin D 23.2–92.8 micromol/L

Oorbak, et. al., West Indian Medical Journal 2007
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**Table 2: Properties of babies**

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<tr>
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<th>Case 1</th>
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<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
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<tbody>
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<td><strong>Age (day)</strong></td>
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<td>50</td>
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<td><strong>Sex</strong></td>
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<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
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<td><strong>Weight (g)</strong></td>
<td>3950</td>
<td>4700</td>
<td>5000</td>
<td>3900</td>
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<td>4000</td>
<td>4800</td>
<td>5300</td>
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<td><strong>Season at birth</strong></td>
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<td>Fall</td>
<td>Fall</td>
<td>Fall</td>
<td>Winter</td>
<td>Fall</td>
<td>summer</td>
<td>Winter</td>
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<td><strong>Type of seizure</strong></td>
<td>GTC*</td>
<td>GTC*</td>
<td>GTC*</td>
<td>GTC*</td>
<td>GTC*</td>
<td>GTC*</td>
<td>PTC**</td>
<td>GTC*</td>
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<tr>
<td><strong>Rachitic rosary</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<td><strong>Soft skull bones</strong></td>
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<td>+</td>
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<tr>
<td><strong>Skeletal sign at radiography</strong></td>
<td>+</td>
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<tr>
<td><strong>Calcium (mmol/L)</strong></td>
<td>1.4</td>
<td>1.65</td>
<td>1.62</td>
<td>1.57</td>
<td>1.72</td>
<td>1.27</td>
<td>1.65</td>
<td>1.9</td>
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<tr>
<td><strong>Phosphorus (mmol/L)</strong></td>
<td>1.16</td>
<td>1.19</td>
<td>1.19</td>
<td>0.93</td>
<td>0.77</td>
<td>1.32</td>
<td>1.35</td>
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<td><strong>Alkaline phosphatase (IU/L)</strong></td>
<td>1492</td>
<td>1722</td>
<td>1175</td>
<td>377</td>
<td>1607</td>
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<td>1642</td>
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<tr>
<td><strong>Parathyroid hormone (micromol/L)</strong></td>
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<td>828</td>
<td>843</td>
<td>1113</td>
<td>675</td>
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<tr>
<td><strong>25-OH-vitamin D (micromol/L)</strong></td>
<td>20.9</td>
<td>6.9</td>
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<td>18.6</td>
<td>11.6</td>
<td>11.6</td>
<td>13.9</td>
<td>9.3</td>
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</table>
Pathophysiology of congenital rickets

Severe maternal calcium depletion

Maternal hypocalcemia

Fetal hypocalcemia

Fetal parathyroids

Fetal bone

Calcium released

PTH

Umbilical cord
Chorionic plate
Chorionic villi
Maternal blood vessels
Intervillous space
Summary

• Fetal calcium and bone development is dependent on placental PTHrP dependent calcium transfer and fetal PTH
• Vitamin D does not play a direct role in fetal calcium and bone development
• Maternal vitamin D supplementation does not effect fetal bone development
• Children with genetic defects of vitamin D metabolism who make no 1,25D or are resistant to 1,25D are normal at birth.
• Intestinal calcium absorption becomes critical after birth and is initially passive but soon becomes vitamin D dependent
• Congenital rickets is very rare and can reliably be excluded as a cause of fractures in young infants in the face of normal calcium, phosphorus, 25D, and alkaline phosphatase
The End!